ISSN: 2664-472X
e-ISSN: 2664-4738
https://doi.org/10.32345/2664-4738.2.2026

Bogomolets National Medical University

MEDICAL SCIENCE OF UKRAINE

Founded in 2005
Frequency: Four issues per year

Vol. 22, No. 2

Kyiv – 2026

Founder and publisher: Bogomolets National Medical University

Year of foundation: 2005

Recommended for printing and distribution
via the Internet by the Academic Council
of Bogomolets National Medical University
(protocol No.13 dated 28.05.2026)

Media ID R40-07279.
Decision of the National Council of Ukraine on Television
and Radio Broadcasting No. 1772, Minutes No. 13 (dated 25 June 2026).

The journal "Medical Science of Ukraine" is included in category "B" – the list of peer-reviewed academic publications of Ukraine recommended for the publication of dissertation materials for obtaining the academic degrees of Doctor of Sciences, Candidate of Sciences (equivalent to PhD), and Doctor of Philosophy in the field of knowledge I Healthcare and Social Welfare, in the following specialties:

0511 – Biology
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0988 – Inter-Disciplinary Programmes and Qualifications Involving Health and Welfare

Order of the Ministry of Education and Science of Ukraine No. 928 of 11 June 2026.

Cluster: Biology, biotechnology, medicine, and rehabilitation.

Journal is presented in international scientometric databases, repositories and scientific systems:

Editors office address:
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
E-mail: msu@medjournal.org.ua
https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/

Medical Science of Ukraine
Медична наука України
Vol. 22,
No. 2, 2026

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No. 2, 2026

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CLINICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 617.713-002.28-022.6:616.379-008.64:577.112:355.01(477) Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.01 Received: 16.01.2026 Revised: 29.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Andrii Hudz*

Doctor of Medical Sciences, Professor
Danylo Halytsky Lviv National Medical University
79010, 69 Pekarska Str., Lviv, Ukraine
https://orcid.org/0009-0009-0146-6367

Solomiia Kadubets

Assistant
Danylo Halytsky Lviv National Medical University
79010, 69 Pekarska Str., Lviv, Ukraine
https://orcid.org/0000-0002-6494-5594

Tear fluid levels of interleukin-6 and tight junction protein ZO-1 and their association with the course of bacterial keratitis in type 2 diabetes mellitus under martial law in Ukraine

Abstract

Relevance. Bacterial keratitis is one of the most common infectious diseases of the cornea and may lead to severe complications, persistent visual impairment, and disability.

Aim. To investigate the levels of interleukin-6 and the tight junction protein zonula occludens-1 in the tear fluid of patients with bacterial keratitis according to the presence of type 2 diabetes mellitus and to assess their association with the clinical course and development of disease complications.

Materials and methods. A prospective comparative multicentre cohort study involving 88 participants was conducted, including patients with bacterial keratitis with and without type 2 diabetes mellitus, as well as healthy controls. Concentrations of interleukin-6 and the tight junction protein zonula occludens-1 in tear fluid were determined using enzyme-linked immunosorbent assay (ELISA).

Results. Significantly elevated concentrations of interleukin-6 and zonula occludens-1 were detected in patients with bacterial keratitis compared with the control group. The highest levels of both biomarkers were observed in patients with concomitant type 2 diabetes mellitus. The concentration of interleukin-6 in patients with bacterial keratitis without diabetes mellitus was 245 [170;390] pg/mL, whereas in patients with concomitant type 2 diabetes mellitus it reached 430 [310;610] pg/mL. The level of zonula occludens-1 was 6.8 [4.9;9.5] ng/mL and 9.6 [7.2;13.4] ng/mL, respectively. Statistically significant positive correlations were found between the levels of the investigated biomarkers and the thickness, width, and area of corneal infiltrates. The strongest correlations were observed between interleukin-6 concentration and infiltrate thickness ($\rho = 0.74$; $p < 0.001$), as well as between zonula occludens-1 level and infiltrate thickness ($\rho = 0.76$; $p < 0.001$) in patients with type 2 diabetes mellitus. Patients with infiltrate ulceration, delayed epithelialisation, and stromal opacity demonstrated significantly higher levels of both biomarkers compared with those without a complicated disease course.

Conclusions. Bacterial keratitis is associated with increased levels of interleukin-6 and the tight junction protein zonula occludens-1 in tear fluid. The investigated biomarkers were associated with morphometric characteristics of corneal infiltrates and the development of clinical complications of the disease.

Keywords: infectious corneal disease; diabetic keratopathy; proinflammatory cytokines; corneal infiltrate; biomarkers.

Suggested Citation:
Hudz A, Kadubets S. Tear fluid levels of interleukin-6 and tight junction protein ZO-1 and their association with the course of bacterial keratitis in type 2 diabetes mellitus under martial law in Ukraine. Med Sci Ukr. 2026;22(2):5–13. DOI: https://doi.org/10.32345/2664-4738.2.2026.01

*Corresponding author (*anhudz@gmail.com*)

INTRODUCTION

Bacterial keratitis is one of the most common and potentially sight-threatening infectious diseases of the cornea, as it may lead to the development of corneal ulceration, scarring, opacification, and even corneal perforation, resulting in permanent impairment of visual function. Patients with type 2 diabetes mellitus represent a particular clinical challenge because disturbances in glucose metabolism, chronic inflammation, and delayed tissue repair are associated with a more severe disease course and an increased risk of complications. The problem has become even more relevant in Ukraine under martial law, where restricted access to timely specialist ophthalmic care and pathogenetically targeted treatment may adversely affect the course of bacterial keratitis, promote the development of complications, and worsen functional treatment outcomes, particularly in patients with concomitant type 2 diabetes mellitus. Consequently, investigating the mechanisms of local inflammation and disruption of corneal epithelial integrity, which may determine the clinical course of bacterial keratitis and the development of its complications, is of considerable importance.

Current knowledge regarding the epidemiology, risk factors, and clinical characteristics of infectious keratitis has been summarised by D. Ting *et al*. [1]. The authors emphasised that disease severity is determined not only by the virulence of the causative pathogen but also by the characteristics of the host local immune response. Similar conclusions were reached by M. Cabrera-Aguas *et al*. [2], who demonstrated that the intensity of the inflammatory response directly influences the extent of corneal damage and the risk of adverse clinical outcomes. One of the principal mechanisms of tissue damage in bacterial keratitis is local inflammation. Pro-inflammatory cytokines play a central role in this process, with interleukin-6 (IL-6) being of particular importance. H. Alenezi *et al*. [3], investigating the tear cytokine profile in bacterial keratitis, reported a marked increase in the levels of pro-inflammatory mediators, including IL-6. They concluded that IL-6 concentration reflects the activity of the local inflammatory response and may be associated with the severity of the infectious process.

An equally important component of the pathogenesis of infectious corneal disease is the integrity of the epithelial barrier. The protective function of the ocular surface is maintained by a system of tight junctions, which regulate epithelial permeability and preserve structural integrity. S. Kaur *et al.* [4] demonstrated that disruption of tight junction architecture is associated with impairment of the corneal barrier function and facilitates the penetration of pathogenic microorganisms into corneal tissue. W. Kuo *et al.* [5] established that the zonula occludens-1 (ZO-1) protein is one of the key regulators of intercellular junctions, supporting epithelial cell proliferation, survival, and functional activity. Alterations in ZO-1 levels may therefore indicate disruption of epithelial structural integrity and the extent of epithelial damage. These mechanisms are of particular importance in patients with diabetes mellitus. L. Ladea *et al.* [6] demonstrated that chronic hyperglycaemia is associated with structural alterations of the corneal epithelium, impairment of barrier function, and delayed regenerative processes. Similar findings were reported by F. Buonfiglio *et al*. [7], who showed that oxidative stress and chronic inflammation are the principal mechanisms underlying diabetic keratopathy and contribute to the progression of corneal tissue damage. Thus, concomitant diabetes mellitus may exacerbate both inflammatory and structural alterations in bacterial keratitis.

Considerable attention has recently been devoted to the identification of non-invasive biomarkers for ocular surface diseases. Tear fluid represents a promising biological medium because its composition reflects local pathological processes. In a systematic review and meta-analysis, M. Polkamp *et al*. [8] demonstrated that changes in tear fluid composition may reflect the development of diabetic ophthalmic complications. Likewise, N. Gospodarczyk *et al*. [9] highlighted the potential of tear biomarkers for assessing ocular surface status and monitoring the course of pathological processes. Collectively, current evidence indicates that local inflammation and disruption of the corneal barrier function play a pivotal role in the pathogenesis of bacterial keratitis. Interleukin-6 reflects inflammatory activity, whereas the ZO-1 protein characterises the integrity of intercellular junctions and the structural condition of the epithelial barrier. Simultaneous assessment of these biomarkers may therefore provide a comprehensive evaluation of both inflammatory activity and the extent of structural corneal damage. However, data regarding their concurrent measurement in the tear fluid of patients with bacterial keratitis remain limited. The relationship between IL-6 and ZO-1 levels, the influence of concomitant type 2 diabetes mellitus on these biomarkers, and their value in predicting the clinical course, complications, and treatment outcomes of bacterial keratitis have not yet been sufficiently investigated.

The aim of this study was to determine the concentrations of interleukin-6 and the ZO-1 protein in the tear fluid of patients with bacterial keratitis with and without type 2 diabetes mellitus and to evaluate their association with the clinical course and complications of the disease.

MATERIALS AND METHODS

A prospective comparative multicentre cohort study was conducted. The clinical investigation was performed in accordance with the principles of the World

Medical Association Declaration of Helsinki, the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, and Order No. 690 of the Ministry of Health of Ukraine [10-12]. The study protocol was approved by the Bioethics Committee of Danylo Halytsky Lviv National Medical University (Protocol No. 12, 16 December 2024). Written informed consent was obtained from all participants before enrolment. The diagnosis of bacterial keratitis was established on the basis of a comprehensive ophthalmological examination, including medical history taking, slit-lamp biomicroscopy of the anterior segment, fluorescein staining, and assessment of stromal infiltrate, epithelial defect, conjunctival injection, and other clinical signs of infection. The bacterial aetiology of the disease was confirmed by bacterioscopic and bacteriological examination of corneal ulcer specimens obtained before the initiation of antibacterial therapy.

The study included 88 participants (88 eyes), comprising 60 patients with bacterial keratitis and 28 apparently healthy individuals in the control group. The participants were divided into three groups. Group 1 consisted of 32 patients with bacterial keratitis without disturbances of glucose metabolism. Group 2 included 28 patients with bacterial keratitis and confirmed type 2 diabetes mellitus. The control group comprised 28 apparently healthy individuals without corneal pathology, diabetes mellitus, or other systemic diseases. The inclusion criteria were age over 18 years, clinically and laboratory-confirmed bacterial keratitis, the ability to undergo a complete ophthalmological examination, and the availability of tear fluid samples for laboratory analysis. For the main study group, confirmed type 2 diabetes mellitus was an additional inclusion criterion. Exclusion criteria included viral, fungal, Acanthamoeba, or autoimmune keratitis, type 1 diabetes mellitus, severe concomitant systemic diseases, immunosuppressive therapy, and recent corneal surgery.

All participants underwent a standard ophthalmological examination, including assessment of visual acuity, refraction, intraocular pressure, slit-lamp biomicroscopy, and fundus examination. Optical coherence tomography of the anterior segment was used to evaluate the morphometric characteristics of the cornea. Corneal infiltrate thickness, width, and area were measured. Tear fluid samples were collected following instillation of 60 μL of sterile 0.9% sodium chloride solution into the conjunctival sac. After 30 seconds, tear fluid was collected using sterile capillary tubes, transferred into microcentrifuge tubes, and stored at -70°C until laboratory analysis. IL-6 concentrations were determined using a solid-phase enzyme-linked immunosorbent assay (ELISA) with the High Sensitivity Human Interleukin-6 ELISA Kit (MyBioSource, USA). The results were expressed in pg/mL. ZO-1 concentrations were measured using ELISA with the Human Tight Junction Protein 1 (ZO-1) ELISA Kit (MyBioSource, USA) and expressed in ng/mL.

To evaluate the pathogenetic significance of the investigated biomarkers, their relationships with the morphometric characteristics of the corneal infiltrate (thickness, width, and area) and with the development of clinical complications, including delayed epithelialisation, stromal opacity, and corneal ulceration, were analysed. Statistical analysis was performed using Statistica version 13.3 (StatSoft Inc., USA) and IBM SPSS Statistics version 27.0. Normality of data distribution was assessed using the Shapiro-Wilk test. Quantitative variables with a non-normal distribution are presented as the median and interquartile range (Me [Q1; Q3]). Comparisons between independent groups were performed using the Kruskal-Wallis test followed by Dunn's post hoc test or the Mann-Whitney U test, as appropriate. Correlation analysis was performed using Spearman's rank correlation coefficient. Differences were considered statistically significant at $p < 0.05$.

The authors declare that the views expressed in this article are their own and do not represent the official position of their institution.

RESULTS AND DISCUSSION

To evaluate the characteristics of the local inflammatory response and the integrity of the corneal epithelial barrier, the concentrations of interleukin-6 (IL-6) and the tight junction protein ZO-1 were analysed in the tear fluid of patients with bacterial keratitis with and without type 2 diabetes mellitus. Tear fluid IL-6 concentrations differed significantly between the study groups (Table 1). In the control group, the median IL-6 concentration was 18 [12;25] pg/mL. In patients with bacterial keratitis without concomitant type 2 diabetes mellitus, the IL-6 concentration was 245 [170;390] pg/mL, representing a 13.6-fold increase compared with the control group ($p < 0.001$). In patients with bacterial keratitis and type 2 diabetes mellitus, the median IL-6 concentration reached 430 [310;610] pg/mL, which was 23.9-fold higher than in the control group ($p < 0.001$) and 1.8-fold higher than in patients with bacterial keratitis without type 2 diabetes mellitus ($p = 0.02$). The highest IL-6 concentrations were observed in patients with bacterial keratitis and type 2 diabetes mellitus.

Similar changes were observed in the analysis of ZO-1 levels in tear fluid (Table 2). In patients with bacterial keratitis without type 2 diabetes mellitus, the median ZO-1 level was 6.8 [4.9;9.5] ng/mL, which was significantly higher than that of the control group ($p < 0.001$). In patients with bacterial keratitis and type 2 diabetes mellitus, the ZO-1 level increased to 9.6 [7.2;13.4] ng/mL, exceeding the corresponding value in the control group by 4.6-fold and that in the group without type 2 diabetes mellitus by 1.4-fold ($p = 0.01$).

Table 1. IL-6 levels in the tear fluid of patients in the study groups, Me [Q1; Q3]

Study group (number of eyes)	IL-6, pg/mL	p
Control group (n = 28)	18 [12;25]	–
Bacterial keratitis (n = 32)	245 [170;390]	p < 0.001[1]
Bacterial keratitis + type 2 diabetes mellitus (n = 28)	430 [310;610]	p < 0.001[1]; p = 0.02[2]

Note: normality of data distribution was assessed using the Shapiro-Wilk test. As the data were not normally distributed, non-parametric statistical methods were applied. Statistical analysis was performed using the Kruskal-Wallis test followed by Dunn's post hoc test. Data are presented as the median and interquartile range, Me [Q1; Q3]. [1] Statistically significant differences compared with the control group; [2] statistically significant differences compared with the bacterial keratitis group without concomitant type 2 diabetes mellitus
Source: authors' own research

Table 2. ZO-1 concentration in the tear fluid of patients in the study groups, Me [Q1;Q3]

Study group (number of eyes)	ZO-1, ng/mL	p
Control group (n = 28)	2.1 [1.4;3.2]	–
Bacterial keratitis (n = 32)	6.8 [4.9;9.5]	p < 0.001[1]
Bacterial keratitis + type 2 diabetes mellitus (n = 28)	9.6 [7.2;13.4]	p < 0.001[1]; p=0.01[2]

Note: normality of data distribution was assessed using the Shapiro-Wilk test. As the data were not normally distributed, non-parametric statistical methods were applied. Statistical analysis was performed using the Kruskal-Wallis test followed by Dunn's post hoc test. Data are presented as the median and interquartile range, Me [Q1; Q3]. [1] Statistically significant differences compared with the control group; [2] statistically significant differences compared with the bacterial keratitis group without concomitant type 2 diabetes mellitus
Source: authors' own research

To assess the relationship between tear fluid IL-6 levels and the clinical characteristics of the disease, a correlation analysis was performed with the morphometric parameters of the corneal infiltrate (thickness, width, and area) (Table 3). Statistically significant positive correlations were identified between IL-6 levels and all investigated parameters. In patients with bacterial keratitis without type 2 diabetes mellitus, the correlation coefficients ranged from 0.45 to 0.52, whereas in the group with type 2 diabetes mellitus they ranged from 0.66 to 0.74. The strongest association was observed between IL-6 levels and corneal infiltrate thickness in patients with type 2 diabetes mellitus ($\rho = 0.74$; $p < 0.001$). Analysis of the relationship between tear fluid ZO-1 levels and the morphometric characteristics of the corneal infiltrate also revealed statistically significant positive correlations (Table 4). In the bacterial keratitis group without type 2 diabetes mellitus, the correlation coefficients ranged from 0.47 to 0.55, whereas in patients with type 2 diabetes mellitus they ranged from 0.69 to 0.76. The highest correlation coefficient was recorded between ZO-1 levels and corneal infiltrate thickness in the bacterial keratitis with type 2 diabetes mellitus group ($\rho = 0.76$; $p < 0.001$).

Table 3. Correlation between tear fluid IL-6 levels and the morphometric characteristics of the corneal infiltrate at initial presentation in patients with bacterial keratitis and type 2 diabetes mellitus

Morphometric characteristic of the infiltrate (μm)	Group	IL-6 (pg/mL)	Value	Spearman's ρ	p
Infiltrate thickness (μm)	Bacterial keratitis (n = 32)	245 [170;390]	378.4 ± 83.2	0.52	0.003
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	430 [310;610]	401.8 ± 82.9	0.74	<0.001
Infiltrate width (μm)	Bacterial keratitis (n = 32)	245 [170;390]	1,655.2 ± 162.1	0.48	0.006
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	430 [310;610]	1,728.6 ± 168.4	0.69	<0.001
Infiltrate area	Bacterial keratitis (n = 32)	245 [170;390]	0.53 ± 0.15	0.45	0.009
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	430 [310;610]	0.57 ± 0.14	0.66	<0.001

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. The morphometric parameters of the infiltrate are presented as the mean ± standard deviation (M ± SD). Correlation analysis was performed using Spearman's rank correlation coefficient (ρ)
Source: authors' own research

Table 4. Correlation between tear fluid ZO-1 levels and the morphometric characteristics of the corneal infiltrate at initial presentation in patients with bacterial keratitis and type 2 diabetes mellitus

Morphometric characteristic of the infiltrate (μm)	Group	ZO-1 (ng/mL)	Value	Spearman's ρ	p
Infiltrate thickness (μm)	Bacterial keratitis (n = 32)	6.8 [4.9;9.5]	378.4 ± 83.2	0.55	0.002
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	9.6 [7.2;13.4]	401.8 ± 82.9	0.76	<0.001

Table 4. *Continued*

Morphometric characteristic of the infiltrate (μm)	Group	ZO-1 (ng/mL)	Value	Spearman's ρ	p
Infiltrate width (μm)	Bacterial keratitis (n = 32)	6.8 [4.9;9.5]	1,655.2 ± 162.1	0.51	0.004
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	9.6 [7.2;13.4]	1,728.6 ± 168.4	0.71	<0.001
Infiltrate area	Bacterial keratitis (n = 32)	6.8 [4.9;9.5]	0.53 ± 0.15	0.47	0.007
	Bacterial keratitis + type 2 diabetes mellitus (n = 28)	9.6 [7.2;13.4]	0.57 ± 0.14	0.69	<0.001

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. The morphometric parameters of the infiltrate are presented as the mean ± standard deviation (M ± SD). Correlation analysis was performed using Spearman's rank correlation coefficient (ρ)
Source: authors' own research

Analysis of tear fluid IL-6 levels according to the development of clinical complications demonstrated statistically significant differences between patients with and without complications. Patients who developed complications had significantly higher IL-6 levels than those without the corresponding clinical manifestations. In the group without type 2 diabetes mellitus, the highest IL-6 levels were recorded in patients with corneal infiltrate ulceration, reaching 420 [340;520] pg/mL compared with 250 [180;345] pg/mL in patients without ulceration (p = 0.018). In the group with type 2 diabetes mellitus, the corresponding values were 660 [520;780] pg/mL and 375 [290;490] pg/mL, respectively (p < 0.001) (Tables 5 and 6).

Table 5. Development of complications in patients with bacterial keratitis without type 2 diabetes mellitus according to tear fluid IL-6 levels (n = 32)

Complication	Complication present	Complication absent	Mann-Whitney U	p
Delayed epithelialisation (>10 days)	365 [290;470] (n = 8)	228 [170;310] (n = 24)	52.0	0.010
Development of stromal opacity	385 [300;490] (n = 11)	235 [175;325] (n = 21)	46.0	0.006
Corneal infiltrate ulceration	420 [340;520] (n = 5)	250 [180;345] (n = 27)	28.0	0.018

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. Between-group comparisons were performed using the Mann-Whitney U test. Differences were considered statistically significant at p < 0.05
Source: authors' own research

Table 6. Development of complications in patients with bacterial keratitis and type 2 diabetes mellitus according to tear fluid IL-6 levels (n = 28)

Complication	Complication present	Complication absent	Mann-Whitney U	p
Delayed epithelialisation (>10 days)	595 [470;710] (n = 12)	330 [250;440] (n = 16)	31.0	<0.001
Development of stromal opacity	610 [490;735] (n = 14)	345 [260;460] (n = 14)	26.0	<0.001
Corneal infiltrate ulceration	660 [520;780] (n = 8)	375 [290;490] (n = 20)	19.0	<0.001

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. Between-group comparisons were performed using the Mann-Whitney U test. Differences were considered statistically significant at p < 0.05
Source: authors' own research

A similar pattern was observed for the ZO-1 protein (Tables 7 and 8). In patients without type 2 diabetes mellitus, the highest ZO-1 level was detected in those with corneal infiltrate ulceration, reaching 11.6 [9.4;13.8] ng/mL compared with 6.1 [4.6;7.8] ng/mL in patients without this complication (p = 0.006). In the group of patients with type 2 diabetes mellitus, the highest ZO-1 levels were likewise recorded in those with infiltrate ulceration, reaching 15.8 [12.7;18.4] ng/mL compared with 8.4 [6.7;10.6] ng/mL, respectively (p < 0.001).

Table 7. Development of complications in patients with bacterial keratitis without type 2 diabetes mellitus according to tear fluid ZO-1 levels (n = 32)

Complication	Complication present	Complication absent	Mann-Whitney U	p
Delayed epithelialisation (>10 days)	8.9 [7.2;10.8] (n = 8)	5.9 [4.3;7.6] (n = 24)	48.0	0.008
Development of stromal opacity	9.8 [8.0;11.9] (n = 11)	6.0 [4.5;7.8] (n = 21)	41.0	0.003
Corneal infiltrate ulceration	11.6 [9.4;13.8] (n = 5)	6.1 [4.6;7.8] (n = 27)	18.0	0.006

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. Between-group comparisons were performed using the Mann-Whitney U test. Differences were considered statistically significant at p < 0.05
Source: authors' own research

Table 8. Development of complications in patients with bacterial keratitis and type 2 diabetes mellitus according to tear fluid ZO-1 levels (n = 28)

Complication	Complication present	Complication absent	Mann-Whitney U	p
Delayed epithelialisation (>10 days)	13.1 [10.4;15.6] (n = 12)	8.0 [6.4;10.2] (n = 16)	29.0	<0.001
Development of stromal opacity	14.0 [11.2;16.5] (n = 15)	8.2 [6.6;10.4] (n = 13)	22.0	<0.001
Corneal infiltrate ulceration	15.8 [12.7;18.4] (n = 8)	8.4 [6.7;10.6] (n = 20)	12.0	<0.001

Note: data are presented as the median and interquartile range, Me [Q1; Q3]. Between-group comparisons were performed using the Mann-Whitney U test. Differences were considered statistically significant at $p < 0.05$
Source: authors' own research

One of the principal findings of the present study was the significant increase in IL-6 and ZO-1 concentrations in the tear fluid of patients with bacterial keratitis, with the highest levels of both biomarkers observed in the presence of concomitant type 2 diabetes mellitus. Specifically, the IL-6 concentration in patients with bacterial keratitis and type 2 diabetes mellitus was almost 1.8-fold higher than that in patients without diabetes. These findings indicate a more pronounced activation of the local inflammatory response in patients with metabolic disturbances. Similar observations have been reported by A. Konstantopoulos *et al*. [13], who demonstrated an association between the cytokine profile and the clinical characteristics of bacterial keratitis. Likewise, K. Cheng *et al.* [14] emphasised that excessive production of pro-inflammatory cytokines represents one of the key mechanisms underlying corneal tissue damage during infectious keratitis. The clinical relevance of the observed immunoinflammatory alterations is further supported by studies investigating predictors of bacterial keratitis severity and risk factors for the development of disease complications [15].

Another important finding of this study was the identification of positive correlations between IL-6 concentration and the morphometric characteristics of the corneal infiltrate. The strongest association was observed between IL-6 concentration and infiltrate thickness in patients with type 2 diabetes mellitus ($\rho = 0.74$; $p < 0.001$). This finding suggests that the intensity of the local inflammatory response is directly related to the extent of structural corneal damage. Of particular interest is the observation that these correlations were stronger in patients with type 2 diabetes mellitus than in those without diabetes. This may be explained by the presence of chronic low-grade inflammation, oxidative stress, and impaired reparative processes, which are characteristic features of diabetic keratopathy. A similar interpretation has been proposed by F. Buonfiglio *et al.* [7].

The findings regarding the ZO-1 protein are equally important. In the present study, ZO-1 concentrations were significantly higher in patients with bacterial keratitis, with the highest values observed in those with concomitant type 2 diabetes mellitus. Moreover, strong positive correlations were identified between ZO-1 levels and the thickness, width, and area of the corneal infiltrate. These findings suggest that disruption of intercellular junctions and impairment of the epithelial barrier constitute important components of the pathogenesis of bacterial keratitis. S. Alfuraih *et al.* [16] demonstrated that hyperglycaemia adversely affects tight junction proteins and the barrier function of the ocular surface epithelium. Similar findings were reported by S. Casarella *et al.* [17] and A. Ebrahim *et al*. [18], who described structural and functional alterations of the corneal epithelium in diabetic keratopathy. Furthermore, M. Yu *et al.* [19] showed that activation of pro-inflammatory signalling pathways is accompanied by disruption of corneal epithelial barrier integrity and contributes to the progression of structural corneal damage. The clinical significance of these pathogenetic alterations is further supported by epidemiological studies demonstrating an increased susceptibility of patients with diabetes mellitus to severe corneal disease [20].

Particular attention should be paid to the observed association between elevated IL-6 and ZO-1 levels and the development of clinical complications. Patients with infiltrate ulceration, delayed epithelialisation, and stromal opacity exhibited significantly higher concentrations of both biomarkers than patients with an uncomplicated disease course. The highest levels were consistently observed in patients with type 2 diabetes mellitus. These findings indicate that local inflammation and impairment of the corneal barrier function may represent interrelated mechanisms contributing to the development of complications in bacterial keratitis. Similar conclusions regarding risk factors for adverse outcomes in bacterial keratitis have been reported by C. Bertret *et al*. [15], A. Nayel *et al.* [21], and E. Österhed *et al*. [22], who highlighted the importance of clinical, microbiological, and therapeutic factors in predicting treatment outcomes. Particular emphasis has also been placed on the integrity of the corneal epithelial barrier, the disruption of which is regarded as one of the key factors promoting disease progression and the development of complications [23].

Thus, the findings of the present study expand current understanding of the pathogenetic mechanisms underlying bacterial keratitis in patients with type 2 diabetes mellitus. Concomitant type 2 diabetes mellitus was associated with greater increases in IL-6 and ZO-1 concentrations, larger corneal infiltrates, and a higher incidence of clinical complications. Determination of these biomarkers in tear fluid may therefore have

practical value for assessing disease severity and predicting the risk of developing complications in patients with bacterial keratitis.

CONCLUSIONS

1. It was established that the median tear fluid IL-6 level in patients with bacterial keratitis and type 2 diabetes mellitus was 1.8-fold higher than in patients without diabetes and 23.9-fold higher than in the control group. The ZO-1 level in this group was also significantly elevated, exceeding that of the bacterial keratitis group without type 2 diabetes mellitus by 1.4-fold and the control group by 4.6-fold. These findings indicate more pronounced disruption of the corneal epithelial barrier and a more intense local inflammatory response in the presence of concomitant metabolic disturbances.

2. Statistically significant positive correlations were identified between IL-6 and ZO-1 levels and the morphometric characteristics of the corneal infiltrate. In patients with bacterial keratitis and type 2 diabetes mellitus, strong correlations were observed between the investigated biomarkers and infiltrate thickness, width, and area ($\rho = 0.66$-0.76; $p < 0.001$), whereas in patients without diabetes the correlations were of moderate strength ($\rho = 0.45$-0.55; $p < 0.01$). These findings demonstrate a close relationship between the severity of local inflammation, the degree of disruption of intercellular junctions, and the extent of structural corneal changes.

3. Elevated IL-6 and ZO-1 levels were shown to be associated with the development of clinical complications of bacterial keratitis. The highest levels of both biomarkers were recorded in patients with corneal infiltrate ulceration, whereas lower levels were observed in patients without complications. Similar patterns were identified for delayed epithelialisation and the development of stromal opacity. These changes were more pronounced in patients with type 2 diabetes mellitus, confirming the adverse effect of metabolic disturbances on the course of the infectious process and the reparative capacity of the cornea.

4. The obtained findings support the potential use of IL-6 and ZO-1 as promising biomarkers of inflammatory activity, epithelial barrier damage, and the risk of a complicated course of bacterial keratitis, particularly in patients with type 2 diabetes mellitus.

5. Future research should focus on investigating the dynamics of IL-6 and ZO-1 levels in response to treatment, evaluating their prognostic value for long-term functional outcomes, and developing models for the early prediction of bacterial keratitis complications based on a combination of clinical and laboratory parameters.

6. Study limitations. The findings should be interpreted in the context of the relatively small sample size of the study groups and the absence of long-term follow-up to assess changes in the investigated biomarkers over time.

ACKNOWLEDGEMENTS

The authors have no specific acknowledgements related to the conduct of this study.

FUNDING

No funding was received.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Андрій Гудзь

Доктор медичних наук, професор
ДНТ «Львівський національний медичний університет імені Данила Галицького»
79010, вул. Пекарська, 69, м. Львів, Україна
https://orcid.org/0009-0009-0146-6367

Соломія Кадубець

Асистент
ДНТ «Львівський національний медичний університет імені Данила Галицького»
79010, вул. Пекарська, 69, м. Львів, Україна
https://orcid.org/0000-0002-6494-5594

Вміст інтерлейкіну-6 та білка щільних контактів ZO-1 у слізній рідині та їх зв'язок із перебігом бактеріального кератиту при цукровому діабеті 2 типу в умовах воєнного стану в Україні

Анотація

Актуальність. Бактеріальний кератит є одним із найбільш поширених інфекційних захворювань рогівки та може призводити до розвитку тяжких ускладнень, стійкого зниження гостроти зору й інвалідизації пацієнтів.

Мета. Вивчити вміст інтерлейкіну-6 та білка щільних міжклітинних контактів zonula occludens-1 у слізній рідині пацієнтів із бактеріальним кератитом залежно від наявності цукрового діабету 2 типу та оцінити їх зв'язок із клінічним перебігом і розвитком ускладнень захворювання.

Матеріали та методи. Проведено проспективне порівняльне когортне мультицентрове дослідження за участю 88 осіб, серед яких пацієнти з бактеріальним кератитом за наявності та відсутності цукрового діабету 2 типу, а також особи контрольної групи. Концентрації інтерлейкіну-6 та білка щільних міжклітинних контактів zonula occludens-1 у слізній рідині визначали методом імуноферментного аналізу.

Результати. Встановлено достовірне підвищення концентрацій інтерлейкіну-6 та білка щільних міжклітинних контактів zonula occludens-1 у пацієнтів із бактеріальним кератитом порівняно з контрольною групою. Найвищі значення обох показників визначалися у пацієнтів із супутнім цукровим діабетом 2 типу. Концентрація інтерлейкіну-6 у пацієнтів із бактеріальним кератитом без цукрового діабету становила 245 [170;390] пг/мл, тоді як у хворих із супутнім цукровим діабетом 2 типу досягала 430 [310;610] пг/мл. Вміст білка щільних міжклітинних контактів zonula occludens-1 становив відповідно 6,8 [4,9;9,5] нг/мл та 9,6 [7,2;13,4] нг/мл. Виявлено статистично значущі прямі кореляційні зв'язки між рівнями досліджуваних біомаркерів і товщиною, шириною та площею інфільтрату рогівки. Найбільш сильні кореляції встановлено між концентрацією інтерлейкіну-6 та товщиною інфільтрату ($\rho = 0,74$; $p < 0,001$), а також між рівнем білка щільних міжклітинних контактів zonula occludens-1 та товщиною інфільтрату ($\rho = 0,76$; $p < 0,001$) у пацієнтів із цукровим діабетом 2 типу. У хворих із виразкуванням інфільтрату, уповільненою епітелізацією та стромальним помутнінням рівні обох біомаркерів були достовірно вищими порівняно з пацієнтами без ускладненого перебігу захворювання.

Висновки. Бактеріальний кератит супроводжується підвищенням вмісту інтерлейкіну-6 та білка щільних міжклітинних контактів zonula occludens-1 у слізній рідині. Встановлено зв'язок досліджуваних показників із морфометричними характеристиками інфільтрату рогівки та розвитком клінічних ускладнень захворювання.

Ключові слова: інфекційне ураження рогівки; діабетична кератопатія; прозапальні цитокіни; корнеальний інфільтрат; біомаркери.

CLINICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 617.741:616-097:612.017
DOI: https://doi.org/10.32345/2664-4738.2.2026.02

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 10.01.2026 Revised: 01.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Olga Guzun*

PhD in Medical Sciences, Senior Research Fellow
State Institution "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine"
65061, 49/51 Frantsuzskiy Blvd., Odesa, Ukraine
https://orcid.org/0009-0003-6873-8503

Liudmyla Velychko

Doctor of Medical Sciences
State Institution "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine"
65061, 49/51 Frantsuzskiy Blvd., Odesa, Ukraine
https://orcid.org/0009-0008-8485-3698

Systemic biomarkers of apoptosis and endothelial activation in the pathogenesis of rubeosis iridis and iridocorneal angle neovascularisation in secondary neovascular glaucoma

Abstract

Aim. To assess systemic levels of CD95 (Fas) and ICAM-1 (CD54) in patients with secondary neovascular glaucoma (NVG), to determine the relationship with the severity of iris rubeosis and the iridocorneal angle, and to evaluate the role of endothelial apoptosis in neovascular remodelling of the anterior segment of the eye.

Materials and methods. A single-centre cross-sectional study included 186 eyes with secondary NVG (96 associated with proliferative diabetic retinopathy and 90 following retinal vein occlusion) and 34 eyes in the control group. The severity of rubeosis was assessed using the Weiss grading scale. CD95 and ICAM-1 levels in peripheral blood were measured using an immunocytochemical method.

Results. In patients with NVG, CD95 and ICAM-1 levels were significantly higher compared with controls ($p < 0.001$). Both markers positively correlated with the severity of rubeosis according to Weiss (CD95: $rs = 0.46$; ICAM-1: $rs = 0.45$; $p < 0.001$) and with intraocular pressure. In a multivariable ordinal logistic regression model, CD95 and ICAM-1 remained independently associated with more severe rubeosis after adjustment for aetiology and intraocular pressure (CD95: OR = 2.31; 95% CI 1.27-4.18; $p = 0.006$; ICAM-1: OR = 2.48; 95% CI 1.56-3.95; $p < 0.001$). ROC analysis demonstrated moderate discriminative ability of the markers for detecting clinically significant rubeosis (Weiss ≥ II): AUC = 0.729 for CD95 and AUC = 0.730 for ICAM-1. Cut-off values were 687 cells/μL and 542 cells/μL, respectively.

Conclusions. CD95 (Fas) and ICAM-1 (CD54) are associated with the severity of rubeosis in secondary NVG and may serve as systemic biomarkers for neovascular remodelling and risk stratification of disease progression.

Keywords: CD95 (Fas); ICAM-1 (CD54); angiogenesis; neovascular remodelling; endothelial dysfunction; apoptosis; risk stratification.

INTRODUCTION

Secondary neovascular glaucoma is among the most severe forms of glaucomatous eye damage and remains one of the leading causes of irreversible vision loss in patients with ischaemic retinal diseases. The disease most commonly develops in association with proliferative diabetic retinopathy (PDR) and retinal vein occlusion (RVO). Both conditions are characterised by chronic tissue hypoxia, activation of angiogenesis and the formation of pathological newly formed vessels in the anterior and/or posterior segment of the eye. Rubeosis iridis and neovascularisation of the iridocorneal angle are key clinical manifestations of this process. These clinical signs determine further progression of ophthalmic hypertension and the development of refractory glaucoma. Despite the

Suggested Citation:
Guzun O, Velychko L. Systemic biomarkers of apoptosis and endothelial activation in the pathogenesis of rubeosis iridis and iridocorneal angle neovascularisation in secondary neovascular glaucoma. Med Sci Ukr. 2026;22(2):14–23. DOI: https://doi.org/10.32345/2664-4738.2.2026.02

*Corresponding author (*olga.v.guzun@gmail.com*)

use of vascular endothelial growth factor (VEGF) inhibitors and modern laser technologies, the clinical course of the disease remains highly variable. Such variability suggests that additional pathophysiological mechanisms are involved and that the disease process extends beyond local angiogenesis alone.

In the latest review of NVG, S. Gerçeker Demircan & A. Şanal Doğan [1] pointed out that the clinical course of the disease is determined by a complex interaction between retinal ischaemia, pathological angiogenesis, inflammation and remodelling of the anterior segment of the eye. S. Senthil *et al*. [2] noted that progression of rubeosis iridis and neovascularisation of the anterior chamber angle depends not only on VEGF-mediated mechanisms. Concomitant activation of inflammatory and vascular signalling pathways also affects it, influencing disease severity and treatment outcomes. D. Urbonavičiūtė *et al*. [3] also showed that neovascular glaucoma has a multicomponent pathogenesis, in which ischaemia, angiogenesis, inflammation and fibrovascular remodelling form a single pathological cascade.

Particular attention has been paid to endothelial activation as one of the key mechanisms of neovascular remodelling. Analysing current views on the pathogenesis of RVO, M. Lendzioszek *et al*. [4] showed that ischaemic damage is accompanied by activation of pro-inflammatory signalling pathways, impaired endothelial homeostasis and remodelling of the vascular wall. The authors stressed that endothelial dysfunction is not only a consequence of retinal ischaemia. It can also actively contribute to further progression of the pathological process. J. Tang & T.S. Kern [5] noted that chronic retinal hypoxia stimulates the production of VEGF and other pro-angiogenic mediators. These mediators support the development of rubeosis iridis, neovascularisation of the iridocorneal angle and pathological vascular remodelling.

Intercellular adhesion molecule-1, ICAM-1 (CD54), is of particular interest in this context. It reflects endothelial activation and enhanced leukocyte-endothelial interaction. In a comprehensive review of vascular complications of diabetes mellitus, D.R. Yang *et al*. [6] showed that endothelial dysfunction is accompanied by increased expression of adhesion molecules, including ICAM-1, microvascular inflammation and impaired vascular homeostasis. The authors underlined that endothelial activation is an essential mechanism in the progression of vascular remodelling and tissue ischaemia. Similar findings were reported by S.F. Abcouwer [7], who showed that activation of pro-inflammatory cytokines and adhesion molecules is an important component of ischaemic retinal injury and pathological angiogenesis, contributing to chronic inflammation and vascular remodelling.

Apoptosis-associated mechanisms are also critical alongside endothelial activation. L. Hu *et al.* [8] showed that the CD95 (Fas) system is not only one of the key regulators of programmed cell death. It also participates in inflammation, intercellular signalling and tissue remodelling. The authors emphasised that Fas-mediated signalling pathways can influence the course of chronic vascular-inflammatory diseases through a combination of apoptotic and immunoregulatory effects. These data broaden the understanding of CD95. It may act both as a marker of cellular damage and a potential participant in pathological angiogenesis and neovascular tissue remodelling.

C. Mishra & J.J. Meyer [9], analysing the mechanisms of iris neovascularisation, concluded that the interaction of ischaemia, inflammation, endothelial activation and tissue remodelling forms the biological basis for rubeosis progression. The authors also outlined the need to determine systemic biomarkers capable of reflecting the activity of these processes. O.V. Guzun *et al.* [10] showed that elevated ICAM-1 levels were linked to a more severe course of diabetic NVG and a less favourable response to treatment. In another study, E. Doğan *et al*. [11] found increased systemic inflammatory biomarkers, including NLR, SII and TyG, in patients with neovascular glaucoma. These findings support further investigation of systemic biological mechanisms involved in the development and progression of the disease.

Despite growing evidence on the role of inflammation, endothelial dysfunction and apoptosis in ischaemic eye diseases, the relationship between systemic levels of CD95 (Fas), ICAM-1 (CD54) and the severity of rubeosis iridis and neovascularisation of the iridocorneal angle in secondary NVG remains insufficiently studied. Further research is needed to clarify systemic mechanisms of neovascular remodelling in the anterior segment of the eye and to identify biomarkers that can reflect the biological activity of rubeosis and disease severity. The purpose of the study was to assess systemic levels of CD95 (Fas) and ICAM-1 (CD54) in patients with secondary neovascular glaucoma associated with proliferative diabetic retinopathy and retinal vein occlusion. The framework of the above purpose encompassed defining the relationship with the severity of rubeosis iridis and the iridocorneal angle, and evaluating the possible role of systemic apoptosis-endothelial disturbances in neovascular remodelling of the anterior segment of the eye.

MATERIALS AND METHODS

Study design and ethical considerations. A single-centre cross-sectional observational study was conducted. It included 186 patients, corresponding to 186 eyes, with secondary neovascular glaucoma. The study was carried out at the State Institution "V.P. Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" during 2018-2024. The study was performed in accordance with the World Medical Association Declaration of Helsinki [12] and the standards of the International

Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [13]. The Bioethics Committee of the State Institution "V.P. Filatov Institute of Eye Diseases and Tissue Therapy" (Protocol No. 4, 2024) approved it. All participants provided written informed consent. The data were anonymised in line with confidentiality requirements. All procedures remained within standard ophthalmological practice.

Participants and groups. The study researched the sample of 186 eyes with NVG: 96 with NVG related to proliferative diabetic retinopathy (NVG/PDR) and 90 with NVG following retinal vein occlusion (NVG/RVO). The control group consisted of 34 eyes from age-matched individuals without rubeosis iridis or glaucoma. The inclusion criteria were a confirmed diagnosis of NVG associated with PDR or RVO, the presence of rubeosis iridis, and uncontrolled intraocular pressure (IOP) ≥ 30 mmHg. The exclusion criteria were secondary NVG of another origin, severe systemic disease that could affect immune parameters, and the absence of clinical signs of anterior segment neovascularisation.

Clinical examination. All participants underwent a standard ophthalmological examination, including visual acuity testing, biomicroscopy, ophthalmoscopy and gonioscopy. IOP was measured by Goldmann applanation tonometry. The degree of iris neovascularisation was assessed using the classic Weiss grading scale (1971), which presupposes four stages. Stage I refers to scattered neovascular vessels located near the pupillary margin. Stage II describes neovascular proliferation extending to the mid-periphery of the iris. Stage III is characterised by a vascular network associated with anterior synechiae and incomplete angle closure. Stage IV indicates a dense neovascular network with anterior synechiae and complete closure of the iridocorneal angle [14]. No patients with Weiss stage IV were present in the study cohort. Weiss ≥ II was used as a quantitative measure of clinically significant rubeosis.

Biomarker assessment. Expression of CD95 (Fas) and ICAM-1 (CD54) on lymphocytes was determined in peripheral venous blood samples by indirect immunofluorescence using monoclonal antibodies against the corresponding antigens. The R.E. Kavetsky Institute of Experimental Pathology, Oncology, and Radiobiology of the National Academy of Sciences of Ukraine, Kyiv, Ukraine produces the antibodies. Fluorescein isothiocyanate (FITC) from the same manufacturer was used to visualise the immunological reaction. A lymphocyte suspension was obtained by centrifuging peripheral blood on a Ficoll density gradient (1.076 g/cm^3; Simesta, Ukraine), followed by two rounds of cell washing. After smear preparation and fixation, the samples were incubated with specific monoclonal antibodies, washed, and then incubated with FITC for 3 hours. After the final wash, the slides were examined using an iSCOPE fluorescence microscope (Euromex, the Netherlands). During the analysis, the proportion of positively stained cells among 100 lymphocytes was defined. To standardise the results, the obtained values were recalculated as the absolute number of CD95$^+$ and CD54$^+$ cells per 1 μL of peripheral blood, taking into account the absolute lymphocyte count in the complete blood count. All analyses were performed in the same laboratory according to a unified protocol, using the same reagents and analytical conditions [15].

Endpoints. The primary endpoint was the severity of rubeosis iridis and neovascularisation of the iridocorneal angle according to the Weiss grading scale, considered as an ordinal clinical characteristic of neovascular process activity. The secondary endpoint was the presence of clinically significant rubeosis (Weiss ≥ II). It was employed for ROC analysis and stratification of neovascular process activity. Clinical characteristics and biomarker levels in patients with neovascular glaucoma and in the control group are presented in Table 1.

Table 1. Clinical characteristics and biomarker levels in patients with neovascular glaucoma and in the control group

Parameters	NVG/PDR (n = 96)	NVG/RVO (n = 90)	Control (n = 34)
	Me (Q1-Q3), n (%)		
Male/female	42 (44%) / 54 (56%)	40 (44%) / 50 (56%)	13 (38%) / 21 (62%)
Age, years	66 (62-68.5) * ‡	63 (61-66)	63.5 (60-66)
Intraocular pressure, mmHg	36 (33-40) *	34 (33-40) *	15 (14-17)
Rubeosis of the iris (Weiss)			
⬡ I degree	50 (52%)	52 (58%)	–
⬡ II degree	28 (29%)	29 (32%)	–
⬡ III degree	18 (19%)	9 (10%)	–
CD95 (Fas), cells/μL	653 (610-832) *	612 (553-691) *	263.5 (220-283)
ICAM-1 (CD54), cells/μL	373 (345-566) *	368 (339-542) *	190.5 (186-197)

Table 1. Continued

Parameters	NVG/PDR (n = 96)	NVG/RVO (n = 90)	Control (n = 34)
	Me (Q1-Q3), n (%)		
Duration of diabetes/ Duration of retinal vein occlusion, months	132 (84-168) * ‡	15 (12-18) *	–
Cardiovascular diseases	56 (58%) *	53 (59%) *	15 (44%)

Note: data are presented as median (interquartile range) or number (%). * – $p < 0.05$ between control and PDR/RVO group; ‡ – $p < 0.05$ between NVG/PDR and NVG/RVO group at the corresponding Weiss stage. NVG – neovascular glaucoma; PDR – proliferative diabetic retinopathy; RVO – retinal vein occlusion; ICAM-1 – intercellular adhesion molecule-1. CD95 and ICAM-1 levels are presented as the absolute number of positive lymphocytes per microlitre of peripheral blood
Source: developed by the authors

Statistical processing was Statistical analysis was performed using JASP software, version 0.19.2, and Python. Normal distribution of the biomarkers was rejected by the Shapiro-Wilk test (CD95: $p < 0.001$; ICAM-1: $p < 0.001$). This justified the use of non-parametric methods: the Mann-Whitney test for between-group comparisons, the Kruskal-Wallis test for multiple-group comparisons, and Spearman's coefficient (r_s) for correlations. Quantitative variables were presented as the median and interquartile range (Q1-Q3). To ensure statistical independence of observations, only one eye from each patient was included in the analysis. In cases of bilateral involvement, the eye with more pronounced manifestations of rubeosis iridis and neovascularisation of the iridocorneal angle according to the Weiss grading scale was selected.

Multivariable regression analysis was performed to identify independent predictors of rubeosis severity, with adjustment for NVG aetiology (PDR/RVO) and IOP. The diagnostic ability of CD95 and ICAM-1 for clinically significant rubeosis (Weiss ≥ II) was assessed using ROC analysis, with calculation of the area under the curve (AUC), the optimal cut-off value according to the Youden index, sensitivity, and specificity. Quartile analysis was performed to define dose-dependent effects, with the frequency of Weiss ≥ II calculated in each quartile. Values of $p < 0.05$ were considered statistically significant.

RESULTS AND DISCUSSION

CD95 and ICAM-1 levels in patients with NVG. Given the presumed role of apoptosis-associated and endothelial-inflammatory mechanisms in the development of the neovascular process, systemic levels of CD95 (Fas) and ICAM-1 (CD54) were assessed. Patients with NVG had significantly higher CD95 and ICAM-1 levels compared with controls ($p < 0.001$). The highest CD95 levels were observed in the NVG/PDR group. This may be an indication of a more pronounced activation of apoptosis-associated mechanisms in diabetic ischaemic injury. ICAM-1 levels were also higher in the NVG groups compared with controls, reflecting activation of systemic endothelial inflammation.

Association between biomarkers and the severity of rubeosis. In the overall NVG cohort, significant positive correlations were found between the severity of rubeosis according to Weiss and biomarker levels: $r_s = 0.46$ for CD95 and $r_s = 0.45$ for ICAM-1 (both $p < 0.001$). Significant associations with IOP were also identified: $r_s = 0.58$ for CD95 and $r_s = 0.61$ for ICAM-1 ($p < 0.001$).

Multivariable analysis. In the multivariable ordinal logistic regression model, increased CD95 and ICAM-1 levels were independently associated with more severe rubeosis iridis. The strongest association was observed for ICAM-1 (OR = 2.48; 95% CI 1.56-3.95; $p < 0.001$) (Table 2). This finding supports the pivotal role of endothelial activation and vascular inflammation in the development of neovascular remodelling of the anterior segment of the eye.

Table 2. Multivariate ordinal logistic regression analysis of the association between CD95, ICAM-1 and clinically significant rubeosis (Weiss ≥ II) in secondary NVG

Indicator	β	SE	OR (95% CI)	Wald χ^2	p
CD95	0.84	0.31	2. 31 (1.27-4.18)	7.41	0.006
ICAM-1 (CD54)	0.91	0.24	2. 48 (1.56-3.95)	14.36	<0.001
IOP	0.07	0.03	1.07 (1.01-1.14)	5.12	0.024
NVG/PDR (vs. NVG/RVO)	0.42	0.28	1.52 (0.88-2.64)	2.21	0.137
Cardiovascular pathology	0.29	0.25	1.34 (0.82-2.20)	1.37	0.241

Note: dependent variable: degree of rubeosis according to Weiss; OR – odds ratio; CI – confidence interval; NVG – neovascular glaucoma; IOP – intraocular pressure; PDR – proliferative diabetic retinopathy; RVO – retinal vein occlusion
Source: developed by the authors

Elevated CD95 was also associated with a higher likelihood of more severe rubeosis (OR = 2.31; 95% CI 1.27-4.18; $p = 0.006$). This reflects the involvement of apoptosis-associated signalling in the progression of ischaemic-reparative processes. After adjustment for IOP, NVG aetiology and concomitant cardiovascular

disease, the aetiological factor (PDR/RVO) lost statistical significance. This may suggest that systemic biological activity of the process plays a greater role than the nosological background of the disease.

Stratification of clinically significant rubeosis. ROC demonstrated comparable discriminative ability of CD95 (Fas) and ICAM-1 (CD54) for detecting clinically significant rubeosis (Weiss ≥ II) in patients with secondary neovascular glaucoma (Fig. 1).

Figure 1 shows that the areas under the ROC curves were 0.729 for CD95 and 0.730 for ICAM-1. These values correspond to moderate prognostic accuracy for both markers. Similar AUC values indicate a comparable contribution of apoptosis-associated and endothelial-inflammatory mechanisms to the progression of neovascular changes in the anterior segment of the eye. A non-parametric Kruskal-Wallis rank analysis was additionally performed to assess the association between biomarker levels and rubeosis grades according to Weiss in the NVG cohort (n = 186). For CD95, highly significant between-group differences were found across rubeosis grades ($H(2) = 43.149$; $p < 0.001$). Mean ranks increased consistently from Weiss I (n = 102; mean rank 74.26) to Weiss II (n = 57; 101.57) and Weiss III (n = 27; 149.13). This pattern reflects a monotonic increase in CD95 levels with greater severity of neovascular changes. A similar gradient pattern was observed for ICAM-1 (CD54): $H(2) = 42.30$; $p < 0.001$. Mean ranks were 74.20 for Weiss I (n = 102), 102.23 for Weiss II (n = 57) and 147.98 for Weiss III (n = 27). These results confirm the dose-dependent nature of the association between CD95, ICAM-1 and the degree of rubeosis. The findings are also consistent with the regression analysis and further emphasise the pathogenetic significance of both markers in the formation of active anterior segment neovascularisation. Biomarker levels progressively increased with greater severity of rubeosis iridis (p-trend < 0.001).

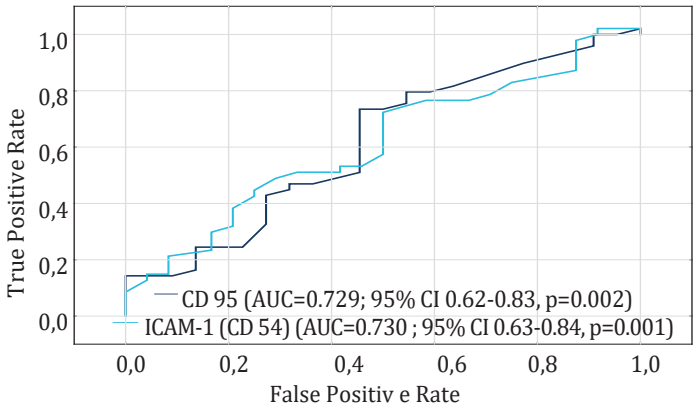

Figure 1. ROC curves for differentiating clinically significant rubeosis (Weiss ≥ II)

Note: receiver operating characteristic (ROC) curves showing the diagnostic performance of CD95 (Fas) and ICAM-1 (CD54) for detecting clinically significant rubeosis iridis (Weiss ≥ II) in patients with neovascular glaucoma. The diagonal dashed line indicates the random classification level

Source: developed by the authors

For stratification of clinically significant rubeosis (Weiss ≥ II), ROC analysis was performed with calculation of optimal cut-off values according to the Youden index. For CD95, the optimal cut-off value was 687 cells/μL. This corresponded to a sensitivity of 63.1% and a specificity of 83.3%, with an AUC of 0.729. For ICAM-1 (CD54), the optimal cut-off value was 542 cells/μL, with a sensitivity of 59.5% and a specificity of 85.3% at an AUC of 0.730. These values confirm the clinical applicability of both markers for quantitative identification of clinically significant rubeosis (Table 3).

Table 1. Optimal threshold values (Youden index) and diagnostic efficiency of CD95 and ICAM-1

Biomarker	AUC (95% CI)	Optimal threshold (Youden)	Sensitivity, %	Specificity, %
CD95 (Fas)	0.729 (0.62-0.83)	687.0	63.1	83.3
ICAM-1 (CD54)	0.730 (0.63-0.84)	542.0	59.5	85.3

Note: the values are obtained from the results of ROC analysis for the differentiation of clinically significant rubeosis of the iris (Weiss ≥ II). The optimal threshold values were determined by the Youden index (J = sensitivity + specificity − 1). AUC – area under the ROC curve

Source: developed by the authors

Quartile analysis showed a dose-dependent increase in the frequency of severe rubeosis iridis with rising CD95 and ICAM-1 levels. The proportion of patients with Weiss II-III rubeosis increased from 12.5%

in the lowest CD95 quartile to 71.2% in the highest quartile. A similar trend was observed for ICAM-1, with an increase from 15.1% to 74.5%, respectively. These findings display a graded increase in neovascular activity as systemic apoptosis-endothelial signalling becomes more pronounced (Fig. 2).

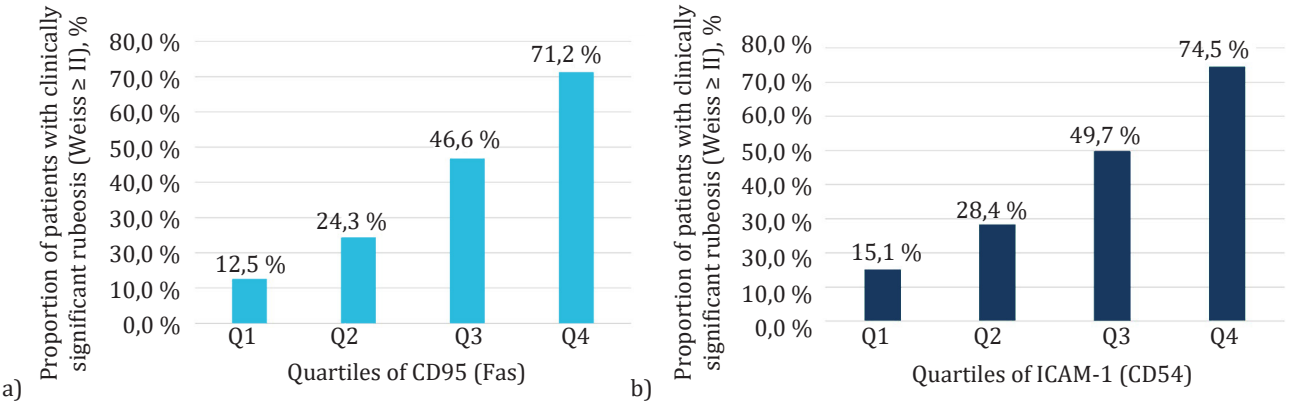

Figure 2. Frequency of clinically significant Weiss rubeosis ≥ II depending on the quartiles of CD95 (a) and ICAM-1 (CD54) (b) levels

Note: Q1 is the lowest quartile (25% of patients with the lowest marker values); Q4 is the highest quartile (25% of patients with the highest marker values). A statistically significant dose-dependent trend was found for both biomarkers (p-trend < 0.001)

Source: developed by the authors

Quartile analysis demonstrated a clear dose-dependent relationship between CD95 (Fas), ICAM-1 (CD54) levels and the frequency of clinically significant rubeosis (Weiss ≥ II) (Fig. 2). As the values increased from the lowest quartile (Q1) to the highest quartile (Q4), the frequency of pronounced neovascular changes in the anterior segment of the eye rose steadily for both biomarkers. The highest rates of rubeosis were recorded in patients whose CD95 and ICAM-1 levels corresponded to the fourth quartile. In contrast, clinically significant rubeosis was least frequent in the groups with the lowest marker concentrations. The statistically significant trend (p-trend < 0.001) validates a graded association between increasing systemic apoptosis-endothelial activation and progression of the neovascular process. These findings suggest that elevated CD95 and ICAM-1 levels are correlated with higher biological activity of rubeosis iridis and iridocorneal angle neovascularisation. The above findings may also reflect increasing pathological neovascular remodelling in secondary NVG.

The results prove a major role of systemic apoptosis-endothelial activation in the development and progression of rubeosis iridis and iridocorneal angle neovascularisation in secondary neovascular glaucoma. NVG is known to result from a complex interaction between retinal ischaemia, pathological angiogenesis, inflammation and remodelling of anterior segment tissues [1, 2]. Chronic retinal hypoxia stimulates the production of VEGF and other pro-angiogenic mediators. These mediators support the development of rubeosis iridis and neovascularisation of the anterior chamber angle [3, 5]. Current views on NVG pathogenesis, however, extend beyond VEGF-dependent mechanisms alone. The above views also involve endothelial dysfunction, systemic inflammation and immune activation [4].

In the present study, systemic markers of endothelial activation (ICAM-1/CD54) and apoptosis (CD95/Fas) were significantly elevated in patients with secondary NVG. In addition to it, these markers were also independently related to the severity of rubeosis. After adjustment for intraocular pressure and disease aetiology, both indicators retained a statistically significant association with the severity of neovascular changes. These findings presume that defining the biological activity of the process comprises local haemodynamic changes or the level of ophthalmic tone. Systemic mechanisms of vascular and cellular remodelling also appear to play a pivotal role.

The findings are consistent with the modern concept of NVG as a multifactorial vascular-inflammatory disease. In this model, anterior segment neovascularisation reflects an integrated ischaemic-inflammatory cascade [2, 3]. S. Gerçeker Demircan & A. Şanal Doğan [1] emphasised that the clinical course of NVG is determined by the degree of retinal ischaemia. Furthermore, it is shaped by the intensity of the inflammatory response, vascular remodelling and endothelial dysfunction. Similarly, M. Lendzioszek *et al.* [4] considered endothelial dysfunction one of the key mechanisms supporting the ischaemic-neovascular process in retinal vascular diseases.

ICAM-1 (CD54) deserves particular attention as a marker of endothelial activation and intercellular adhesion. D.R. Yang *et al.* [6] showed that in diabetic microangiopathy, endothelial dysfunction is accompanied by increased ICAM-1 expression, microvascular inflammation and impaired vascular homeostasis. S.F. Abcouwer [7]

also highlighted the important role of adhesion molecules in maintaining ischaemic inflammation and pathological angiogenesis. The present results support these observations, since the independent association between ICAM-1 and the severity of rubeosis persisted even after intraocular pressure had been taken into account. Additional support comes from the data of K. Siddiqui *et al*. [16] and the meta-analysis by Y. Yao *et al*. [17], which underscored systemic elevation of ICAM-1 levels in diabetic retinopathy and other ischaemic retinal diseases. The present findings are also consistent with previous data from the authors, who showed an association between elevated ICAM-1 levels, a more severe clinical course of diabetic neovascular glaucoma and a less favourable response to treatment [10]. In summary, these observations suggest that endothelial activation is not only a marker of ischaemic injury. It may also be a potential component of neovascular process progression.

The results also align well with data on the local cytokine microenvironment in NVG. S. Ohira *et al*. [18] demonstrated a marked increase in IL-6, IL-8, CCL2, TNF-α and VEGF levels in the aqueous humour of eyes with NVG. This increase partially persisted even after anti-VEGF therapy. T. Kokubun *et al.* [19] identified characteristic profiles of pro-inflammatory cytokines in patients with different forms of glaucoma, including NVG. These data highlight that impaired aqueous humour outflow in NVG should not be regarded only as a mechanical consequence of neovascularisation. It can also reflect persistent inflammatory-endothelial remodelling of anterior segment tissues.

Alongside endothelial activation, apoptosis-associated mechanisms play an important role in the formation of the neovascular phenotype. K. Seyrek *et al*. [20] and L. Hu *et al*. [8] showed that the CD95/Fas system is a multifunctional signalling platform. It regulates programmed cell death, inflammation, cell survival and tissue remodelling. Under conditions of chronic tissue injury, CD95 activation may involve non-apoptotic signalling pathways, including NF-κB, MAPK and PI3K/Akt. These pathways support a pro-inflammatory microenvironment and pathological remodelling. The elevated systemic CD95 levels found in patients with more severe rubeosis are consistent with these concepts. The involvement of Fas-mediated signalling in maintaining the neovascular process can be substantiated.

M. Lendzioszek *et al*. [4] noted that ischaemic retinal diseases are accompanied by a complex interaction between hypoxia, inflammation, endothelial dysfunction and vascular remodelling. The authors emphasised that progression of retinal ischaemia is related to activation of pro-inflammatory and pro-angiogenic signalling pathways. Such pathways may maintain the neovascular process even after the primary vascular injury has been eliminated. The present findings coincide with these views and submit a possible contribution of systemic mechanisms to the maintenance of pathological angiogenesis in secondary NVG. The role of systemic inflammation is supported by the findings of E.W. Böhm *et al*. [21]. The authors established an association between elevated systemic inflammatory indicators and the severity of clinical manifestations of retinal vein occlusion, as well as the impact on functional disease outcomes. Higher ICAM-1 and CD95 levels in NVG linked to proliferative diabetic retinopathy, compared with post-occlusive NVG, may reflect the chronic systemic nature of diabetic microangiopathy. Prolonged endothelial activation and inflammation accompany this process [6, 10]. Similar conclusions were reported by M. Kozman *et al*. [22], who showed that the risk of NVG in proliferative diabetic retinopathy is determined by local retinal ischaemia. Meanwhile, systemic metabolic factors, including poor glycaemic control and concomitant manifestations of diabetic microangiopathy, also become prerequisites for this risk. In retinal vein occlusion, by contrast, acute ischaemic and VEGF-mediated mechanisms appear to dominate to a greater extent [5].

The dose-dependent association of CD95 and ICAM-1 with the severity of rubeosis confirms the systemic nature of the pathological processes underlying neovascular remodelling of the anterior segment of the eye in secondary NVG. Given this, the findings support the inclusion of apoptosis and endothelial activation markers in the comprehensive assessment of patients. The use of the results may improve the objectivity of disease course prediction and help justify personalised treatment strategies.

CONCLUSIONS

1. Patients with secondary NVG had significantly elevated systemic levels of CD95 (Fas) and ICAM-1 (CD54) compared with the control group ($p < 0.001$). This makes activation of apoptosis-associated and endothelial-inflammatory mechanisms in neovascular remodelling of the anterior segment of the eye evident. The study also found a significant positive association between both biomarker levels and the severity of rubeosis iridis and iridocorneal angle neovascularisation according to Weiss. Significant associations with intraocular pressure were also observed, confirming the relationship with neovascular process activity.

2. In the multivariable ordinal logistic regression analysis, CD95 and ICAM-1 remained independent predictors of more severe rubeosis after adjustment for disease aetiology and intraocular pressure (CD95: OR = 2.31; 95% CI 1.27-4.18; $p = 0.006$; ICAM-1: OR = 2.48; 95% CI 1.56-3.95; $p < 0.001$). This specifies an independent contribution of apoptosis-endothelial mechanisms to the progression of neovascular changes. ROC analysis demonstrated moderate discriminative ability of both markers for detecting clinically significant rubeosis (AUC = 0.729 for CD95 and AUC = 0.730 for ICAM-1). The cut-off values of 687 cells/μL and 542 cells/μL, respectively, may be used for risk stratification of a more severe disease course.

3. Quartile analysis revealed a statistically significant dose-dependent association between increasing

CD95 and ICAM-1 levels and the frequency of clinically significant rubeosis (p-trend < 0.001). This further supports the role of systemic apoptosis-endothelial activation in the pathogenesis of secondary NVG. The findings suggest that CD95 and ICAM-1 may serve as additional biomarkers for assessing the biological activity of rubeosis, objectifying the risk of disease progression and improving personalised approaches to patient management.

4. A promising direction for later research is to study the prognostic value of these biomarkers during long-term follow-up and to integrate aforementioned biomarkers into multivariable models for predicting the course and treatment outcomes of secondary NVG.

ACKNOWLEDGEMENTS

The authors express the sincere gratitude to Oleh Zadorozhnyi, Deputy Director for Research at the State Institution "V.P. Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine", Doctor of Medical Sciences, for his scientific consultation, valuable methodological recommendations and support at all stages of the study. His professional expertise, critical analysis of the obtained results and scientific advice contributed to improving the study design, statistical data processing and interpretation of the findings.

The authors also express the sincere gratitude to Oleksandra Bohdanova, PhD in Biological Sciences, for conducting the immunological studies, providing methodological assistance in determining the expression of CD95 (Fas) and ICAM-1 (CD54), and demonstrating high professionalism during the laboratory stage of the work. Her contribution ensured the appropriate quality and reproducibility of the immunological data, which formed a crucial part of the present study.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Ольга Гузун

Кандидат медичних наук, старший науковий співробітник
ДУ «Інститут очних хвороб та тканинної терапії ім. В. П. Філатова НАМН України»
65061, бульв. Французький, 49/51, м. Одеса, Україна
https://orcid.org/0009-0003-6873-8503

Людмила Велічко

Доктор медичних наук
ДУ «Інститут очних хвороб та тканинної терапії ім. В. П. Філатова НАМН України»
65061, бульв. Французький, 49/51, м. Одеса, Україна
https://orcid.org/0009-0008-8485-3698

Системні біомаркери апоптозу та ендотеліальної активації у патогенезі рубеозу райдужки та іридокорнеального кута при вторинній неоваскулярній глаукомі

Анотація

Мета. Оцінити системні рівні CD95 (Fas) та ICAM-1 (CD54) у пацієнтів із вторинною неоваскулярною глаукомою (НВГ), визначити їх зв'язок із тяжкістю рубеозу райдужки та іридокорнеального кута, а також оцінити роль апоптоз-ендотеліальних порушень у неоваскулярному ремоделюванні переднього сегмента ока.

Матеріали та методи. В одноцентрове перехресне дослідження включено 186 очей із вторинною НВГ (96 – на тлі проліферативної діабетичної ретинопатії та 90 – після оклюзії вен сітківки) і 34 ока контрольної групи. Тяжкість рубеозу оцінювали за шкалою Weiss. Рівні CD95 та ICAM-1 у периферичній крові визначали імуноцитохімічним методом.

Результати дослідження. У пацієнтів із НВГ рівні CD95 та ICAM-1 були достовірно вищими порівняно з контролем ($p < 0,001$). Обидва маркери позитивно корелювали з тяжкістю рубеозу за Weiss (CD95: $rs = 0,46$; ICAM-1: $rs = 0,45$; $p < 0,001$) та рівнем внутрішньоочного тиску. У багатофакторній ordinal logistic regression моделі CD95 та ICAM-1 залишалися незалежно асоційованими з більш тяжким рубеозом після корекції на етіологію та внутрішньоочний тиск (CD95: OR = 2,31; 95 % CI 1,27-4,18; $p = 0,006$; ICAM-1: OR = 2,48; 95 % CI 1,56-3,95; $p < 0,001$). ROC-аналіз показав помірну дискримінаційну здатність маркерів щодо виявлення клінічно значущого рубеозу (Weiss ≥ II): AUC = 0,729 для CD95 та AUC = 0,730 для ICAM-1. Порогові значення становили 687 кл/мкл та 542 кл/мкл відповідно.

Висновок. CD95 (Fas) та ICAM-1 (CD54) асоціюються з тяжкістю рубеозу при вторинній НВГ і можуть розглядатися як системні біомаркери неоваскулярного ремоделювання та стратифікації ризику прогресування захворювання.

Ключові слова: CD95 (Fas); ICAM-1 (CD54); ангіогенез; неоваскулярне ремоделювання; ендотеліальна дисфункція; апоптоз; стратифікація ризику

CLINICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 618.14-002-089:616-089.819:616-089.87
DOI: https://doi.org/10.32345/2664-4738.2.2026.03

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 27.12.2025 Revised: 04.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Andrii Hryhorenko*

Doctor of Medical Sciences, Professor
National Pirogov Memorial Medical University
21018, 56 Pyrohov Str., Vinnytsya, Ukraine
https://orcid.org/0000-0002-8843-9995

Comparative effectiveness of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis

Abstract

Relevance. The importance of the study is determined by the high prevalence of endometriosis among women of reproductive age and by the substantial negative effect of deep infiltrating endometriosis on the functional state of the pelvic organs, the quality of life of patients, and treatment outcomes. Despite the active development of minimally invasive gynaecological surgery, the choice of the optimal surgical approach for complex infiltrative forms of the disease remains debatable. An analysis of current scientific data on the effectiveness of robot-assisted and laparoscopic procedures is therefore especially relevant.

Aim. To summarise current scientific data on the use of robot-assisted and laparoscopic surgical procedures in deep infiltrating endometriosis and to analyse their clinical outcomes and features of use in minimally invasive gynaecological surgery.

Materials and methods. The study used methods of analysis, systematisation, and generalisation of current scientific sources devoted to the problem of surgical treatment of deep infiltrating endometriosis. The results of clinical studies, systematic reviews, and meta-analyses concerning the effectiveness and safety of robot-assisted and laparoscopic procedures were analysed. Approaches to analytical generalisation of perioperative indicators and clinical treatment outcomes were applied.

Results. Current approaches to the surgical treatment of deep infiltrating endometriosis were examined, and the role of laparoscopic and robot-assisted technologies in minimally invasive gynaecological surgery was determined. A generalisation of scientific data indicated that laparoscopic procedures remain the main method of surgical treatment for this pathology, whereas robot-assisted technologies broaden the possibilities for performing complex operations in cases of deep tissue infiltration and involvement of adjacent pelvic organs. It was established that, according to perioperative indicators such as intraoperative blood loss, complication rate, and length of hospitalisation, the results of both approaches were similar in most studies. Robotic systems may provide improved visualisation of the surgical field and greater precision of manipulation during treatment of complex anatomical localisations of the pathological process.

Conclusions. The analysis of the contemporary scientific sources indicated that the effectiveness of treatment for deep infiltrating endometriosis depends largely on the correct choice of surgical tactics and on individualisation of the surgical approach. Laparoscopic surgery remains the basic method of surgical treatment, whereas robot-assisted technologies should be used in complex clinical cases requiring high precision of surgical manipulation. The results obtained confirm the need for further accumulation of evidence on the long-term outcomes of different minimally invasive surgical technologies in deep infiltrating endometriosis.

Keywords: minimally invasive gynaecological surgery; pelvic pain syndrome; surgical tissue dissection; perioperative indicators; postoperative recovery.

Suggested Citation:
Hryhorenko A. Comparative effectiveness of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis. Med Sci Ukr. 2026;22(2):24–30. DOI: https://doi.org/10.32345/2664-4738.2.2026.03

*Corresponding author (*nickonpn1@gmail.com*)

INTRODUCTION

Endometriosis is one of the most common gynaecological diseases among women of reproductive age and is characterised by a chronic course, complex pathogenesis, and a marked negative effect on reproductive health and the quality of life of patients. Deep infiltrating endometriosis is a particularly complex clinical form, accompanied by penetration of endometriotic lesions into deep tissue layers with involvement of the bowel, bladder, ureters, and other pelvic structures. The high frequency of pain syndrome, dysfunction of adjacent organs, and disease recurrence determines the need to improve approaches to the surgical treatment of this pathology. The active development of minimally invasive surgery has promoted the wide introduction of laparoscopic and robot-assisted technologies, but the choice of optimal surgical tactics for complex forms of the disease remains debatable.

The problem of surgical treatment for deep infiltrating endometriosis is extensively covered in modern scientific literature. H. Ong *et al.* [1], in a systematic review on the treatment of deep infiltrating endometriosis with bowel involvement, concluded that robot-assisted surgery is a safe and technically feasible treatment method that provides high precision of manipulation and improved visualisation of the surgical field in complex anatomical areas. M. Koteliukh [2], in turn, emphasised the importance of predicting clinical outcomes and using evidence-based approaches when choosing treatment tactics, which underlines the relevance of evaluating the long-term outcomes of modern surgical technologies. M. Cherniak & O. Korchynska [3] noted that, in widespread forms of endometriosis, surgical treatment is often the most effective way to eliminate symptoms and restore the functional state of the pelvic organs. A. Balan & L. Yurieva [4] stressed that deep infiltrating endometriosis is characterised by diagnostic complexity, considerable variability of clinical manifestations, and a high frequency of adjacent organ involvement, which requires an individualised approach to treatment. When comparing robotic and conventional laparoscopy for colorectal endometriosis, M. Le Gac *et al.* [5] indicated that both approaches produce similar clinical outcomes, whereas robotic surgery may provide additional technical advantages during complex surgical procedures.

A. Osaki & M. de Oliveira [6] specified that bowel or ovarian involvement substantially affects the duration of surgery regardless of the chosen surgical approach, which confirms the importance of careful preoperative planning and individualisation of surgical tactics. A meta-analysis of current publications by M. Pavone *et al.* [7] indicated that robot-assisted procedures are highly effective and safe, but they do not have substantial advantages over laparoscopic surgery for most perioperative indicators. Similar conclusions were reached by X. Zhang & X. Zhang [8], who demonstrated similar results for robotic and laparoscopic operations in colorectal endometriosis and the absence of important differences in the main clinical indicators. T. Hebert [9] noted that the use of robotic systems broadens the possibilities of minimally invasive surgery through improved surgeon ergonomics, three-dimensional visualisation, and high-precision instrument control during treatment of complex forms of deep infiltrating endometriosis. However, Á. Csirzó *et al.* [10], in a systematic review and meta-analysis, did not identify convincing evidence of substantial clinical advantages of robot-assisted surgery over conventional laparoscopy. The authors concluded that the available results remain heterogeneous, and that the evidence base needs further expansion through high-quality multicentre studies. Thus, the existing scientific studies confirm the prospects for using robotic technologies in the treatment of deep infiltrating endometriosis, while the question of their clinical advantages over conventional laparoscopy remains unresolved. The ambiguity of the results obtained, differences in study design, and the insufficient number of long-term clinical observations determine the need for further generalisation of current scientific data on the use of different minimally invasive surgical technologies.

This study aimed to analyse current scientific data on the effectiveness and safety of robot-assisted and laparoscopic surgical procedures in deep infiltrating endometriosis and to determine the features of their use in modern minimally invasive gynaecological surgery.

MATERIALS AND METHOD

The study was designed as a review of scientific literature concerning the use of laparoscopic and robot-assisted surgical procedures in deep infiltrating endometriosis. The literature search was conducted in the international scientometric and bibliographic databases PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Combinations of the following English-language keywords were used for the search: “deep infiltrating endometriosis”, “robot-assisted surgery”, “robotic surgery”, “laparoscopic surgery”, “minimally invasive gynecologic surgery”, “colorectal endometriosis”, “surgical treatment of endometriosis”, “robotic-assisted laparoscopy”, “perioperative outcomes”, and “clinical effectiveness”. The search used the Boolean operators AND and OR to broaden or refine the results.

The inclusion criteria for the review were: availability of the full text of the publication; relevance to the study topic; publication in peer-reviewed scientific journals; coverage of the results of laparoscopic or robot-assisted surgical procedures for endometriosis; and availability of data on clinical effectiveness, safety, perioperative indicators, or technical features of surgical performance. Systematic reviews, meta-analyses, clinical studies, randomised controlled trials, and

clinical trial protocols published mainly during 2020-2025 were included in the analysis. The exclusion criteria were duplicate publications, conference abstracts without full text, articles with insufficient description of treatment outcomes, studies devoted exclusively to drug therapy for endometriosis, and works that did not contain information on the use of laparoscopic or robot-assisted surgical technologies.

At the initial stage of the search, 86 publications were identified. After removing duplicates and analysing titles, abstracts, and full texts for compliance with the defined criteria, 20 of the most relevant sources were included in the final review. These sources directly concerned current approaches to the surgical treatment of deep infiltrating endometriosis and the comparison of laparoscopic and robot-assisted technologies. Methods of systematisation, critical analysis, comparison, and logical generalisation of scientific information were used to process the selected materials. Primary attention was given to the analysis of data on the technical characteristics of surgical procedures, perioperative outcomes, complication rates, length of hospitalisation, and features of postoperative recovery in patients. The results were generalised through a qualitative synthesis of the available evidence, with identification of common tendencies and discrepancies between studies. A meta-analysis was not performed in this study because of the heterogeneity of the available publications, differences in study design, characteristics of clinical samples, localisation of endometriotic lesions, and approaches to evaluating treatment outcomes. For this reason, the results obtained are presented as a qualitative review and analytical generalisation of current scientific data.

RESULTS AND DISCUSSION

In gynaecological surgery, treatment of deep infiltrating endometriosis is based on the use of minimally invasive surgical technologies that provide accurate removal of endometriotic lesions with minimal tissue trauma and preservation of the functional integrity of the pelvic organs. Laparoscopic surgery remains the most common method of surgical treatment and has formed the basis of minimally invasive gynaecology over recent decades. The development of high-technology medical equipment has also promoted the active introduction of robot-assisted tools, which open new prospects for performing complex surgical procedures in widespread forms of endometriosis. In clinical practice, these approaches are considered complementary elements of minimally invasive surgery, and the choice between them depends on the anatomical features of the lesion and the technical capacity of the medical institution (Table 1).

Table 1. Current surgical approaches to the treatment of deep infiltrating endometriosis in minimally invasive gynaecological surgery

Surgical approach	Main technological characteristics	Clinical significance in treatment
Conventional laparoscopic surgery	Use of laparoscopic instruments and a video-optical system for minimally invasive access	Provides effective removal of endometriotic lesions, reduces surgical trauma, and promotes faster postoperative recovery
Robot-assisted laparoscopic surgery	Three-dimensional visualisation of the surgical field and use of robotic instruments with high movement precision	Enables complex dissections in difficult-to-access anatomical areas and increases the precision of manipulation
Multidisciplinary minimally invasive procedures	Combined use of gynaecological, colorectal, and urological surgery	Provides comprehensive treatment of widespread forms of infiltrative endometriosis involving adjacent organs

Source: compiled by the author based on [3, 4, 9]

The choice of surgical technology is determined primarily by the anatomical localisation and depth of infiltration of endometriotic lesions. W. Huang *et al.* [11] stated that, when complex minimally invasive procedures are performed, the technical capabilities of the surgical system and the capacity to ensure precision of manipulation in difficult-to-access anatomical areas are decisive. Similar views were expressed by C. Alboni *et al.* [12], who considered robot-assisted surgery a promising direction for the treatment of widespread forms of deep infiltrating endometriosis involving adjacent pelvic organs. According to J. Hiltunen *et al.* [13], robot-assisted laparoscopy is a technically feasible and safe method for treating deep infiltrating endometriosis, especially when the pathological process is localised in the rectosigmoid area. Z. Song *et al.* [14], in a meta-analysis, reported that robotic and laparoscopic procedures demonstrated similar results for blood loss, complication rate, and length of hospitalisation in most studies.

M. Renso *et al.* [15] emphasised the need for randomised clinical trials to provide a more objective comparison of robot-assisted and laparoscopic approaches in the treatment of complex forms of endometriosis. A systematic review by S. Di Michele *et al.* [16] underscored that robotic technologies may be useful during reconstructive procedures on the urinary system because of the high precision of surgical manipulation. K. Kanno *et al.* [17] reported positive results from the use of robot-assisted nerve-sparing surgical procedures in deep endometriosis. E. Kivekäs *et al.* [18] also drew attention to the importance of

evaluating long-term clinical outcomes of minimally invasive technologies, as these outcomes provide an objective assessment of the effectiveness of the surgical approach. A meta-analysis by S. Restaino *et al.* [19] demonstrated that robotic and laparoscopic procedures are generally associated with similar clinical outcomes, while A. Terho *et al.* [20] stressed the need for further accumulation of evidence on the optimal choice of minimally invasive technology in severe forms of deep infiltrating endometriosis.

Thus, laparoscopic and robot-assisted technologies are considered complementary tools of modern minimally invasive surgery, and the choice between them is determined by the localisation of the pathological process, the complexity of the surgical procedure, and the technical capacity of a specialised medical centre. The clinical and surgical characteristics of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis are based on the analysis of perioperative indicators that reflect the technical complexity of the operation, the level of intraoperative safety, and the rate of postoperative recovery in patients. The main parameters include duration of surgery, volume of blood loss, frequency of intraoperative complications, length of hospitalisation, and functional recovery. These indicators are used in clinical studies for the comparative evaluation of the effectiveness of different minimally invasive surgical technologies (Table 2).

Table 2. Perioperative clinical indicators for evaluating robot-assisted and laparoscopic procedures in deep infiltrating endometriosis

Perioperative indicator	Clinical characteristic	Practical significance for outcome evaluation
Duration of surgery	Time from the beginning of surgical access to completion of the main surgical stage	Reflects the technical complexity of the procedure and the efficiency of the surgical process organisation
Intraoperative blood loss	Volume of blood lost during surgery	Characterises the degree of tissue trauma and the precision of surgical manipulation
Frequency of intraoperative complications	Damage to vessels, bowel, bladder, or nerve structures	Enables assessment of the safety of the surgical technique
Length of hospitalisation	Number of days the patient remains in the hospital after surgery	Reflects the speed of postoperative stabilisation and recovery
Functional postoperative recovery	Restoration of bowel function, reduction of pain syndrome, and return to physical activity	Characterises the clinical effectiveness of treatment and the quality of rehabilitation

Source: compiled by the author based on [7, 8, 10, 14]

In contemporary clinical studies, perioperative indicators are considered the main criteria for evaluating the results of minimally invasive surgical treatment of deep infiltrating endometriosis. M. Pavone *et al.* [7] indicated that duration of surgery, intraoperative blood loss, and complication rate are among the most informative indicators when comparing robot-assisted and laparoscopic procedures. A similar approach was used by X. Zhang & X. Zhang [8], who, in their analysis of treatment outcomes in colorectal endometriosis, primarily evaluated blood loss, duration of surgery, and length of hospitalisation.

According to Á. Csirzó *et al.* [10], an important criterion of clinical effectiveness is not only the immediate result of surgery but also the rate of functional postoperative recovery. Z. Song *et al.* [14] reported that, in most of the analysed studies, blood loss, complication rate, and length of hospitalisation were similar for robotic and laparoscopic procedures. S. Restaino *et al.* [19] emphasised that treatment success is determined not only by the radicality of endometriotic lesion removal but also by the speed of recovery after surgery. A similar position was taken by A. Terho *et al.* [20], who stressed the need for standardised evaluation of both perioperative and long-term treatment outcomes. Thus, duration of surgery, intraoperative blood loss, complication rate, length of hospitalisation, and functional recovery remain key indicators for evaluating the effectiveness and safety of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis.

Comparative evaluation of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis is based on analysis of perioperative indicators that reflect the technical features of surgery, the level of intraoperative safety, and the dynamics of postoperative recovery. Taken together, the available studies indicate that both approaches are effective according to the main criteria, but they differ in the technological characteristics of surgical performance, which determines their appropriateness depending on the complexity of the anatomical localisation of the pathological process [3]. According to current scientific reviews, robot-assisted surgery provides more precise visualisation of the surgical field and greater instrument stability, which is important during resection of infiltrative lesions of the bowel or retrocervical space [12]. The results of meta-analyses also indicate that the overall clinical indicators of effectiveness of the two methods are mostly similar (Table 3).

Table 3. Comparative characteristics of the effectiveness and safety of robot-assisted and laparoscopic procedures in deep infiltrating endometriosis

Evaluation criterion	Robot-assisted surgery	Laparoscopic surgery
Visualisation of the surgical field	Three-dimensional, stable	Two-dimensional
Precision of surgical manipulation	High due to robotic instruments	Depends on the manual technique of the surgeon
Intraoperative blood loss	Low or similar	Low
Complication rate	Low in specialised centres	Low with sufficient surgeon experience
Postoperative recovery	Rapid	Similar to robotic procedures

Source: compiled by the author based on [7, 10, 12, 13]

Evaluation of the results of surgical treatment for deep infiltrating endometriosis extends beyond the purely technical characteristics of the surgical procedure. Current studies increasingly focus not only on the duration of surgery or the volume of blood loss but also on the rate of functional recovery in patients and their quality of life after treatment. M. Pavone *et al.* [7] indicated that duration of surgery, intraoperative blood loss, and complication rate are among the most informative criteria for evaluating the effectiveness of minimally invasive procedures. A similar approach was used by X. Zhang & X. Zhang [8], who, in their analysis of treatment outcomes in colorectal endometriosis, primarily evaluated blood loss, duration of surgery, and length of hospitalisation. The literature analysis suggests that isolated evaluation of separate perioperative indicators does not always provide an objective basis for determining the advantages of a particular surgical technology. In most studies, robotic and laparoscopic procedures demonstrate similar results for the main clinical parameters, whereas differences most often concern the technical aspects of surgical performance and the complexity of a particular clinical case [10, 14].

Evaluation of postoperative recovery in patients is especially important. The speed of return to usual physical activity, reduction of pain syndrome, and restoration of the function of adjacent organs largely determine the clinical effectiveness of treatment. This is emphasised by S. Restaino *et al.* [19] and A. Terho *et al.* [20], who stress the need for a comprehensive analysis of both immediate and long-term outcomes of surgery. A generalisation of study results reveals that the current tendency in the development of minimally invasive surgery for endometriosis lies not in opposing laparoscopic and robot-assisted technologies, but in identifying the most appropriate field of application for each approach depending on the clinical situation. Therefore, when evaluating the effectiveness of surgical treatment, it is appropriate to consider not only perioperative indicators but also the features of localisation of the pathological process, the complexity of the procedure, and the predicted functional outcomes. In the author's view, the choice of surgical tactics in deep infiltrating endometriosis should be based not only on the characteristics of the surgical technology but also on comprehensive consideration of the localisation of the pathological process, the functional state of adjacent organs, and the capacities of a specialised centre. A rational combination of laparoscopic and robot-assisted approaches can individualise treatment, improve the safety of surgery, and improve long-term clinical outcomes. The development of a multidisciplinary treatment model, which provides comprehensive management of patients with complex forms of the disease, is especially important.

CONCLUSIONS

1. It was established that minimally invasive surgical technologies form the basis of modern treatment for deep infiltrating endometriosis. Laparoscopic surgery remains the standard surgical approach due to its effectiveness and well-established technique, whereas robot-assisted technologies broaden the possibilities for performing complex operations in widespread infiltrative pelvic lesions.

2. A comparative analysis of clinical studies indicated that, according to the main perioperative indicators – blood loss, complication rate, and length of hospitalisation – the results of robot-assisted and laparoscopic operations are similar in most cases, although robotic systems may provide greater precision of manipulation in complex anatomical areas.

3. It was determined that the choice of optimal surgical tactics is difficult because of the technical complexity of operations in deep tissue infiltration, the variability of clinical outcomes, and the limited evidence base on the long-term effectiveness of robot-assisted procedures.

4. The appropriateness of an individualised approach to the choice of surgical technology was substantiated, considering the localisation of the pathological process, the clinical features of the disease, and the technical capacities of the medical institution.

The limitations of the study were its primarily review-based nature and the heterogeneity of the included clinical studies in terms of design, sample size, and criteria for outcome assessment. Further research should focus on multicentre clinical studies and the development of standardised algorithms for choosing minimally invasive surgical tactics in deep infiltrating endometriosis.

ACKNOWLEDGEMENTS

The author expresses gratitude to the researchers whose studies formed the theoretical basis of this literature review.

FUNDING

The study was performed without external funding.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Андрій Григоренко
Доктор медичних наук, професор
Вінницький національний медичний університет імені М.І. Пирогова
21018, вул. Пирогова, 56, м. Вінниця, Україна
https://orcid.org/0000-0002-8843-9995

Порівняльна ефективність робот-асистованих та лапароскопічних втручань при глибокому інфільтративному ендометріозі

Анотація
Актуальність. Значущість дослідження зумовлена високою поширеністю ендометріозу серед жінок репродуктивного віку та суттєвим негативним впливом глибокого інфільтративного ендометріозу на функціональний стан органів малого таза, якість життя пацієнток і результати лікування. Незважаючи на активний розвиток малоінвазивної гінекологічної хірургії, питання вибору оптимального оперативного підходу при складних інфільтративних формах захворювання залишається дискусійним. Особливої актуальності набуває аналіз сучасних наукових даних щодо ефективності робот-асистованих і лапароскопічних втручань.
Мета. Узагальнити сучасні наукові дані щодо застосування робот-асистованих і лапароскопічних оперативних втручань при глибокому інфільтративному ендометріозі та проаналізувати їх клінічні результати й особливості використання в малоінвазивній гінекологічній хірургії.
Матеріали та методи. У роботі використано методи аналізу, систематизації та узагальнення сучасних наукових джерел, присвячених проблемі хірургічного лікування глибокого інфільтративного ендометріозу. Проведено аналіз результатів клінічних досліджень, систематичних оглядів і метааналізів щодо ефективності та безпеки робот-асистованих і лапароскопічних втручань. Застосовано підходи аналітичного узагальнення періопераційних показників і клінічних результатів лікування.
Результати. Проаналізовано сучасні підходи до хірургічного лікування глибокого інфільтративного ендометріозу та визначено місце лапароскопічних і робот-асистованих технологій у структурі малоінвазивної гінекологічної хірургії. Узагальнення наукових даних засвідчило, що лапароскопічні втручання залишаються основним методом оперативного лікування цієї патології, тоді як робот-асистовані технології розширюють можливості виконання складних операцій при глибокій інфільтрації тканин і залученні суміжних органів малого таза. Встановлено, що за такими періопераційними показниками, як інтраопераційна крововтрата, частота ускладнень і тривалість госпіталізації, результати обох підходів у більшості досліджень були співставними. Водночас роботизовані системи можуть забезпечувати покращену візуалізацію операційного поля та вищу точність маніпуляцій під час лікування складних анатомічних локалізацій патологічного процесу.
Висновки. Аналіз сучасних наукових джерел засвідчив, що ефективність лікування глибокого інфільтративного ендометріозу значною мірою залежить від правильного вибору хірургічної тактики та індивідуалізації оперативного підходу. Лапароскопічна хірургія залишається базовим методом оперативного лікування, тоді як робот-асистовані технології доцільно використовувати у складних клінічних випадках, що потребують високої точності хірургічних маніпуляцій. Отримані результати підтверджують необхідність подальшого накопичення доказової бази щодо довгострокових результатів застосування різних малоінвазивних хірургічних технологій при глибокому інфільтративному ендометріозі
Ключові слова: малоінвазивна гінекологічна хірургія; тазовий больовий синдром; хірургічна дисекція тканин; періопераційні показники; післяопераційне відновлення.

CLINICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 618.177-089.888.11:618.2/.4:618.33
DOI: https://doi.org/10.32345/2664-4738.2.2026.04

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 09.01.2026 Revised: 27.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Mykola Kovalenko*

Postgraduate Student
Limited Liability Company "Leleka"
04057, 56 Kvitky Tsisyk Str., Kyiv, Ukraine
https://orcid.org/0009-0002-1191-6834

Olha Hryshchenko

Doctor of Medical Sciences, Professor, Honoured Worker of Science and Technology of Ukraine
V.N. Karazin Kharkiv National University
61022, 6 Svobody Sq., Kharkiv, Ukraine
https://orcid.org/0000-0002-2410-861X

Features of the course of pregnancy and labour and the condition of newborns in women after *in vitro* fertilisation

Abstract

Background. Infertility remains a significant issue in reproductive medicine, and pregnancy following IVF requires specialised medical supervision due to differences in its course compared with physiological pregnancy.

Aim. To determine the characteristics of pregnancy, labour, and neonatal outcomes in women whose pregnancies resulted from *in vitro* fertilisation.

Materials and methods. A retrospective clinical and statistical analysis was conducted of 318 pregnancy and delivery records, as well as medical records of newborns of women whose pregnancies resulted from IVF (Group I), and 137 pregnancy and delivery records of women who conceived spontaneously (Group II). All patients received treatment and delivery care in the obstetric department of the multidisciplinary medical centre "Leleka" (Kyiv) during the period from 2020 to 2024.

Results. Women in Group I were characterised by a higher incidence of moderate pre-eclampsia – 94 cases (29.6%), compared with 21 cases (15.3%) in Group II ($p < 0.05$), placental dysfunction – 198 cases (62.3%) versus 43 cases (31.4%) in Group II ($p < 0.05$), which was accompanied by foetal growth restriction – 99 cases (31.1%) compared with 19 cases (13.9%), abnormal amniotic fluid volume – 141 cases (44.3%) versus 14 cases (10.2%) in Group II ($p < 0.05$), and vaginitis – 177 cases (55.7%) compared with 29 cases (21.1%) in Group II ($p < 0.05$). The incidence of severe pre-eclampsia, 19 cases (5.9%) in Group I and 2 cases (2.1%) in Group II, showed no statistically significant difference ($p > 0.05$). Regarding the timing of delivery, women in Group I had a lower rate of term births – 186 cases (58.5%) compared with 107 cases (78.1%) in Group II ($p < 0.05$), against a background of an increased number of preterm births – 87 cases (27.4%) versus 14 cases (10.2%) ($p < 0.05$), and post-term births – 45 cases (14.1%) compared with 16 cases (11.7%) in Group II ($p > 0.05$). Within the structure of preterm births among women in Group I, 10 cases (3.1%) occurred at 22-27 weeks + 6 days. There was no significant difference in the number of preterm births at 28-33 weeks + 6 days (Group I – 26 cases (8.2%), Group II – 4 cases (2.9%), $p > 0.05$) or at 34-36 weeks + 6 days (Group I – 51 cases (16.0%), Group II – 10 cases (7.3%), $p > 0.05$). Analysis of labour demonstrated a higher incidence of abnormalities of labour activity among women in Group I – 94 cases (29.6%) compared with 19 cases (13.8%) in Group II ($p < 0.05$), mainly due to uterine inertia – 66 cases (20.7%) versus 7 cases (5.1%) ($p < 0.05$), with successful medical correction achieved in 59 cases (62.7%) in Group I and 16 cases (84.2%) in Group II ($p < 0.05$).

Conclusions. During 2022-2024, the number of pregnancies and births following IVF increased by 56%, and their complicated course may be associated with obstetric history, impaired placentation, and the specific characteristics of pregnancy after IVF.

Keywords: obstetric complications, gestation, course of pregnancy, assisted reproductive technologies, condition of newborns.

Suggested Citation:
Kovalenko M, Hryshchenko O. Features of the course of pregnancy and labour and the condition of newborns in women after *in vitro* fertilisation. Med Sci Ukr. 2026;22(2):31–39. DOI: https://doi.org/10.32345/2664-4738.2.2026.04

*Corresponding author (*niko_pm@ukr.net*)

INTRODUCTION

Infertility remains one of the most widely debated issues in contemporary obstetrics, gynaecology and reproductive medicine. An analysis of current sources shows that one in six married couples in Ukraine are unable to conceive within a year of regular sexual intercourse, whilst in some regions of Ukraine the prevalence of infertility reaches 20% [1-2] It should be noted that one of the main causes of infertility in Ukraine is considered to be dysfunction of the reproductive system in both women and men, particularly when delayed onset of reproductive function is combined with advanced parental age [3-4]. Globally, and in Ukraine in particular, there is a trend towards delaying the birth of the first child. This is linked to a shift in priorities from parenthood towards career advancement, which results in both parents being older at the stage of planning the birth of their first child. Equally important factors include the deterioration in the general health of both women and men, and stressful situations – including those arising from the war in Ukraine – which force married couples to postpone their reproductive plans at a young age, and subsequently lead to reproductive failures and pregnancy losses [2-4]. The most common causes of infertility among Ukrainian married couples, as noted by O.I. Krotik [3] and A.G. Salmanov *et al.* [4], are endometriosis, acute and chronic inflammatory diseases of the pelvic organs – particularly those caused by specific pathogens and viruses and the associated scarring processes – a history of abortion, and a diminished ovarian reserve. In the current context, one of the main ways of overcoming the problem of infertility is the use of assisted reproductive technologies (ART), the use of which has been steadily increasing over recent decades, as emphasised by A.G. Salmanov *et al.* [4] and S.A. Carson & A.N. Kallen [5]. According to V.L. Baker *et al.* [6], by early 2017 alone, the number of ART cycles performed worldwide stood at around three million, and by the end of 2018, this figure had already reached three and a half million, indicating the significant prevalence and incidence of infertility. A.G. Salmanov *et al*. [2, 4] noted that in Ukraine, as of 2021, out of 21,000 pregnancies, nearly 1,500 (around 6.7%) resulted from the use of ART. According to the authors, around 1.6% of newborns in Ukraine as of 2018 were born as a result of ART. However, the success rate of reproductive cycles in Ukraine is almost 20% lower than in many Central European countries.

ART procedures have undergone changes and have evolved significantly; specifically, they have come a long way from retrieving oocytes during laparoscopic surgery to the use of transvaginal access, and from retrieving oocytes in natural cycles to the introduction of ovulation stimulation protocols, which has significantly improved their effectiveness [7-8]. In modern reproductive medicine, the range of options available to prospective parents facing infertility has expanded considerably. As emphasised by C.M. Cox *et al.* [9] and V.N. Varlas *et al*. [10], this has been made possible by the successful use of donor reproductive cells, surrogacy, *in vitro* fertilisation (IVF), laparoscopically and/or sonographically guided techniques for transferring male and female gametes, as well as zygotes, directly into the fallopian tubes, testicular sperm extraction and intracytoplasmic sperm injection. At the same time, it should be emphasised that a pregnancy resulting from the use of ART proceeds under specific conditions that differ significantly from physiological ones, requiring doctors to pay particular attention to and care for the condition of the pregnant woman, as well as the antenatal and intranatal condition of the foetus. Researchers believe that pregnant women who have undergone IVF to achieve pregnancy should be classified as high-risk, primarily due to the very fact of ART itself, as well as in connection with a complicated somatic and gynaecological history, more advanced age and a prolonged period of infertility [9, 11]. The available scientific findings regarding the characteristics of pregnancy and labour, as well as the condition of foetuses and newborns, are rather contradictory. Despite the existence of a fairly substantial number of scientific publications comparing the course of gestation and labour in women with spontaneously conceived pregnancies and those resulting from IVF, there are only a few studies, notably [6, 12], which compare the characteristics of the course of pregnancy and labour, as well as the condition of the foetus and newborns, depending on the IVF technique used. The aim – to analyse the course of pregnancy and labour, and to assess the condition of newborns in patients whose pregnancies resulted from *in vitro* fertilisation.

MATERIALS AND METHODS

A retrospective cohort study was conducted involving 318 pregnancy and delivery records, as well as medical records of newborns whose mothers' pregnancies resulted from IVF (Group I), and 137 pregnancy and delivery records of women whose pregnancies occurred naturally (Group II), who were treated and delivered in the obstetrics department of the "Leleka" Multidisciplinary Medical Centre (Kyiv) between 2020 and 2024. Data collection was carried out through a comprehensive retrospective analysis of medical records: pregnancy and delivery records (Form 111/o) and medical records of newborns (Form 097/o). Data validation was performed by means of a double independent check of the recorded parameters. Group I was formed by a complete sample of all cases of childbirth following IVF between 2020 and 2024. Group II was formed using a systematic random sampling method from among women whose pregnancies occurred spontaneously and who gave birth between 2020 and 2024 at the "Leleka" Multidisciplinary Medical Centre (Kyiv). The ratio of the groups was 2.3:1, which is acceptable for retrospective cohort studies. Inclusion criteria for Group I: pregnancy

and delivery records of women whose pregnancies resulted from IVF, singleton pregnancies. For Group II: singleton pregnancies. Inclusion criteria for Group II: singleton pregnancies. Exclusion criteria for both groups: multiple pregnancy; pregnancy following other assisted reproductive technologies (ART) (intrauterine insemination and intracytoplasmic sperm injection as standalone procedures without IVF). The identification and classification of obstetric complications were carried out in accordance with the current standards and guidelines of the Ministry of Health of Ukraine: the evidence-based clinical guideline "Hypertensive Disorders in Pregnant Women" No. 151 dated 24 January 2022 [13], the standard of medical care "Foetal growth restriction" No. 1718 dated 2 October 2023 [14], and the unified clinical protocol for primary, secondary (specialised) and tertiary (highly specialised) medical care "Caesarean section" No. 8 of 5 January 2022 [15], the evidence-based clinical guideline "Normal pregnancy" No. 1437 of 9 August 2022 [16], the standard of medical care "Preterm Prelabour Rupture of Membranes" No. 1533 dated 25 August 2023 [17] and the evidence-based clinical guideline "Physiological Childbirth" No. 170 dated 26 January 2022 [18].

This study utilised categorical variables – the presence or absence of obstetric complications, mode of delivery, and Apgar score by grade – as well as quantitative variables – the patients' age and gestational age at delivery. Potential confounders were identified as the women's age, the presence of extragenital pathology, and a complicated medical history. It should be noted that, within the framework of this retrospective study, no statistical adjustment for these factors was carried out. It is also worth noting that the characteristics of IVF protocols (cycle types, embryo types) were not systematically available in the medical records. The investigation of obstetric and perinatal complications in women following IVF, depending on the type of protocol, is the subject of further prospective studies. The analysis of the assessment of the newborns' condition was based on data obtained from the newborns' medical records, which were assessed using the Apgar score at one and five minutes after birth in accordance with standard methodology. The scale comprises five clinical parameters: heart rate, breathing, muscle tone, reflex responsiveness and skin colour. Each parameter was scored on a scale of 0 to 2, with a maximum total score of 10. Statistical analysis of the study results was performed using the χ^2 test (with Yates' correction where necessary). Fisher's exact test was used only in cases where the expected frequency in at least one cell of the contingency table was less than 5 (placenta praevia, preterm birth at 22-27 weeks); calculations were performed using Statistica 14.0.1 for Windows and Microsoft Excel 2019 (version 16.0). Differences were considered statistically significant at $p < 0.05$. The study was conducted in accordance with the principles of the Declaration of Helsinki [19] and Ukrainian legislation, and was approved by the Commission on Ethics and Bioethics at V.N. Karazin Kharkiv National University (Protocol No. 3/1 dated 7 January 2026). The views expressed in this article are those of the authors and do not represent the official position of the institution.

RESULTS AND DISCUSSION

Between 2020 and 2024, 7,492 births took place at the "Leleka" Multidisciplinary Medical Centre, of which 728 (9.7%) occurred in women whose pregnancies had been achieved through assisted reproductive technologies (ART). Among the women who became pregnant following ART, 318 patients (43.7%) conceived as a result of IVF. The mean age of women in Group I was 34.1 ± 3.4 years, which is 22.3% higher than the mean age of women in Group II (26.3 ± 3.7 years, $p < 0.05$). In terms of age distribution, Group I was dominated by women aged 30-35 years – 148 (46.6%); Group II – 30 (21.9%, $p < 0.05$), whilst among women in Group II, those aged 25-30 accounted for 63 (45.9%), compared with 43 (13.5%) in Group I ($p < 0.05$). According to current literature, advanced parental age should be regarded as one of the main factors contributing to unsuccessful IVF attempts, as well as one of the leading factors in the development of obstetric and perinatal complications [20]. In the infectious and somatic medical histories of women in Group I, herpesvirus infection was the most common – 110 (34.6%), Group II – 22 (16.1%, $p < 0.05$), chickenpox – 164 (51.6%), Group II – 52 (37.9%, $p < 0.05$), acute respiratory viral infections – 100 (31.4%), Group II – 15 (10.9%, $p < 0.05$), cardiovascular diseases – 89 (40.6%), Group II – 14 (22.2%, $p < 0.05$) and endocrine system disorders – 61 (27.8%), Group II – 9 (12.7%, $p < 0.05$), which is consistent with the findings of contemporary researchers who emphasise the need to classify women whose pregnancy resulted from the use of ART as being at high risk of developing obstetric complications based on the presence of cardiovascular disease [21-22]. In the vast majority of women in Group I, gynaecological history revealed inflammatory diseases of the pelvic organs – 199 (67.0%); Group II – 34 (38.2%, $p < 0.05$), as well as conditions associated with endometriosis – 207 (69.7%), Group II – 14 (15.7%), $p < 0.05$). Endometrial pathology in the form of polyps and hyperplasia was identified in almost half of the women – 148 (49.8%), Group II – 22 (24.7%, $p < 0.05$), which led to a statistically significantly higher number of surgical interventions on the pelvic organs – 181 (60.9%), Group II – 19 (21.3%, $p < 0.05$). At the same time, no statistically significant difference was observed in the number of cases of underlying cervical conditions (Group I – 174 (58.6%), Group II – 41 (46.1%), $p > 0.05$) or reported cases of sexually transmitted infections (Group I – 39 (13.1%), Group II – 6 (6.7%), $p > 0.05$) against a background of a higher number of cases of precancerous cervical conditions among

pregnant women in Group I – 68 (22.9%), Group II – 8 (8.9%), p < 0.05. Chronic inflammatory conditions of the pelvic organs, caused by endometriosis and infectious processes, are the leading factors contributing to the development of pelvic adhesions and have an extremely negative impact on the quality of the ovaries, oocytes and embryo implantation. These factors have a negative impact on embryo implantation, increasing the likelihood of early pregnancy loss [3, 23]. In the vast majority of women in Group I, infertility was of the secondary type – 194 (61.1%) – and among the leading causes of infertility were tubal-peritoneal factors – 251 (78.9%) and infectious factors – 214 (67.3%) – which are directly linked to the pattern of gynaecological morbidity and the prevalence of inflammatory and endometriosis-associated factors of infertility. The number of women with a duration of infertility of 3-6 years was 109, accounting for 34.3%, and those with a duration of more than 6 years numbered 130 (40.6%); there was no statistically significant difference, p > 0.05, however, in the vast majority of these cases, two IVF cycles were required to achieve pregnancy – 163 (51.3%), as shown in Figure 1.

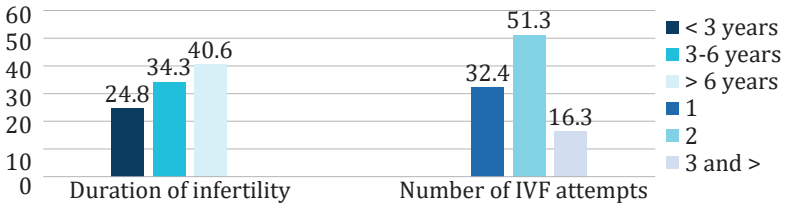

Figure 1. Duration of infertility and number of IVF attempts among the women examined in Group I (%)
Source: compiled by the authors

According to data from G. Mburu *et al*. [24], the duration of infertility is a prognostic indicator of unsuccessful IVF attempts and outcomes, regardless of the pregnant woman's age and the chosen protocol, and also reflects the severity of the factor that was the direct cause of infertility. When assessing the course of the current pregnancy, it was found that women in Group I were characterised by a higher number of cases of moderate pre-eclampsia – 94 (29.6%), Group II – 21 (15.3%), p < 0.05, and placental dysfunction – 198 (62.3%), Group II – 43 (31.4%), p < 0.05, accompanied by foetal growth restriction – 99 (31.1%), Group II – 19 (13.9%), abnormal amniotic fluid volume – 141 (44.3%), Group II – 14 (10.2%), p < 0.05, as well as vaginitis – 177 (55.7%), Group II – 29 (21.1%), p < 0.05 (Table 1).

Table 1. Data on the course of the current pregnancy in the women examined (absolute numbers, %)

Indicator	Value of the indicator in the groups of women examined (n)	
	Group I (n = 318)	Group II (n = 137)
Gestational hypertension	67 (21.1)	17 (12.4)
Pre-eclampsia: ○ moderate ○ severe	 94 (29.6)* 19 (5.9)	 21 (15.3) 3 (2.1)
Placental abnormalities: ○ placenta praevia ○ low-lying placenta ○ placenta accreta	 39 (12.3) 69 (21.7) 10 (3.1)	 14 (10.2) 33 (24.1) 0 (0.0)
Bleeding during pregnancy	89 (27.9)*	21 (15.3)
Placental dysfunction	198 (62.3)*	43 (31.4)
Foetal growth restriction (FGR)	99 (31.1)*	19 (13.9)
Abnormal amniotic fluid volume: ○ oligohydramnios ○ polyhydramnios	 141 (44.3)* 24 (7.5)	 14 (10.2) 13 (9.4)
Threatened miscarriage	241 (75.7)*	69 (50.4)
False labour before 37 weeks	216 (67.9)	51 (37.2)
PROM: ○ PPTR ○ PTRM	 67 (21.1) 27 (8.5)	 7 (5.1) 31 (22.6)
Cervical insufficiency	49 (15.4)	16 (11.7)
Metabolic complications	59 (18.6)	11 (8.0)
Anaemia in pregnancy	131 (41.2)	49 (35.8)
Vaginitis	177 (55.7)*	29 (21.1)

Note: * – statistically significant differences; PROM – premature rupture of membranes in a full-term pregnancy; PPTR – premature pre-term rupture of membranes; PTRM – pre-term rupture of membranes
Source: compiled and calculated by the authors

The number of cases of severe pre-eclampsia (Group I – 19 (5.9%), Group II – 2 (2.1%), p > 0.05) showed no statistically significant differences; however, women in Group I were characterised by the early onset of this complication, which served as the basis for premature, including surgical delivery, and was consistent with the findings of contemporary researchers, who noted an association between pregnancies resulting from IVF and early and severe forms of pre-eclampsia, compared with spontaneous pregnancies [25]. It is interesting to note the absence of a statistically significant difference in the number of cases of preterm prelabour rupture of membranes among the pregnant women in the study groups (Group I – 94 (29.6%), Group II – 38 (27.7%), p > 0.05). However, it should be noted that women in Group I were more frequently characterised by PPTR, whereas women in Group II were characterised by PTRM. Placenta-associated pregnancy complications in women following IVF may result from impaired invasion of the extravillous trophoblast, inadequate remodelling of the spiral arteries, changes in endometrial receptivity, and lead to early disturbances in placentation processes with atypical placental localisation and trophoblastic vascular dysfunction [25-27]. With regard to the timing of delivery, Group I was characterised by a reduction in the number of full-term births – 186 (58.5%), Group II – 107 (78.1%), p < 0.05, against a background of an increase in the number of preterm births – 87 (27.4%), Group II – 14 (10.2%), p < 0.05) and post-term births – 45 (14.1%), Group II – 16 (11.7%), p > 0.05. In the breakdown of preterm births among women in Group I, 10 (3.1%) occurred at 22-27 weeks + 6 days, whilst there was no difference in the number of preterm births at 28-33 weeks + 6 days (Group I – 26 (8.2%), Group II – 4 (2.9%), p > 0.05) and at 34-36 weeks + 6 days (Group I – 51 (16.0%), Group II – 10 (7.3%), p > 0.05). The onset of labour was characterised by a reduction in the number of cases of spontaneous onset of labour in women in Group I – 188 (59.1%), Group II – 99 (72.3%), p > 0.05, largely due to cases of labour induction – 67 (21.1%), Group II – 9 (6.6%), p < 0.05, and elective caesarean sections – 63 (19.8%), Group II – 29 (21.2%), p > 0.05. When analysing the course of labour among women in Group I, a higher number of cases of abnormal labour was noted – 94 (29.6%), Group II – 19 (13.8%), p < 0.05, predominantly due to weak labour – 66 (20.7%), Group II – 7 (5.1%), p < 0.05, with successful medical correction in 59 (62.7%) cases; Group II – 16 (84.2%), p < 0.05 (Table 2).

Table 2. Analysis of the course of labour in the women studied (absolute numbers, %)

Indicator	Value of the indicator in the study groups (n)	
	Group I (n = 318)	Group II (n = 137)
Abnormalities of labour:		
○ primary	66 (20.7)	7 (5.1)
○ secondary	28 (8.8)	12 (8.7)
Foetal distress:		
○ in the first stage of labour	19 (5.9)	6 (4.3)
○ in the second stage of labour	10 (3.1)	4 (1.2)
Premature placental abruption:		
○ in the first stage of labour	22 (6.9)	4 (2.9)
○ in the second stage of labour	6 (1.9)	0 (0.0)
Clinically narrow pelvis	18 (5.7)	7 (5.1)
Retained placenta	19 (5.9)	7 (5.1)
Placental defect	33 (10.4)	9 (6.5)
Trauma to the birth canal	37 (11.6)	16 (11.7)
Episiotomy/perineotomy	66 (20.7)	21 (15.3)
Postpartum haemorrhage	64 (20.1)	10 (7.2)

Note: * – statistically significant differences
Source: compiled and calculated by the authors

The number of cases of operative delivery by caesarean section was found to be almost twice as high among pregnant women in Group I – 129 (40.5%, p < 0.05) – compared with Group II – 39 (28.4%). These findings are consistent with those of the study by N.A. Lodge-Tulloch *et al.* [28], in which, based on a systematic review and meta-analysis of 34 cohort studies, it was reported that pregnancy following IVF or ICSI is associated with an almost twofold increase in the likelihood of a caesarean section compared with a spontaneously conceived pregnancy. These findings apply to both elective and emergency caesarean sections. Pathological conditions identified during labour may result from impaired uterine contractility against a background of clinical and subclinical placental dysfunction, which is predominantly characteristic of pregnancies resulting from IVF. These findings are consistent with the results of a cohort population study by F. Kong *et al.* [29], which demonstrated abnormalities in placental development and function in women whose pregnancies resulted from IVF, accompanied by a higher incidence of placental abruption, pre-eclampsia, foetal distress and

foetal growth restriction. Pregnancies resulting from an assisted reproductive cycle involving the implantation of a frozen embryo are characterised by the absence of a corpus luteum, which leads to changes in the oestrogen-progesterone ratio and is accompanied by impaired cervical ripening. At the same time, placental dysfunction leads to delayed activation of prostaglandin and oxytocin receptors in the myometrium, which is one of the main causes of weak labour. The findings are partly consistent with the results of F. Waschkies *et al.* [30], obtained from an analysis of pregnancies following cryotransfer of embryos in an artificial cycle without a corpus luteum. The publication states that the absence of a corpus luteum can be considered an independent predictor of adverse maternal and neonatal outcomes, including an increased risk of hypertensive disorders during pregnancy.

In women in Group I, 311 (97.5%) newborns were born alive, and the perinatal mortality rate was 22.0‰. Cases of stillbirth were attributed to antenatal foetal asphyxia caused by purulent-destructive changes in the placenta, intrapartum death of extremely preterm foetuses, and acute foetal distress caused by premature abruption of a normally situated placenta. Analysis of the Apgar scores for newborns at one and five minutes revealed a statistically significantly lower number of infants scored at 9 points among women in Group I – 79 (22.6%), in Group II – 57 (41.6%), $p < 0.05$, against a background of an increase in the number of newborns scored at 7 – 67 (21.6%), in Group II – 11 (8.0%), $p < 0.05$, and those scoring 6 points or less – 59 (19.0%), in Group II – 8 (5.9%), $p < 0.05$. At the fifth minute after birth, a non-significant trend towards a decrease in the number of newborns scored 6 or below on the Apgar scale was observed among women in Group I (first minute – 59 (19.0%), fifth minute – 27 (8.7%), $p > 0.05$). However, their number was not significantly higher than the corresponding figure for women in Group II – 3 (2.2%), $p > 0.05$. The number of newborns scored at 10 points (Group I – 37 (11.9%), Group II – 49 (35.8%), $p < 0.05$) and at 9 points (Group I – 89 (28.7%), in Group II – 65 (47.4%), $p < 0.05$) was significantly higher among women in Group II, against a non-significant trend towards a decrease in the number of newborns scored at 8 and 7 points.

CONCLUSIONS

1. The results of a retrospective study of pregnancy and delivery records and newborn medical records show an increase in the number of pregnancies and deliveries among women following IVF treatment, from 85 in 2022 to 133 in 2024.

2. Complications during pregnancy (a higher number of cases of moderate pre-eclampsia – 94 (29.6%), Group II – 21 (15.3%), $p < 0.05$), placental dysfunction – 198 (62.3%), Group II – 43 (31.4%), $p < 0.05$), accompanied by foetal growth restriction – 99 (31.1%), Group II – 19 (13.9%), abnormal amniotic fluid volume – 141 (44.3%), Group II – 14 (10.2%), $p < 0.05$), as well as vaginitis – 177 (55.7%), Group II – 29 (21.1%), $p < 0.05$).

3. Complications during labour (a higher number of cases of abnormal labour – 94 (29.6%), Group II – 19 (13.8%), $p < 0.05$) due to weak labour – 66 (20.7%), Group II – 7 (5.1%), $p < 0.05$) with successful medical management in 59 (62.7%) cases (Group II – 16 (84.2%), $p < 0.05$) and caesarean sections among pregnant women in Group I – 129 (40.5%), in Group II – 39 (28.4%), $p < 0.05$).

4. A more severe condition among newborns (a significantly lower number of infants scored at 9 points among women in Group I – 79 (22.6%), in Group II – 57 (41.6%), $p < 0.05$) against a background of an increase in the number of newborns scored at 7 – 67 (21.6%), in Group II – 11 (8.0%), $p < 0.05$) and those scoring 6 points or less – 59 (19.0%), in Group II – 8 (5.9%), $p < 0.05$) in women whose pregnancies resulted from *in vitro* fertilisation are, to a certain extent, attributable to a history of significant infectious, somatic and gynaecological histories and are the result of impaired trophoblast invasion, inadequate remodelling of the spiral arteries, and changes in endometrial receptivity, all of which have an extremely negative impact on the processes of placentation; and, according to the study results, may be attributable to the fact that the pregnancy resulted from IVF.

Limitations of the study. The interpretation of the study results should take into account the study's limitations, namely: its retrospective, single-centre nature; the unequal group sizes in the comparison groups; and the lack of stratification by IVF protocol type, which may limit the generalisability of the results.

Prospects for further research. Given the lack of information on the types of protocols used, as well as the types of embryos used during *in vitro* fertilisation, it is deemed appropriate to continue research into the characteristics of clinical, laboratory, immunological, hormonal, ultrasound and Doppler parameters; this will enable the identification of specific features of the course of pregnancy, childbirth, and the condition of foetuses and newborns in women, depending on the *in vitro* fertilisation technique used and the type of embryos, with the aim of optimising diagnostic measures, predicting complications, and improving antenatal and intranatal care for women whose pregnancies resulted from *in vitro* fertilisation.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Микола Коваленко

Аспірант
Товариство з обмеженою відповідальністю «Лелека»
04057, вул. Квітки Цісик, 56, м. Київ, Україна
https://orcid.org/0009-0002-1191-6834

Ольга Грищенко

Доктор медичних наук, професор, заслужений діяч науки і техніки України
Харківський національний університет імені В. Н. Каразіна
61022, майдан Свободи, 6, м. Харків, Україна
https://orcid.org/0000-0002-2410-861X

Особливості перебігу вагітності і пологів та стан новонароджених у жінок після екстракорпорального запліднення

Актуальність. Проблема неплідності залишається актуальною в репродуктивній медицині, а вагітність після ЕКЗ потребує особливого медичного супроводу через відмінність її перебігу від фізіологічної.
Ціль. Визначити особливості перебігу вагітності, пологів та стан новонароджених у жінок, вагітність яких настала в результатів застосування екстракорпорального запліднення.
Матеріали та методи. Проведено ретроспективний клініко-статистичний аналіз 318 історій вагітності і пологів, а також медичних карт новонароджених у жінок, вагітність яких настала в результатів застосування ЕКЗ (Група I) і 137 історій вагітності і пологів жінок, вагітність яких виникла самостійно (Група II), які знаходились на лікуванні та розродженні в акушерському відділенні багатопрофільного медичного центру «Лелека» (м. Київ) в період з 2020 по 2024 роки.
Результати. Для жінок Групи I виявилась характерною більша кількість випадків помірної прееклампсії – 94 (29,6 %), Група II – 21 (15,3 %, $p < 0,05$), плацентарної дисфункції – 198 (62,3 %), Група II – 43 (31,4 %, $p < 0,05$), що супроводжувалась затримкою росту плоду – 99 (31,1 %), Група II – 19 (13,9 %) аномальної кількості амніотичної рідини – 141 (44,3 %), Група II – 14 (10,2 %, $p < 0,05$), а також вагінітами – 177 (55,7 %), Група II – 29 (21,1 %, $p < 0,05$). Кількість випадків тяжкої прееклампсії, Група I – 19 (5,9 %), Група II – 2 (2,1 %) при $p > 0,05$ не мала достовірних відмінностей. Для термінів розродження жінок Групи I було характерним зменшення кількості термінових пологів – 186 (58,5 %), Група II – 107 (78,1 %, $p < 0,05$), на фоні збільшення кількості передчасних – 87 (27,4 %), Група II – 14 (10,2 %, $p < 0,05$) та запізнілих – 45 (14,1 %), Група II – 16 (11,7 %, $p > 0,05$) пологів. В структурі передчасних пологів серед жінок групи I відзначено 10 (3,1 %) в 22-27 тижнів + 6 днів при відсутності різниці в кількості передчасних пологів в 28-33 тижнів + 6 днів (Група I – 26 (8,2 %), Група II – 4 (2,9 %) при $p > 0,05$) та в 34-36 тижнів + 6 днів (Група I – 51 (16,0 %), Група II – 10 (7,3 %) при $p > 0,05$). Аналізуючи перебіг пологів серед жінок групи I відзначено більшу кількість випадків аномалій пологової діяльності – 94 (29,6 %), Група II – 19 (13,8 %, $p < 0,05$), переважно, за рахунок слабкості пологової діяльності – 66 (20,7 %), Група II – 7 (5,1 %, $p < 0,05$) з успішною медикаментозною корекцією в 59 (62,7 %) випадках, Група II – 16 (84,2 %, $p < 0,05$).
Висновки. У 2022-2024 роках кількість вагітностей і пологів після ЕКЗ зросла на 56 %, а їх ускладнений перебіг може бути пов'язаний з анамнезом, порушеннями плацентації та особливостями вагітності після ЕКЗ.
Ключові слова: акушерські ускладнення, гестація, гестаційний перебіг, допоміжні репродуктивні технології, стан новонароджених

THEORETICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616-091.8+616-092.9:616.611-002+616.379-008.64 Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.05 Received: 19.12.2025 Revised: 22.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Oleksandr Nahornyi*

Senior Lecturer
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-8271-5151

Volodymyr Likhodievskyi

PhD in Medical Sciences, Assistant
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-7596-1207

Morphological features of renal glomerular injury in experimental diabetes mellitus and their correction through the inhibition of cellular protein kinases

Abstract

Relevance. Diabetic nephropathy significantly impairs patients' quality of life, leads to loss of working capacity, and is associated with high mortality. Current scientific trends demonstrate a transition from a conventional approach focused solely on normalising blood glucose levels towards developing comprehensive preventive strategies that block pathogenetic mechanisms directly at the molecular level.

Aim. To investigate the impact of the protein kinase inhibitor sorafenib on the histological structure of the kidney in a model of type 2 diabetes mellitus and during treatment.

Materials and methods. An experimental study was conducted on laboratory rats to model diabetes using a hypercaloric, high-fat diet for 150 days, followed by the induction of diabetes mellitus with streptozotocin. The animals were divided into the following experimental groups and subgroups: Group I: normal-calorie diet. Group II: diabetes modelling comprising subgroups IIa (placebo treatment), IIb (sorafenib treatment), IIc (insulin treatment) and IId (combined insulin and sorafenib treatment). Treatment following the induction of diabetes lasted for 30 days. The animals' kidneys were then examined using general histological and morphometric methods. Paraffin sections were stained with haematoxylin and eosin. The areas of the renal corpuscles and glomeruli, as well as the cell density within the glomeruli, were measured.

Results. Animals in the experimental subgroups IIa, IIb and IIc exhibited moderate changes that predominantly affected the glomeruli. This was manifested by an increase in the glomerular area compared to that of intact animals. Animals in subgroup IIa were more frequently characterised by the presence of both obliterated and dilated capillaries. These capillaries were found within the glomerular loops. In animals in subgroups IIb and IIc, enlargement of the glomeruli was accompanied by dilatation of the capillary loops. The histological structure and morphometric parameters of the renal glomeruli in animals in subgroup IId were similar to those observed in group I. The morphological changes identified in subgroups IIa, IIb and IIc are characteristic of the early stages of diabetic nephropathy, indicating compression of the capillaries due to mesangial expansion and excessive dilatation of other capillaries as a result of hyperfiltration.

Conclusions. Using the protein kinase inhibitor sorafenib alongside the standard insulin therapy regimen prevented the development of the renal glomerular lesions characteristic of diabetic nephropathy.

Keywords: diabetic nephropathy; protein kinase inhibitors; sorafenib; glomerular mesangium; signalling pathways.

Suggested Citation:
Nahornyi O, Likhodievskyi V. Morphological features of renal glomerular injury in experimental diabetes mellitus and their correction through the inhibition of cellular protein kinases. Med Sci Ukr. 2026;22(2):40–47. DOI: https://doi.org/10.32345/2664-4738.2.2026.05

*Corresponding author (*doctorsanches94@gmail.com*)

INTRODUCTION

Diabetic nephropathy is one of the most severe and clinically significant complications of diabetes mellitus. It is a leading cause of disability, a substantial reduction in quality of life and high mortality among patients worldwide. For many years, the conventional approach to preventing this condition focused exclusively on achieving intensive glycaemic control. However, evidence has shown that this approach is insufficient to prevent renal failure and kidney fibrosis. Consequently, the modern understanding of the condition's pathophysiology has shifted considerably, moving away from a glucose-centred model and towards identifying and developing strategies that target the molecular and cellular cascades involved in renal injury. Chronic hyperglycaemia triggers a complex cascade of intracellular signalling pathways, in which excessive protein kinase activation plays a pivotal role by inducing oxidative stress, endothelial dysfunction and extracellular matrix expansion. Therefore, investigating the morphological features of renal glomerular injury under conditions of experimentally modelled type 2 diabetes mellitus, together with searching for pharmacological methods of correcting these changes using cellular protein kinase inhibitors, is an important objective of modern fundamental medicine. Such research could lead to new possibilities for developing combined therapeutic regimens aimed at protecting the kidneys.

A review of recent scientific literature reveals a significant interest among researchers in the molecular mechanisms that cause renal tissue damage in diabetes mellitus. H. Xu *et al*. [1] provided a detailed characterisation of the ERK1/2 signalling pathway's role in diabetes mellitus, emphasising its significance in the development of the disease and its potential as a therapeutic target for reducing cellular stress. Investigating the same cascade, Y. Hu *et al*. [2] concluded that activation of the RAF/MEK/ERK signalling pathway in the tubular epithelium directly stimulates epithelial-mesenchymal transition, thereby promoting fibrosis of the renal parenchyma. In an experimental study, C. Lavoz *et al*. [3] demonstrated that blocking VEGFR2 receptors significantly reduces the severity of renal damage in diabetic nephropathy by inhibiting pathological angiogenesis and normalising the permeability of the glomerular barrier. L. Feng *et al*. [4] emphasised the importance of the condition of the mesangium, demonstrating that mesangial cell proliferation and excessive matrix synthesis induced by protein kinases constitute the morphological basis of early glomerular changes. At the systemic level, S. Hu *et al*. [5] identified various therapeutic targets, noting that molecularly targeting intracellular kinases is the most promising strategy for overcoming resistance to standard therapy.

Sorafenib, a multikinase inhibitor that suppresses key components of the RAF/MEK/ERK, VEGFR and PDGFR pathways, is of particular interest in terms of its potential impact on the mechanisms underlying diabetic complications. K. Usenko *et al*. [6] found that the combination of sorafenib and insulin, when used to block protein kinases, effectively prevented the pathological expression of the growth factors VEGF and HIF-1α. This, in turn, reduced the severity of neurodegeneration in retinopathy. In another study, K. Usenko *et al*. [7] demonstrated that sorafenib substantially reduced glial activation and suppressed proliferative processes caused by prolonged metabolic stress. Furthermore, Y. Chen *et al*. [8] confirmed the high biological efficacy of novel sorafenib nanoparticle formulations in preserving tissue histology under conditions of experimental diabetes.

Parallel studies have confirmed the potential of other kinase inhibitors for renal protection. For example, J. Wang *et al*. [9] showed that, in a rat model of diabetes, administration of a selective protein kinase C α and β inhibitor could halt the progressive decline in renal function and substantially reduce the severity of morphological changes in the glomeruli. Meanwhile, X. Zhu *et al*. [10] found that combining the multikinase inhibitor dasatinib with quercetin protected the kidneys against diabetic injury by activating autophagy and restoring podocyte structure. This was directly correlated with improvements in the organ's overall histological parameters. K. Matoba [11] found that inhibiting Rho-associated protein kinase (ROCK) stabilised the glomerular capillary architecture at the tissue level.

The objective of this study was to determine the nature and extent of morphological changes in the renal glomeruli of rats during long-term modelling of type 2 diabetes mellitus, and to evaluate the effectiveness of their therapeutic correction through the administration of the multikinase inhibitor sorafenib, either alone or in combination with insulin.

MATERIALS AND METHODS

The experimental study was conducted on three-month-old male Wistar rats, which were kept in an experimental animal facility under standard conditions: an air temperature of 20-24°C, a relative humidity of 45-65%, natural daylight, and unrestricted access to water and food. All experimental procedures, animal identification, housing, and care were carried out in accordance with Directive 2010/63/EU [12], as well as the provisions of the Ukrainian Law No. 3447-IV [13]. The study protocol was reviewed and approved by the Commission on Bioethical Expertise and Research Ethics of Bogomolets National Medical University (Approval No. 204, 23 March 2026). The sample size was calculated using G*Power software (version 3.1.9.7, Heinrich Heine University Düsseldorf) with the "ANOVA: Fixed effects, omnibus, one-way" statistical test to compare mean values among five groups. A significance level of $\alpha = 0.05$ and a statistical power of 80% were adopted for the power analysis.

The experimental animals were allocated to groups using simple randomisation. Before the start of the

study, identification numbers were assigned to all rats by marking their tails. The animals were randomised into the following groups using a random number generator – the RANDBETWEEN function in Microsoft Excel: Group I (n = 9; normal-calorie diet): the animals received standard pelleted feed (PK 120-1, Rezon Private Enterprise, Ukraine) before and after reaching three months of age. This feed contained 3,295 kcal/kg, 23% crude protein, 6.6% fibre, and 6% fat. Group II (n = 36, high-calorie diet and induction of insulin resistance): after reaching three months of age, the animals received a high-calorie diet enriched with fat and fructose for 150 days. This diet contained 5,260 kcal/kg and had a fat content of 56.7%. At the end of this period, the animals received a single intraperitoneal injection of streptozotocin at a dose of 25 mg/kg. They then continued to receive the high-calorie diet for a further 30 days and were divided into the following subgroups: Subgroup IIa (n = 9, placebo treatment): the animals received 5 ml of physiological saline orally once daily; Subgroup IIb (n = 9, sorafenib treatment): the animals received an oral suspension of sorafenib in 5 ml of physiological saline at a dose of 50 mg/kg (Soranib, Cipla, India); Subgroup IIc (n = 9, insulin treatment): the animals received ultra-short-acting insulin intraperitoneally at a dose of 30 IU/kg (Actrapid HM, Novo Nordisk, Denmark) every other day; Subgroup IId (n = 9, combined sorafenib and insulin treatment): the animals received insulin and sorafenib according to the protocols used for subgroups IIb and IIc.

On day 180, all the animals were euthanised with an overdose of thiopental, which was administered intraperitoneally at a dose of 75 mg/kg. Kidney fragments were collected for light microscopic examination and fixed by immersion in 10% buffered formalin (PBS, pH 7.2; Sigma-Aldrich, USA) for 72 hours. The samples were then dehydrated in a graded series of isopropyl alcohol solutions and embedded in Paraplast Plus (McCormick, USA). Sections were prepared using an Accu-Cut Sakura SRM-200 microtome (Sakura, USA). The resulting sections were stained with haematoxylin and eosin. The stained histological specimens were photographed using a MicroMed Evolution ES-4130 microscope (MicroMed, People's Republic of China) and analysed using version 1.50 of the ImageJ biomedical image analysis software (National Institutes of Health, USA). For the morphometric analysis, the areas of the renal corpuscles and glomeruli, as well as the cell density within the glomeruli, were calculated in randomly selected microscopic fields. The distribution of the numerical data was tested for normality using the D'Agostino-Pearson test. Intergroup comparisons were performed using the Kruskal-Wallis test in Prism statistical software (version 11.0.0, GraphPad, USA). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Light microscopic examination of haematoxylin- and eosin-stained sections from Group I animals on a normal-calorie diet revealed that the histoarchitecture of the organ, consisting of parenchyma and stroma, was intact. The renal parenchyma consisted of renal corpuscles and tubules belonging to different segments of the nephron (Fig. 1A). The renal corpuscles consisted of capillary glomeruli and capsules. A wide, clearly visible urinary space was present. The capsule looked like a thin, rounded structure made up of flattened epithelial cells. In transverse sections, the capillary lumina were clearly visible and round or triangular in shape. Tubules of different diameters were observed. The tubular epithelial cells had uniformly stained eosinophilic cytoplasm. The nuclei were centrally located. In some tubules, the epithelial cells exhibited a surface brush border corresponding to the microvilli of proximal tubular epithelial cells.

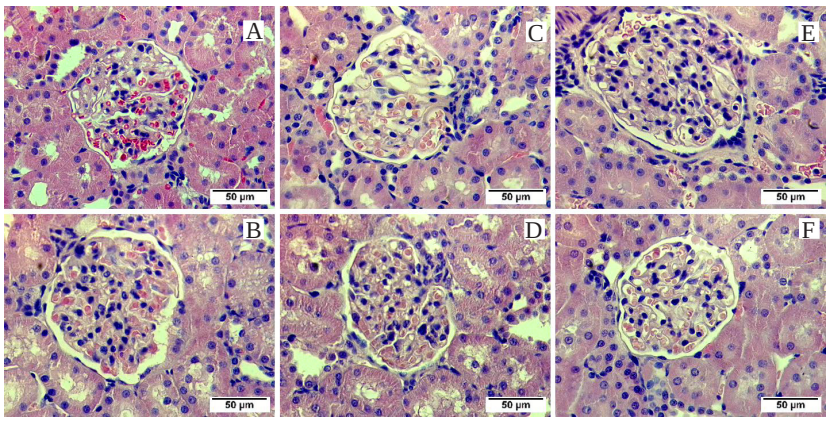

Figure 1. Histological structure of the renal corpuscles in rats from the different group

Note: A – Group I; B and C – Subgroup IIa (diabetes induction and placebo treatment); D – Subgroup IIb (diabetes induction and sorafenib treatment); E – Subgroup IIc (diabetes induction and insulin treatment); F – Subgroup IId (diabetes induction and insulin and sorafenib treatment). Haematoxylin and eosin stainin

Source: compiled by the authors

In subgroup IIa animals, which were fed a high-calorie diet, made diabetic and given a placebo, the histoarchitecture of the organ was preserved and similar to that observed in the previous group. The renal parenchyma contained renal corpuscles and tubules of various diameters. The renal corpuscles consisted of a capsule and a capillary glomerulus. The glomeruli were visibly enlarged. Unlike Group I animals, most of the glomeruli in this subgroup contained capillaries without a clearly visible lumen (Fig. 1B), or exhibited dilated capillaries with increased diameters within the glomerular loops (Fig. 1C). The mesangium appeared as a homogeneous mass containing a moderate number of cells. The tubules contained eosinophilically stained desquamated epithelial cells.

In subgroup IIb animals, which received a high-calorie diet, underwent diabetes induction, and were treated with sorafenib, the renal structure was preserved. The parenchyma was made up of renal corpuscles and tubules that corresponded to different parts of the nephron. In more than half of the renal corpuscles, the urinary space was clearly visible around the periphery of the glomerulus. Most glomeruli were enlarged with a narrowed urinary space and consisted of capillaries with narrowed lumina. More than half of the capillaries had no clearly visible lumen (Fig. 1D). The mesangium contained a moderate number of cells, which were unevenly distributed within the glomerulus and which were present in areas without cells. The tubules contained eosinophilically stained desquamated epithelial cells. In animals in subgroup IIc that received a high-calorie diet, underwent diabetes induction, and were treated with insulin, the renal structure was similar to that observed in the previous subgroup, characterised by enlarged glomeruli. However, a greater number of glomerular capillaries exhibited visible round or linear lumina depending on their orientation relative to the sectioning plane. Some glomeruli contained loops with dilated capillaries (Fig. 1E). The glomeruli exhibited a clearly visible urinary space and a capsule composed of flattened epithelial cells. The mesangium contained a homogeneous, pale pink matrix and a moderate number of evenly distributed cells. In animals in subgroup IId that received a high-calorie diet, underwent diabetes induction, and were treated with insulin and sorafenib, the renal structure was preserved. The renal corpuscles were normal in size, and the glomeruli were clearly separated from the capsule by the urinary space. The glomeruli had a clearly visible urinary space and a capsule composed of flattened epithelial cells (Fig. 1F). The mesangium contained a homogeneous, pale pink matrix and a moderate number of evenly distributed cells.

Morphometric analysis revealed significant differences in renal corpuscle area among animals from the various study groups and subgroups ($p < 0.001$) (Table 1). Intergroup comparisons revealed that this parameter was significantly higher in rats from subgroups IIa, IIb, and IIc than in Group I animals. The renal corpuscle area in subgroup IId, which received combined treatment, did not differ significantly from that in group I animals. The glomerular area followed a similar pattern to the renal corpuscle area across the groups. Intergroup comparisons revealed that the glomerular area was significantly larger in rats from subgroups IIa, IIb, and IIc than in Group I animals. The glomerular area in subgroup IId, which received combined treatment, did not differ significantly from that in group I.

Table 1. Morphometric parameters of renal corpuscles in animals from the different experimental groups

Animal group/ subgroup	Renal corpuscle area, μm², median (25th-75th percentile)	Glomerular area, μm², median (25th-75th percentile)	Cell density, cells per 1,000 μm²
I	7,856 (6,216-8,750)	6,636 (5,327-7,738)	7.1 (6.4-7.9)
IIa (placebo)	9,487 (8,333-10,716)*	8,011 (7,343-8,903)*	6.8 (6.4-7.5)
IIb (sorafenib)	9,741 (8,617-11,770)*	7,724 (6,694-9,280)*	6.6 (6.2-7.4)
IIc (insulin)	9,572 (7,927-11,218)*	7,953 (6,575-9,218)*	7.4 (7.0-8.0)
IId (insulin + sorafenib)	7,235 (6,604-8,123)	6,137 (5,571-7,062)	7.4 (6.6-8.0)

Note: * – $p < 0.05$ compared with Group I animals
Source: compiled by the authors

There was no significant difference in cell density among animals from the different groups and subgroups ($p > 0.05$ for all pairwise comparisons). Under conditions of experimentally induced diabetes mellitus in rats, a statistically significant increase in renal corpuscle and glomerular areas was observed in subgroups IIa (placebo), IIb (sorafenib), and IIc (insulin), compared to Group I animals ($p < 0.05$). The most pronounced changes, including both obliterated and dilated capillary loops, were observed in the placebo group. Sorafenib or insulin monotherapy partially modified the nature of the glomerular changes, but neither prevented glomerular hypertrophy. Only the combined administration of insulin and sorafenib in subgroup IId maintained morphometric parameters of renal corpuscles and glomeruli, which did not differ statistically from those in Group I. This treatment was also associated with an even distribution of cells within the mesangium and preservation of the normal architecture of the glomerular capillaries.

The morphological changes identified in Group II predominantly affected the glomeruli and involved the tubular portion of the nephrons to a lesser extent. The glomerular changes can be regarded as moderate in severity. They may represent the initial manifestations of diabetic nephropathy, which can be explained by the relatively short duration of the experiment. These changes correspond to the early stages of the disease: according to the current Renal Pathology Society classification, Class I is characterised by thickening of the glomerular basement membrane, and Class IIa/IIb is characterised by mild or moderate mesangial expansion. This classification remains the principal instrument for histopathological assessment of diabetic nephropathy, as described by H. Qasim *et al*. [14]. In their review, H. Thomas & A. Ford Versypt [15] analysed the pathophysiology of mesangial expansion in detail. They emphasised the roles of biomechanical stress, signalling pathways such as TGF-β and MAPK, and extracellular matrix accumulation as key mechanisms underlying the early changes that occur in the glomeruli of patients with diabetic nephropathy. Consistent with these findings, animals in subgroups IIa, IIb, and IIc of the experimental group exhibited enlargement of the renal corpuscles due to glomerular hypertrophy, while the urinary space remained relatively intact. Along with the presence of dilated capillary loops, this may be functionally equivalent to hyperfiltration, which is characteristic of the initial manifestations of diabetic nephropathy. This phenomenon is associated with the development of hyperglycaemia and the subsequent increase in glucose and sodium reabsorption in the proximal tubule. This reduces the delivery of sodium and chloride ions to macula densa cells. This suppresses tubuloglomerular feedback, reduces adenosine production, and causes relative dilatation of the afferent arteriole. Ultimately, this increases glomerular hyperfiltration. Y. Yang & G. Xu [16] reported that this process leads to glomerulomegaly and mechanical stress on mesangial cells and podocytes over time, thereby contributing to disease progression.

Narrowing and obliteration of the glomerular capillary lumina were also identified, with the most pronounced signs observed in subgroups IIa and IIb. These changes were likely caused by mesangial expansion. In their review of the risk factors, progression and mechanisms of diabetic nephropathy, V. Natesan & S. Kim [17] emphasised that hyperglycaemia induces the activation of protein kinases, oxidative stress, and the excessive accumulation of extracellular matrix components, including fibronectin, laminin and collagen, within the mesangium. This leads to mesangial expansion and the subsequent mechanical compression of the glomerular capillary loops. In the absence of statistically significant changes in glomerular cell density, the expansion of the mesangial space in subgroups IIa and IIb was likely predominantly caused by the accumulation of non-cellular matrix. However, definitive confirmation of this mechanism requires additional immunohistochemical and electron microscopic investigations.

The effectiveness of insulin therapy in subgroup IIc was demonstrated through the partial preservation of visible capillary lumina. This can be attributed to a reduction in the direct cytotoxic effects of hyperglycaemia on endothelial and mesangial cells. Nevertheless, glycaemic control alone was ineffective in preventing an increase in glomerular area, thus confirming the limitations of this glucose-centred approach. Even after blood glucose normalisation, previously activated intracellular signalling cascades may continue to stimulate matrix synthesis and cellular hypertrophy. D. Viggiano [18] showed that strict blood sugar control can slow down but not stop the progression of diabetic nephropathy because a significant part of the harmful processes, such as inflammation, fibrosis, endothelial dysfunction and matrix accumulation, continue to be active even when blood sugar levels are normalised. Sorafenib, a multikinase inhibitor, would theoretically be expected to block proliferative signals by inhibiting VEGF and PDGF receptors, which play key roles in mesangial expansion, when administered to subgroup IIb. However, when administered as monotherapy without correcting hyperglycaemia, it did not produce a statistically significant improvement in morphometric parameters compared with a placebo. This may indicate that the metabolic stress in the present model was so intense that inhibiting individual kinases without controlling the metabolism was ineffective.

The most pronounced protective effect was demonstrated by the combined treatment of subgroup IId. This may be due to synergism: insulin reduced the direct metabolic impact of hyperglycaemia, while sorafenib blocked residual pathological activation of protein kinases and growth factors. This enabled glomerular morphometric parameters to be maintained at physiological levels. These results are consistent with current strategies for modulating protein kinase signalling pathways. D. Dorotea *et al*. [19] demonstrated that inhibiting pan-Src kinases, particularly Fyn, reduces endoplasmic reticulum stress, inflammation, and fibrosis in models of diabetic kidney injury. In their review of Rho/ROCK signalling in renal diseases, W. Xiong *et al*. [20] demonstrated that inhibiting this pathway reduces proteinuria, mesangial expansion, and fibrosis in models of diabetic nephropathy. S. Al-Masri *et al*. [21] emphasised the potential value of targeting PKC and other kinase pathways in combination with standard treatment. Furthermore, S. Sinha & S. Nicholas [22] confirmed the role of PKC in the development of diabetic microvascular complications, including mesangial expansion.

The scientific novelty of the findings lies in demonstrating for the first time in an experimental model of diabetes mellitus that the multikinase inhibitor

sorafenib may protect the renal glomeruli when administered alongside insulin therapy. These results suggest that developing adjunctive therapeutic regimens for patients with diabetic nephropathy, based on the targeted modulation of molecular mechanisms alongside standard glucose-lowering therapy, could be valuable. They also demonstrate the need for further experimental and clinical studies.

CONCLUSIONS

1. In an experimental model of type 2 diabetes mellitus in rats, statistically significant increases in renal corpuscle and glomerular areas were observed in subgroups IIa (placebo), IIb (sorafenib) and IIc (insulin), compared with intact group I animals ($p < 0.05$). The median renal corpuscle area ranged from 9,487 to 9,741 μm^2, while the median glomerular area ranged from 7,724 to 8,011 μm^2. This is in contrast to the control group, where the respective median values were 7,856 μm^2 and 6,636 μm^2. Morphological examination of subgroups IIa, IIb and IIc revealed changes characteristic of the early stages of diabetic nephropathy. These changes included glomerular hypertrophy and irregularity of the capillary loop lumina, with both obliterated and dilated capillaries present, as well as moderate expansion of the mesangial matrix. These changes indicate the presence of hyperfiltration and mesangial expansion.

2. Administering sorafenib alone in subgroup IIb or insulin alone in subgroup IIc did not prevent glomerular hypertrophy and only produced minor correction of the structural remodelling of the glomeruli.

3. The most pronounced morphoprotective effect was demonstrated by the combined administration of insulin and sorafenib in subgroup IId. The renal corpuscle area was 7,235 μm^2, with a 25th-75th percentile range of 6,604-8,123 μm^2, while the glomerular area was 6,137 μm^2, with a 25th-75th percentile range of 5,571-7,062 μm^2. These values did not differ statistically from those of intact Group I animals ($p > 0.05$). The histological structure of the glomeruli approached normality, with a clearly defined urinary space, even cell distribution within the mesangium, and normal capillary loop architecture.

4. There was no significant difference in glomerular cell density among the groups ($p > 0.05$), which may indicate that accumulation of the extracellular matrix predominates in the mechanism of mesangial expansion during the early stages of diabetic nephropathy.

5. It is important to note that this study has certain methodological limitations. In particular, the findings were based solely on light microscopic morphometric data. A comprehensive understanding of sorafenib's mechanisms of action requires further histochemical, electron microscopic, and immunohistochemical investigations. Future studies should evaluate the effect of cellular protein kinase inhibition on the proportional areas occupied by the mesangial matrix and collagen within the glomeruli, as well as on the expression of inflammatory and angiogenic markers in rat kidneys, employing immunohistochemical methods.

ACKNOWLEDGEMENTS

None.

FUNDING

This study forms part of the Department of Pathophysiology's planned research project at Bogomolets National Medical University, entitled "Pathogenetic Mechanisms and Substantiation of Approaches to the Correction of Organ Damage Caused by the Effects of External Factors on the Body", state registration number 0126U001773.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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Олександр Нагорний

Старший викладач
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-8271-5151

Володимир Ліходієвський

Кандидат медичних наук, асистент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-7596-1207

Морфологічні особливості ураження клубочків нирок при експериментальному цукровому діабеті та їх корекція шляхом гальмування клітинних протеїнкіназ

Анотація

Актуальність. Діабетична нефропатія належить до критичних ускладнень, що суттєво погіршує якість життя пацієнтів, призводить до втрати працездатності та високої летальності. Сучасні наукові тренди демонструють перехід від класичного підходу, зосередженого виключно на нормалізації рівня глюкози, до розробки комплексних стратегій профілактики, які базуються на блокуванні патогенетичних механізмів безпосередньо на молекулярному рівні.

Мета. Визначити вплив інгібітора протеїнкіназ (сорафенібу) на гістологічну структуру нирки при експериментальному моделюванні цукрового діабету другого типу та його лікуванні.

Матеріали та методи. Проведено експериментальне дослідження на лабораторних тваринах (щурах) із моделюванням діабету шляхом використання гіперкалорійної, високожирової дієти протягом 150 діб та подальшої індукції цукрового діабету стрептозотоцином. Тварини були розділені на такі дослідні групи та підгрупи: I група – нормокалорійна дієта; II група – моделювання діабету, підгрупа IIa (лікування плацебо); IIb (лікування сорафенібом), IIc (лікування інсуліном), IId (лікування інсуліном і сорафенібом). Тривалість лікування після індукції діабету становила 30 діб. Нирки тварин забирали для загальногістологічного і морфометричного дослідження. Парафінові зрізи забарвлювали гематоксиліном-еозином, підраховували площу ниркових тілець, площу клубочків, питому кількість клітин у складі клубочка.

Результати. У тварин експериментальних підгруп IIa, IIb, IIc відзначалися помірні зміни переважно у клубочках у вигляді збільшення їх площі, у порівнянні із інтактними тваринами. Для тварин IIa групи більше була характерна наявність як облітерованих, так і розширених капілярів у складі петель клубочків. Для тварин підгруп IIb та IIc поруч із збільшенням у розмірах, відзначалося розширених капілярних петель. Гістологічна структура та морфометричні параметри клубочків нирок у тварин підгрупи IId наближалися до таких у тварин I групи. Виявлені у тварин підгруп IIa, IIb, IIc морфологічні зміни були характерними для початкових стадій діабетичної нефропатії і свідчили як про здавлення капілярів за рахунок розширення мезангіуму, так і перерозширення інших капілярів внаслідок гіперфільтрації.

Висновки. Застосування інгібітора протеїнкіназ сорафенібу як доповнення до стандартної схеми інсулінотерапії попереджало появу характерних для діабетичної нефропатії ознак ураження ниркових клубочків.

Ключові слова: діабетична нефропатія; інгібітори протеїнкіназ; сорафеніб; мезангіум клубочка; сигнальні шляхи.

THEORETICAL MEDICINE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 617.735-007.281:616.379-008.64-06:577.21:616-091.8 Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.06 Received: 17.01.2026 Revised: 03.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Kateryna Usenko*

PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-9907-6109

Serhiy Ziablitsev

Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-5309-3728

Olena Diadyk

Doctor of Medical Sciences, Professor
P.L. Shupyk National Healthcare University of Ukraine
04112, 9 Dorohozhytska Str., Kyiv, Ukraine
https://orcid.org/0000-0002-9912-4286

Expression of PMS2 and p53 proteins in retinal tissues in experimental diabetic retinopathy and the effects of insulin and cellular protein kinase inhibition

Abstract

Relevance. The relevance of the study lies in the need to clarify the role of DNA repair mechanisms and genomic stress in the pathogenesis of diabetic retinopathy for the search for new therapeutic targets.

Aim. To determine the expression of PMS2 and p53 proteins in the retinal tissues of rats with experimental diabetic retinopathy (DR) and to assess the effects of insulin and the cellular protein kinase blocker sorafenib.

Materials and methods. The study was performed on 50 male Wistar rats. Diabetes mellitus was modelled by a single intraperitoneal injection of streptozotocin (50 mg/kg). After 7 days, animals with persistent hyperglycaemia were randomised into groups: no treatment, insulin treatment, and combined treatment with insulin and sorafenib. Animals were withdrawn from the experiment after 7 days, 28 days, and 3 months. Immunohistochemical examination was performed using antibodies against PMS2 and p53. The proportion of immunopositive cells was determined per 100 cells in 5 fields of view.

Results. In intact animals, PMS2 and p53 immunoreactivity was minimal. During the development of experimental DR, the number of positively stained cells progressively increased. PMS2-positive cells were localised mainly in the ganglion cell layer and plexiform layers of the retina, whereas p53-positive cells were more strongly associated with the vascular bed. Treatment with insulin and sorafenib was accompanied by increased expression of both markers, with the most pronounced effect after combined administration of the drugs. After 3 months, combined therapy increased the proportion of PMS2-positive cells 2.5-fold and p53-positive cells 3.5-fold compared with the control group ($p < 0.05$).

Conclusions. The development of experimental DR is accompanied by activation of the PMS2- and p53-associated cellular response to DNA damage in retinal tissues. Increased PMS2 expression during treatment with insulin and sorafenib may reflect activation of MMR-associated reparative and adaptive mechanisms. The results support considering PMS2 as a promising marker of genomic stress in diabetic retinopathy.

Keywords: DNA repair; genomic stress; immunohistochemistry; sorafenib; replication.

Suggested Citation:
Usenko K, Ziablitsev S, Diadyk O. Expression of PMS2 and p53 proteins in retinal tissues in experimental diabetic retinopathy and the effects of insulin and cellular protein kinase inhibition. Med Sci Ukr. 2026;22(2): 48–55. DOI: https://doi.org/10.32345/2664-4738.2.2026.06

*Corresponding author (*usenko1205@gmail.com*)

INTRODUCTION

Since the early 2000s, the attention of researchers in biology and medicine has focused on DNA repair mechanisms. J.A. Awosika *et al*. [1] demonstrated that mismatch repair (MMR) improves the accuracy of DNA replication by several orders of magnitude, whereas loss of MMR leads to a mutator phenotype that predisposes to cancer. M.G. Marinus [2] noted that mismatch repair is a highly conserved mechanism found in all kingdoms of life. Overall, the role of mismatch repair is to preserve the DNA sequence by removing mismatched base pairs created during replication or homologous recombination. In higher organisms, it is also necessary for successful meiosis, mitosis, and immunoglobulin diversity. In humans, defective mismatch repair is associated with sporadic and hereditary cancers, especially non-polyposis colorectal cancer. U. Chakraborty & E. Alani [3] presented the role of key repair proteins. One of the key components of MMR is the PMS2 protein, encoded by the gene of the same name. As Y. He *et al*. [4] indicated, PMS2 is part of the MutLalpha heterodimeric complex (MLH1/PMS2), which ensures recognition and correction of DNA replication errors, including nucleotide mismatches and insertions/deletions that arise during cell division. The PMS2 protein is characterised by endonuclease activity and participates in the initiation of repair by cleaving the damaged DNA region. Disruption of its expression leads to defects in the MMR system, accumulation of mutations, and development of microsatellite instability, which is associated with an increased risk of neoplastic processes [3-4]. According to Y. He *et al*. [4] and V. Lee *et al*. [5], PMS2 expression is assessed immunohistochemically in clinical practice: the absence of nuclear staining in tumour cells in the presence of internal control staining (stroma) is considered a sign of MMR deficiency. Thus, PMS2 is regarded as a marker of impaired genomic stability.

However, data on PMS2 expression in retinal tissues, particularly in diabetic retinopathy (DR), are practically absent. Current understanding of DR pathogenesis, presented by A.K. Morya *et al*. [6], Y. Yudistira *et al*. [7], and A. Callan *et al*. [8], focuses mainly on the roles of oxidative stress, chronic inflammation, neurodegeneration, reactive gliosis, angiogenesis, including the involvement of vascular endothelial growth factor (VEGF), and endothelial dysfunction. According to M. Zhang *et al*. [9] and Y. Long *et al*. [10], excessive generation of reactive oxygen species during hyperglycaemia can directly damage DNA by inducing double-strand breaks and replication errors. Under these conditions, activation of the cellular DNA damage response system can be expected, including p53 protein, poly(ADP-ribose) polymerase (PARP), and components of the MMR system (MLH1, PMS2, MSH2, and MSH6) [5, 11]. In this context, PMS2 and p53 may potentially serve as markers of genomic stress and activation of reparative processes in retinal cells during DR. The aim of the present study was to determine the expression of PMS2 and p53 proteins in the retinal tissues of rats with experimental diabetic retinopathy and to assess the effects of treatment with insulin and the cellular protein kinase blocker sorafenib.

MATERIALS AND METHODS

An experimental study was conducted in a rat model of streptozotocin-induced diabetes mellitus, with randomised allocation of animals to treatment groups. The study included 50 three-month-old male Wistar rats weighing 140-160 g. Type 1 diabetes mellitus was modelled by a single intraperitoneal injection of streptozotocin (50 mg/kg; Sigma-Aldrich, Co, China) dissolved in cold 0.1 M citrate buffer (pH 4.5). Glycaemia was monitored every three days using a glucometer and disposable test strips (ACCU-Chek Instant, Roche, Mannheim, Germany) in fasting blood collected from the tail vein. Three days after injection, blood glucose in the animals was no less than 15 mmol/L. During the experiment, marked polydipsia, polyuria, ketonuria, and glucosuria were observed; the animals lost substantial weight, which provided grounds for considering the used model of insulin-dependent diabetes mellitus with ketosis in rats adequate. In this study, the animals were observed for 3 months. Five intact animals were used to determine baseline data. After 7 days, animals with persistent hyperglycaemia were divided by blind randomisation into 3 groups of 15 animals each. In group 1 (control), hyperglycaemia was not treated. In group 2, short-acting insulin (Actrapid HM Penfill, Novo Nordisk A/S, Bagsvaerd, Denmark) was administered intraperitoneally every other day at a dose of 30 units. Animals in group 3 received insulin according to the group 2 regimen and were also given an aqueous solution of sorafenib (Sorafenib 200 mg; Cipla, India) orally every day at a dose of 50 mg/kg.

Animals were withdrawn from the experiment after 7 days, 28 days, and 3 months, 5 animals at each time point, by lethal thiopental injection (75 mg/kg). For morphological studies, the eyes were immersed in 10% neutral formalin solution and embedded in paraffin. Serial histological sections 2-3 micrometres thick were prepared from paraffin blocks on an HM 325 rotary microtome (Thermo Shandon, England). Immunohistochemical examination was performed using monoclonal antibodies against PMS2 protein (mouse monoclonal anti-PMS2 antibodies; clone A16-4; dilution 1:100; Biocare Medical, USA) and p53 protein (mouse monoclonal anti-p53 antibodies; clone DO-7; dilution 1:100; Abcam, Great Britain). The Master Polymer Plus Detection system (Master Diagnostica, Spain) was used. Antigen retrieval was performed by heat treatment of sections in citrate buffer (pH 6.0) at 95-98°C for 20 min. The sections were counterstained with haematoxylin. Microscopic examination and photographic archiving

were performed using ZEISS light-optical microscopes with the Axio Imager. A2 result-processing system (Germany). For each animal, 5 independent fields of view were analysed, after which the mean proportion of immunopositive cells was calculated. Group results were expressed as percentages and, after normality testing (Shapiro-Wilk test), calculated as medians and interquartile ranges (Me; QI-QIII). Statistical analysis was performed using Statistica 10 software (StatSoft, Inc., USA). Values were compared using the Kruskal-Wallis test, and intergroup comparisons were performed using the Dunn test; differences were considered significant at $p < 0.05$. The study was conducted in accordance with the standards and principles of Directive 2010/63/EU [12], the requirements of Law of Ukraine No. 3447-IV [13], and the expert conclusion of the Commission on Bioethical Expertise and Ethics of Scientific Research at Bogomolets National Medical University (approval of the research implementation plan on 21 November 2022, Minutes No. 164). Animals were kept in vivarium conditions on a standard diet. The opinions expressed in the submitted article represent the views of the researchers and not the official positions of the institution.

RESULTS AND DISCUSSION

The pathological process was accompanied by decreased cell density in the nuclear layers of the retina, the development of diffuse tissue oedema, which was most pronounced in the inner plexiform layer, and the formation of ischaemic areas combined with vacuolisation of neuronal cytoplasm. The vessels of the choroid and inner vascular plexus were dilated, with signs of microthrombus formation in some areas. Numerous vascular abnormalities in the form of microaneurysms were observed along the inner surface of the retina. The number of ganglion cells decreased, and they showed signs of degenerative changes, including cellular oedema and nuclear pyknosis. These morphological changes were progressive over time, from day 7 to 3 months of observation. At the later stages of the experiment, cellular proliferates were detected in the outer nuclear layer as dense clusters of basophilic cells with a tendency towards radial spread beyond the layer. Thickening and compaction of the inner limiting membrane were also noted, accompanied by accumulation of coarse-fibred basophilic structures. Dilation of microvessels along the inner surface of the retina was also observed in intact animals; however, these vessels were characterised by a small diameter, thin wall, and single lumen. By contrast, microaneurysms that formed during the prolonged course of DR had a more complex structure, with several lumens surrounded by a dense membrane. Marked oedema and widespread ischaemic zones were also identified. The number of ganglion cells decreased, and they acquired marked degenerative features. The number and size of Muller cells increased, which corresponded to reactive gliosis.

The use of insulin or sorafenib was accompanied by less pronounced morphological changes. In these groups, no decrease in nuclear-layer cell density was observed, and retinal oedema and ischaemic lesions were minimal or absent. However, individual signs of damage persisted, including a decrease in the number of ganglion cells and the formation of cellular proliferates. The most pronounced protective effect was observed with combined use of insulin and sorafenib. Under these conditions, the retinal structure remained close to normal, and the morphological signs of DR characteristic of the control group were practically absent. In particular, typical manifestations of pathological angiogenesis and cellular proliferative changes were not detected. Specific PMS2-immunopositive staining in the retina of intact rats was practically absent; isolated positive cells were detected mainly in the ganglion cell layer (Fig. 1a).

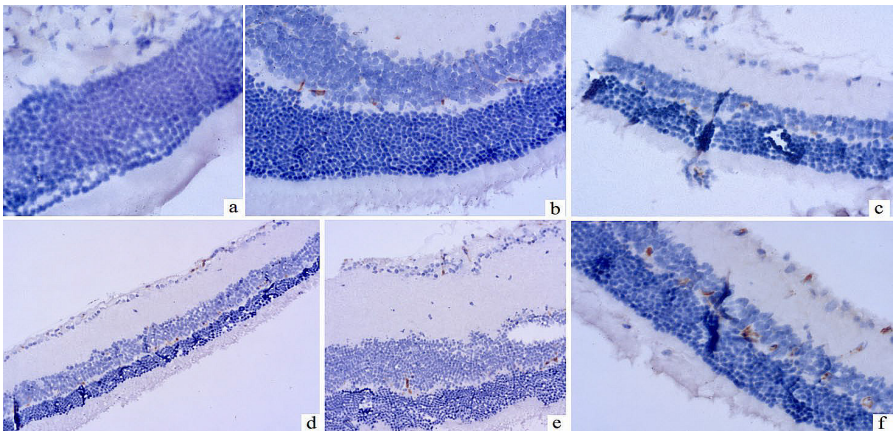

Figure 1. Retinal micropreparations of rats on day 7 and 3 months after modelling diabetic retinopathy: immunohistochemical expression of PMS2 with haematoxylin counterstaining, ×200

Note: a – before streptozotocin administration (intact rat); b – control group (7 days); c – control group (after 3 months); d – insulin administration; e – sorafenib administration; f – insulin and sorafenib administration

Source: developed by the authors

In the control group of animals with experimental DR, PMS2-positive cells were localised mainly along the inner surface of the retina, in the ganglion cell layer and the outer plexiform layer (Fig. 1b, 1c). Immunoreactivity had both nuclear and cytoplasmic localisation, with the intensity of nuclear staining consistently predominating over cytoplasmic staining. Insulin administration was accompanied by an increase in the number of PMS2-positive cells without a change in their predominant localisation (Fig. 1d). A similar effect was observed after sorafenib administration (Fig. 1e). The maximum intensity of PMS2 immunoreactivity was determined after combined administration of insulin and sorafenib (Fig. 1f). A similar pattern was observed for p53 expression (Fig. 2a). p53-positive cells were detected in the ganglion cell layer and the outer plexiform layer. Administration of insulin and sorafenib was accompanied by an increase in the number of positively stained cells (Fig. 2b-2d). However, p53 immunoreactivity was mainly associated with the vascular bed: positive cells were localised along the inner surface of the retina around microaneurysms and in the outer plexiform layer along vessels of the inner plexus.

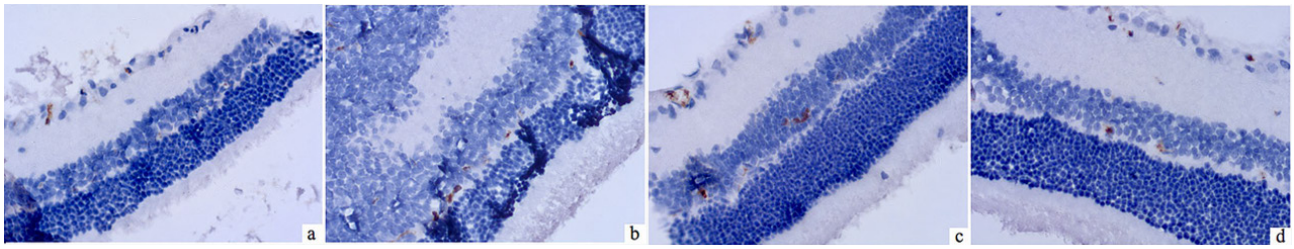

Figure 2. Retinal micropreparations of rats 3 months after modelling diabetic retinopathy: representative results of immunohistochemical staining for p53 with haematoxylin counterstaining, ×400
Note: a – control group; b – insulin administration; c – sorafenib administration; d – insulin and sorafenib administration
Source: developed by the authors

The quantitative characteristics of the proportion of immunopositive cells are presented in Figure 3. In the control group, the proportion of PMS2-positive cells gradually increased during the experiment (1.3-1.8-fold; $p < 0.05$). After 3 months, separate administration of insulin and sorafenib was accompanied by an approximately equal increase in this parameter compared with the control (1.7-fold; $p < 0.05$). The most pronounced changes were observed with combined administration of the drugs, when the proportion of PMS2-positive cells exceeded the control values by 2.5-fold ($p < 0.05$).

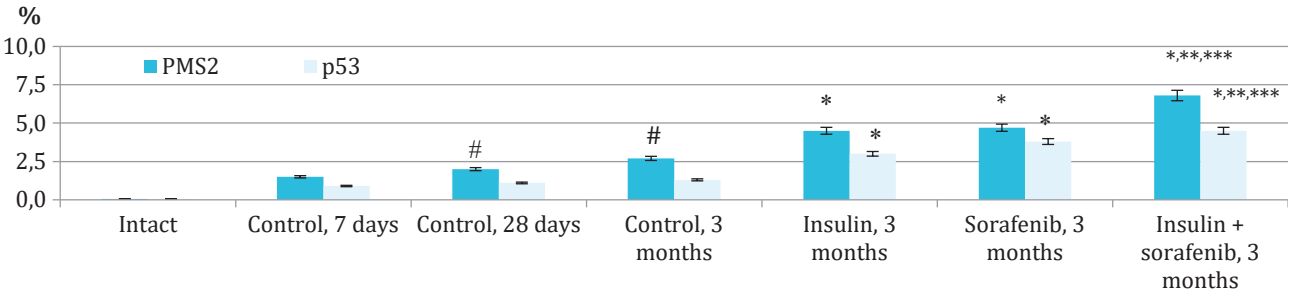

Figure 3. Proportion of PMS2- and p53-positive cells in the retina (% of the total number of cells)
Note: intact – mean data for intact animals; control, 7 and 28 days and 3 months – control-group data; insulin – insulin administration; sorafenib – sorafenib administration; ins+sor – combined administration of insulin and sorafenib; # – $p < 0.05$ compared with the control at day 7; * – $p < 0.05$ compared with the control after 3 months; ** – $p < 0.05$ compared with insulin administration; *** – $p < 0.05$ compared with sorafenib administration
Source: developed by the authors

Similar dynamics were also characteristic of p53, but the changes were less pronounced (Fig. 3). In the control group, a tendency towards an increase in the number of p53-positive cells was observed, but it did not reach statistical significance ($p > 0.05$). Separate use of insulin and sorafenib increased the proportion of positive cells 2.3-2.9-fold ($p < 0.05$), whereas combined administration of the drugs was accompanied by the maximum increase in the indicator, 3.5-fold compared with the control ($p < 0.05$). Thus, the development of experimental DR was accompanied by increased PMS2 and p53 expression in retinal tissues. Treatment with insulin and sorafenib enhanced the immunohistochemical expression of both markers, with more pronounced changes characteristic of PMS2. The highest values were recorded with combined administration of the drugs.

The results reflect increased expression of proteins associated with the cellular response to DNA damage, but they did not allow direct assessment of the functional state of the DNA repair system. This study established increased PMS2 expression in retinal tissues during the development of experimental DR. The results are consistent with data reported by J. Sohn *et al*. [16] and S. Roy *et al*. [15] on the important role of DNA damage and activation of cellular response systems to genotoxic stress in the pathogenesis of diabetic complications. According to M. Zhang *et al*. [9], metabolic stress, hypoxia, tissue acidosis, and excessive formation of reactive oxygen species during hyperglycaemia can directly damage DNA by inducing double-strand breaks and replication errors. Under these conditions, PMS2 activation may reflect involvement of the MMR-associated DNA repair system. The predominance of nuclear localisation of PMS2 immunoreactivity additionally confirmed activation of the cellular response to genetic material damage. PMS2-positive cells were localised mainly in the ganglion cell layer and the plexiform layers of the retina. K.O. Usenko [16] demonstrated that ganglion neurons and Muller cells undergo the earliest and most pronounced changes in experimental DR: degenerative processes progress in neurons, whereas Muller cells enter a state of reactive gliosis. This indicates that DNA damage and activation of repair systems occur most actively in these cell populations. Data reported by J. Ren *et al*. [17] also suggest a possible abortive return of retinal neurons to the cell cycle during neurodegenerative processes, which may be accompanied by activation of MMR-dependent mechanisms.

In parallel with increased PMS2 expression in retinal tissues, p53 expression also increased. W.P. Roos *et al*. [11] noted that activation of p53 is one of the key elements of the cellular response to severe DNA damage and oxidative stress. p53-positive cells were mainly localised along the vascular bed and around microaneurysms, which permits the involvement of endothelial stress and microvascular damage in the formation of this immunoreactivity. However, p53 expression was much less pronounced than PMS2 expression. This dissociation between high PMS2 immunoreactivity and weak focal p53 positivity may suggest predominance of the MMR-associated reparative and adaptive response over the p53-mediated proapoptotic scenario. At first glance, the increase in the number of PMS2- and p53-positive cells under the influence of insulin appears paradoxical. However, reduction of hyperglycaemia and attenuation of metabolic stress under the action of insulin probably create conditions for activation of reparative processes. According to D.D. Liu *et al*. [18], the phenomenon of metabolic memory may be important, since epigenetic changes and DNA damage persist even after normalisation of blood glucose. In this context, increased PMS2 immunopositivity can be regarded as a compensatory mechanism aimed at overcoming accumulated genetic damage in retinal tissues. The substantial increase in the proportion of PMS2-positive cells with combined use of insulin and sorafenib was of particular interest. The results obtained are consistent with the study of A. Callan *et al*. [8] on the role of kinase signalling pathways in the development of DR, including mechanisms of intracellular signalling, neuroinflammation, reactive gliosis, and angiogenic remodelling.

K.O. Usenko *et al*. [19] established that blockade of cellular protein kinases by sorafenib was accompanied by decreased VEGF expression in the retina in experimental DR and suppression of reactive gliosis. The results obtained in the present study supplement these data and suggest the involvement of MMR-associated mechanisms in the protective effect of cellular protein kinase blockade. K.O. Usenko *et al*. also demonstrated that, in experimental DR, caspase-3 expression and Bax protein content in retinal tissues increased sharply, whereas insulin administration, both separately and in combination with sorafenib, reduced the levels of these proapoptotic proteins and inhibited the morphological manifestations of DR. In this regard, increased PMS2 during treatment should not be considered a direct sign of enhanced apoptosis. On the contrary, the data obtained emphasises that treatment with insulin, especially in combination with sorafenib, may shift the cellular response to diabetes-induced damage from a p53-dependent apoptotic scenario towards a reparative and adaptive response associated with activation of the MMR system. According to J.A. Awosika *et al*. [1], PMS2 participates not only in DNA repair processes but also in regulation of p53-dependent apoptosis and the cellular response to severe genetic material damage. This is consistent with data reported by A.J. Barber *et al*. [20] on pericyte apoptosis, neurodegeneration, and ganglion cell death in DR. Thus, increased PMS2 expression may reflect a complex adaptive response of retinal cells aimed at maintaining genomic stability and controlling damaged cells. Notably, PMS2 remains poorly studied in modern ophthalmology. This is because this protein is traditionally considered mainly an oncopathological marker, whereas DR is classically studied in the context of microangiopathy, neuroinflammation, and neurodegeneration [21-22]. However, the current understanding of DR pathogenesis, including studies by J. Sohn *et al*. [14] and S. Roy *et al*. [15], increasingly emphasises the role of DNA damage, cellular ageing, epigenetic alterations, and mitochondrial dysfunction. In this context, assessment of PMS2 immunoreactivity may represent a promising area for studying disorders of DNA repair systems in DR.

CONCLUSIONS

1. During the development of experimental diabetic retinopathy in the retina of rats, a progressive increase in PMS2 expression and, to a lesser extent, p53

expression was observed, which indicated activation of the cellular response to DNA damage.

2. PMS2-positive cells were localised mainly in the ganglion cell layer and plexiform layers of the retina, whereas p53 immunoreactivity was more strongly associated with the vascular bed, which may suggest involvement of both neuronal and microvascular retinal components in genomic stress processes during diabetic retinopathy.

3. The use of insulin and sorafenib was accompanied by increased PMS2 and p53 expression, most pronounced with their combined administration, which may reflect activation of the MMR-associated reparative and adaptive response in retinal cells.

4. The results support considering PMS2 as a promising marker of the cellular response to DNA damage in diabetic retinopathy and justify further study of DNA repair systems in the pathogenesis of diabetic retinal damage.

The limitation of the study is that the assessment of PMS2 and p53 was based exclusively on immunohistochemical analysis without determining the functional activity of DNA repair systems and MMR-associated signalling pathways.

A promising area for further investigation is a comprehensive assessment of the expression and functional activity of PMS2, MLH1, and other components of the DNA repair system in retinal tissues during DR.

ACKNOWLEDGEMENTS

None.

FUNDING

This study was carried out under a budgetary programme of the Ministry of Health of Ukraine, state registration number 0126U001773.

CONFLICT OF INTEREST

There is no conflict of interest. The authors of the article did not take part in the peer-review process or in editorial decisions regarding their own manuscript.

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Катерина Усенко

Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульвар Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-9907-6109

Сергій Зябліцев

Доктор медичних наук, професор
Національний медичний університет імені О. О. Богомольця
01601, бульвар Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-5309-3728

Олена Дядик

Доктор медичних наук, професор
Національний університет охорони здоров'я України імені П. Л. Шупика
04112, вул. Дорогожицька, 9, м. Київ, Україна
https://orcid.org/0000-0002-9912-4286

Експресія протеїнів PMS2 і p53 у тканинах сітківці при експериментальній діабетичній ретинопатії та вплив на неї інсуліну і інгібування клітинних протеїнкіназ

Анотація

Актуальність. Актуальність дослідження полягає у необхідності з'ясування ролі механізмів репарації ДНК та геномного стресу в патогенезі діабетичної ретинопатії для пошуку нових терапевтичних мішеней.

Мета. Визначити експресію протеїнів PMS2 та p53 у тканинах сітківки щурів при експериментальній діабетичній ретинопатії (ДР) та оцінити вплив інсуліну і блокатора клітинних протеїнкіназ сорафенібу.

Матеріали та методи. Дослідження виконано на 50 щурах-самцях лінії Wistar. Цукровий діабет моделювався одноразовим внутрішньоочеревинним введенням стрептозотоцину (50 мг/кг). Через 7 діб тварин зі стійкою гіперглікемією було рандомізовано на групи: без лікування, лікування інсуліном та комбіноване лікування інсуліном і сорафенібом. Тварин було виведено з експерименту через 7, 28 діб та 3 місяці. Імуногістохімічне дослідження виконувалося із використанням антитіл до PMS2 та p53. Частку імунопозитивних клітин визначали на 100 клітин у 5 полях зору.

Результати. У інтактних тварин PMS2- та p53-імунореактивність була мінімальною. При розвитку експериментальної ДР кількість позитивно забарвлених клітин прогресивно збільшувалася. PMS2-позитивні клітини локалізувалися переважно у шарі гангліонарних клітин та плексіформних шарах сітківки, тоді як p53-позитивні клітини були більшою мірою асоційовані із судинним руслом. Лікування інсуліном та сорафенібом супроводжувалося підвищенням експресії обох маркерів, найбільш вираженим при комбінованому введенні препаратів. Через 3 місяці комбінована терапія збільшувала частку PMS2-позитивних клітин у 2,5 раза, а p53-позитивних – у 3,5 раза порівняно з контрольною групою ($p < 0,05$).

Висновки. Розвиток експериментальної ДР супроводжується активацією PMS2- та p53-асоційованої клітинної відповіді на пошкодження ДНК у тканинах сітківки. Підвищення експресії PMS2 при лікуванні інсуліном та сорафенібом може відображати активацію MMR-асоційованих репаративно-адаптивних механізмів. Отримані результати дозволяють розглядати PMS2 як перспективний маркер геномного стресу при діабетичній ретинопатії.

Ключові слова: репарація ДНК; геномний стрес; імуногістохімія; сорафеніб; реплікація.

STOMATOLOGY

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.5-002.44-07:616.31-002.44
DOI: https://doi.org/10.32345/2664-4738.2.2026.07

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 08.01.2026 Revised: 28.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Oleksandr Nesyn
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-9197-4983

Kostiantyn Pechkovskyi*
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-5143-2768

Iryna Pechkovska
PhD in Medical Sciences, Associate Professor
Private Higher Educational Institution "Kyiv Medical University"
02099, 2 Boryspilska Str., Kyiv, Ukraine
https://orcid.org/0000-0003-1795-0566

Serhii Samoilenko
PhD in Medical Sciences, Associate Professor
P.L. Shupyk National Healthcare University of Ukraine
04112, 9 Dorohozytska Str., Kyiv, Ukraine
https://orcid.org/0000-0002-6441-3192

Oleksii Kuvaiev
PhD in Medical Sciences, Assistant Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-0012-333X

Clinical features and diagnostic errors in the manifestations of *pemphigus vulgaris* in the oral cavity

Abstract

Relevance. *Pemphigus vulgaris* is a rare autoimmune bullous disease characterised by the formation of intraepithelial blisters and erosions. Often, the oral mucous membrane is the first and, for quite some time, the only area affected by this disease. The oral manifestation of the disease is often misdiagnosed as erythema multiforme, candidiasis, recurrent herpes simplex infection or common diseases, which results in errors in diagnosis, late referral to a dermatologist, and inappropriate treatment. Timely recognition of the lesion will affect the prognosis and quality of life of the patient.

Aim. To generalise clinical manifestations of the oral cavity affected by *pemphigus vulgaris*, to analyse errors made when diagnosing at the stage of primary diagnosis, and to develop practical recommendations on the order of actions for physicians when suspected of *pemphigus vulgaris*.

Materials and methods. A prospective clinical, descriptive analysis of 42 patients diagnosed with *pemphigus vulgaris*, who were treated at the dental medical centre, O.O. Bogomolets National Medical University, was conducted. The observation period covered 2018-2025. Clinical, cytological (Tzanck smear), and serological methods (ELISA for anti-Dsg1 and anti-Dsg3 antibodies) were used. The quality of life in patients was measured using of the SF-36v2 and DLQI questionnaires. Statistical analysis was performed using of the t-test, the Mann-Whitney test, and Spearman's correlation analysis ($p < 0.05$).

Suggested Citation:
Nesyn O, Pechkovskyi K, Pechkovska I, Samoilenko S, Kuvaiev O. Clinical features and diagnostic errors in the manifestations of *pemphigus vulgaris* in the oral cavity. Med Sci Ukr. 2026;22(2):56–65. DOI: https://doi.org/10.32345/2664-4738.2.2026.07

*Corresponding author (*konpech.work@gmail.com*)

Results. Primary symptoms manifested as lesions of the oral mucous membrane in 83.3% of patients. In these cases, the differential diagnosis was difficult. The duration of the period between the first symptom and the diagnosis was 3.5 ± 0.6 months on average and was shorter in women than in men. At the time of referral, all patients had received incorrect diagnoses (candidiasis, erythema multiforme, recurrent herpes simplex infection) and inappropriate treatment. During the primary examination, acantholytic cells were detected by cytological examination in 47.6% of smears. When examining repeat cytological smear, it was found that acantholytic cells were present in 100% of cases. Serological testing confirmed the presence of anti-Dsg3 antibodies in all patients and anti-Dsg1 antibodies in 41.7%, which is consistent with the phenotype of the isolated and generalised forms. It was found that there was a direct correlation between the time of diagnostic uncertainty and the decline in quality of life ($\rho = 0.62$, $p < 0.01$).

Practical significance. Prompt identification of solitary lesions on the oral mucosa together with the simultaneous use of cytological and serological techniques minimises the time for establishing the correct diagnosis, helps differentiate between the various types of *pemphigus vulgaris* and prevents further evolution of the disease. The suggested pattern of clinical actions can serve as a working guideline to dentists and otolaryngologists to facilitate the timely and accurate detection of disease and the timely referral of patients to the corresponding specialists.

Conclusions. Oral manifestations of *pemphigus vulgaris* can manifest clinically as other pathologies and often lead to misdiagnosis and delayed diagnosis. Tzanck smear test is a very simple diagnostic tool and does not require special equipment, but this method should be performed together with serological research for a more accurate diagnosis of the disease, and as a result, better prognosis and higher quality of life of patients.

Keywords: *pemphigus vulgaris*, differential diagnosis; cytological examination; serological investigation; quality of life.

INTRODUCTION

Pemphigus vulgaris (PV) (pemphigus; International Classification of Diseases, 10th Revision: L10.0) represents a rare yet potentially fatal autoimmune disease with formation of intraepithelial blisters and erosions [1-2]. Oral mucosal lesions constitute the first symptoms in most cases of PV and can be the only manifestation of the disease at early stages, and they can remain the main complaints of the patient for a long time. These symptoms are often covered up by other, more common pathologies such as candidiasis, recurrent herpes simplex infection, erythema multiforme, and other diseases, which may complicate the diagnostic process. Such a picture of overlapping clinical manifestations can be quite a dilemma for doctors, especially at the time of the primary appointment and t he initial stage of the disease, when the possibility of establishing a wrong diagnosis and starting incorrect therapy is quite high. Therefore, these factors should be carefully considered during the diagnostic process in order to ensure timely recognition of the disease and the initiation of appropriate therapy [3-4]. Depending on the region, the incidence of PV ranges from 0.5 to 3 cases per 100,000 population, while more than 70% of patients initially seek medical attention because of oral erosions or ulcers accompanied by mild pain or discomfort in the oral cavity [5]. Clinical manifestations of PV, including fragile blistering of thin wall with rapid rupture, superficial erosion ("clean" erosions), no reaction of the oral mucosa, and variable signs of the Nikolsky sign, often lead to misdiagnosis. In these instances, erosive lesions are erroneously attributed to erythema multiforme, candidiasis, recurrent herpes simplex infection, oral lichen planus, and other conditions, and cytological confirmation of the presence of acantholysis by the Tzanck smear method is often delayed or may be false-negative [6]. Due to insufficient expertise regarding PV at the time of the first patient appointment and a lack of timely cytological and serological tests needed to establish the correct diagnosis, the patient is often prescribed inadequate medical treatment. The medical professional is likely to prescribe antifungals, antimicrobials, or topical antiseptics instead of referring the patient to a dermatologist for specific drug therapy, which may not be effective, and can even further harm the health of the patient as they are treated for another disease [7]. Considering the multidisciplinary character of the problem, it is extremely important to carry out timely cytological and serological verification of the diagnosis of PV [8]. Early detection of the isolated form of oral mucosal lesions of PV allows for decreasing the time of diagnostic search and preventing further development of the disease and deterioration of quality of life in patients [9]. Thus, systematisation of clinical data in PV and analysis of possible diagnostic errors are very important tasks of modern medicine, which will contribute to more efficient diagnosis of disease at the early stage, as well as will reduce the probability of errors at the first examination of patients. Early diagnosis, especially at the initial stage, as well as minimising mistakes at the stage of a primary examination, are important in improving the overall efficiency of treatment and, consequently, improving the quality of care of patients. Therefore, it is necessary to implement such a complex in determining diagnosis that helps not only to detect the disease at an early stage, to avoid delays, but also to ensure a differential diagnosis in PV and avoid

the appointment of incorrect therapy. This study aimed to systematise the oral features of PV, identify prevalent diagnostic mistakes at the initial visit, and formulate practical guidelines for clinicians to follow when PV is suspected.

MATERIALS AND METHODS

This study was conducted as a prospective clinical descriptive analysis (case series) based on data from 42 patients who, between 2018 and 2025, presented with pathological manifestations of the oral mucosa to the Dental Medical Centre of the O.O. Bogomolets National Medical University, which serves as the clinical base of the Department of Therapeutic Dentistry. A clinical diagnosis of PV was established. Patients were enrolled consecutively at the time of their initial presentation, thereby ensuring the prospective design of the study. Patients ranged in age from 44 to 65 years (56.0 ± 6.1 years), with 28 women (66.7%) and 14 men (33.3%) (female-tomale ratio 2:1). The patients were residents of Kyiv and the northern, central, and southern regions of Ukraine. The inclusion criteria comprised erosive and ulcerative lesions of the oral mucosa, a positive Nikolsky sign, and cytological confirmation of acantholysis. The only exclusion criteria were a lack of informed consent. Other diseases were not an exclusion criterion because the purpose of the study was to diagnose PV. The patient's comorbid condition had no bearing on enrolment, but it was discussed in the clinical description of each case. Assessment of the anamnestic data involved identification of the frequency of errors during the previous diagnosis, the time period during which the patients visited the medical institutions and also the frequency of empirical therapy. The diagnosis and treatment protocol utilised a sequential approach including clinical examination, Tzanck smear cytology [10], and serological detection of desmogleins 1 and 3 by enzyme-linked immunosorbent assay (ELISA) [11]. The latter was not performed before two negative cytological results were obtained. This was done to adhere to rational diagnostic principles. According to these guidelines, the sequence of diagnostic methods must progress from relatively simple and easy-to-use methods to more difficult and expensive ones, and each step must be justified by clinical necessity.

Primary diagnosis was based on clinical examination of patients with assessment of characteristic lesions of the mucous membranes and skin. Rubbing the normal oral mucosa near a lesion or skin was used to determine if the Nikolsky sign was positive. A positive sign was identified by epithelial or epidermal detachment and further blister and erosion formation. Cytological examination of the contents of the surface of the bottom of the ulcers and the blisters was carried out by the Tzanck method. When there were no acantholytic cells found in the original smears, smears were re-examined, when necessary, from scrapings of fresh blister bottoms. The re-examination is performed every week (every 7-10 days) in accordance with modern recommendations, since fresh blisters can be collected at the specified interval. Serological testing was subsequently done in 12 patients in whom false-negative results from two cytological examinations were obtained. The presence of autoantibodies against desmogleins 1 and 3 was also investigated in them by ELISA. Serum from venous blood was tested in the private certified laboratory Synevo (Ukraine), which has a license to handle biological samples.

Patients' quality of life was assessed using the standardised Short Form (SF)-36v2 and Dermatology Life Quality Index (DLQI) questionnaires. The surveys were conducted after diagnostic verification and before referral of patients for specialised dermatological treatment. Patients completed the questionnaires independently in accordance with the official instructions translated into and adapted for the Ukrainian language. Data processing was performed in accordance with the standard recommendations for these instruments. For the SF-36v2 questionnaire, the physical and mental health component scales were calculated using the developers' algorithm. For the DLQI questionnaire, the total score (0-30) was calculated and interpreted according to generally accepted categories reflecting the impact of dermatological diseases on quality of life. The results were entered into an electronic database and analysed statistically using descriptive indicators (mean value and standard deviation) together with comparative tests selected according to the structure of the sample. Age, time from diagnosis delay, number of consultations before receiving a diagnosis, number of oral mucosa affected areas, and quality-of-life indicators (SF-36v2 and DLQI) were characterised as descriptive statistics (M ± SD). The t-test was used to compare the mean time of diagnostic delay for men and women. Since the data had a non-parametric distribution, the number of consultations before receiving the diagnosis in groups was compared using the Mann-Whitney test. To determine the connection between the duration of diagnostic delay and quality-of-life indicators (SF-36v2, DLQI), as well as the relationship between the duration of diagnostic delay and the gender of the patients, Spearman correlation analysis was conducted. Statistical analysis was performed in IBM SPSS Statistics (v.26) and Excel (2019). $p < 0.05$ was considered the level of statistical significance.

The study was conducted in accordance with the principles of the Declaration of Helsinki [12] within the framework of the investigator-initiated research project of the P.L. Shupyk National Healthcare University of Ukraine entitled "Improving Methods of Diagnosis and Treatment of Patients with Certain Inflammatory and Oncological Diseases of the Ear, Nose and Throat", (state registration No. 0117U006094, 2017-2021),

as well as the research project of the Department of Therapeutic Dentistry of the O.O. Bogomolets National Medical University entitled "Development and Implementation of S cientifically Based Algorithms for Early Diagnosis and Differentiated Treatment of Diseases of Dental Hard Tissues and Periodontal Tissues" (No. 0119U104010, 2018-2022), and its continuation, "A Multidisciplinary Approach to the Prevention and Treatment of Diseases of Hard Tooth Tissues and Periodontal Diseases in Persons of Working Age" (No. 0119U104010, 2023-2025). The study received no external funding. All patients provided written informed consent for participation in the study.

RESULTS AND DISCUSSION

Discomfort or mild pain in the oral cavity was reported by 95.2% of patients (n = 40), aggravated by an increase in the size of the erosive area. In 83.3% of cases (n = 35), the first blisters and erosions were in the oral cavity and not involving the skin. In 92.9% of patients (n = 39), the process was found to be localised in several areas of the oral cavity, with an average of 3.7 ± 1.5 areas. Most often, erosions are detected on the buccal mucosa (81.0%, n = 34), the soft palate (76.2%, n = 32), and the tongue (57.1%, n = 24). Hoarseness in 73.8% of patients (n = 31) also indicated involvement of the organs located outside the mouth. Nikolsky's symptom was observed in 52.4% (n = 22) of the patients at the primary visit; in 47.6% (n = 20), it appeared only after provocative action performed by the doctor on the oral mucosa. The average period from the onset of symptoms of the disease until the diagnosis was made was 3.5 ± 0.6 months. This period is smaller in women (2.79 ± 0.5 months), while for men, it was longer and amounted to 4.23 ± 0.55 months, which confirms the difference between the groups and a positive correlation ($\rho = 0.62$; $p < 0.01$). Before applying for a referral, the patients received numerous consultations, a preliminary diagnosis, and a prescribed (non-therapeutic) treatment in all (100%) cases. The distribution of patients according to the type of clinical manifestations and laboratory findings is presented in Table 1.

Table 1. Distribution of clinical manifestations

Type of manifestation	Number of patients with verified diagnosis (n = 42)	Percentage (%)
Lesions confined to the oral mucosa	35	83.3
Oral mucosal and skin lesions	7	16.7
Positive Nikolsky sign at presentation	22	52.4
Acantholytic cells were detected in the smear	20	47.6
Anti-Dsg3 antibodies detected	12	100
Anti-Dsg1 antibodies detected	5	41.7

Source: developed by the authors

All patients before applying for a referral to the dental medical centre had visited several doctors: 33.3% (14 patients) were examined by four doctors, 19.0% (8) by five, 14.3% (6) by six, and 33.3% (14) by seven or more, and on average, the patient was visited by 6.2 ± 1.8 doctors. Initially, family physicians or general practitioners (n = 19; 45.2%) were the first ones to see patients diagnosed with PV, followed by otorhinolaryngologists (n = 13; 31.0%), dentists (n = 7; 16.7%) and other specialists (n = 3; 7.1%). Patients had erythema multiforme (n = 13; 31.0%), candidiasis (n = 10; 23.8%), recurrent herpes simplex infection (n = 7; 16.7%), recurrent aphthous stomatitis (n = 5; 11.9%), oral lichen planus (n = 4; 9.5%) and leukoplakia (n = 2; 4.8%) at first diagnosis, and bullous pemphigoid (n = 1; 2.4%). Acantholytic cells were found in 47.6% of smears (n = 20) in primary cytological examination. After repeated research, the number of patients with a positive result increased, so that all patients (100%) were able to verify their diagnosis. Serology (autoantibodies detection for desmogleins 1 and 3) was carried out in 12 (28.6%) patients. Anti-Dsg3 antibodies were detected in 100% of cases, while anti-Dsg1 antibodies were identified in 42%, which was consistent with the clinical manifestations observed, namely isolated oral mucosal involvement or the generalised form of the disease. In 31.0% of patients (n = 13), the final diagnosis of PV was established with a delay of more than 2 weeks, whereas in 16.7% (n = 7), the delay exceeded 3 weeks after the initial presentation. The distribution of patients according to the time required for confirmation of the final diagnosis at the Dental Medical Centre of the Bogomolets National Medical University is presented in Figure 1.

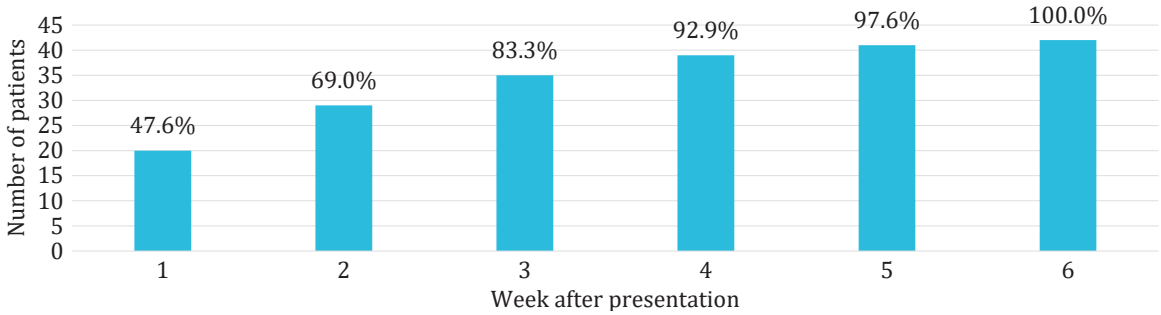

Figure 1. Dynamics of PV diagnostic verification
Source: developed by the authors

The graph demonstrates a progressive increase in the number of patients with a confirmed diagnosis, from 47.6% during the first week to complete diagnostic verification (100%) by the sixth week. Thus, within the first two weeks, the diagnosis of PV was verified in 69% of patients. Patients diagnosed with PV were examined with DLQI and SF-36v2 questionnaires for quality-of-life assessment to assess the effect of the disease. After diagnostic verification, the results showed a decrease in patients' scores in the "emotional functioning", "social functioning" and "pain" domains. The mean score was 13.4 ± 3.2 points for DLQI, which confirms the significant influence of the disease on daily life activities. When comparing different clinical forms of PV, it was found that the average DLQI score for patients with isolated oral mucosal lesions was 12.1 ± 2.8, but with combined oral and skin lesions reached 16.8 ± 3.1 ($p < 0.05$). Thus, generalised PV has a much greater impact on daily life. A positive correlation between the time until the diagnosis was confirmed and patients' DLQI scores ($\rho = 0.62$, $p < 0.01$) was found: the higher the number of days until a confirmed diagnosis, the lower the quality of life for these patients. In SF-36v2 questionnaire data, a reduction in the domains of "emotional functioning", "social functioning" and "pain" was the most noticeable. Patients had reduced physical functions, decreased working capacity and impaired social interaction. The combined analysis of the SF-36v2 summary indices revealed a significant decrease in both Physical Component Summary and the Mental Component Summary, showing a decline in physical and psycho-emotional domains in patients with PV. To illustrate the clinical manifestations of PV, Figures 2-13 are presented, demonstrating the characteristic features of the disease.

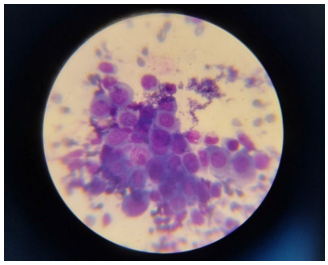

Figure 2. Acantholytic epithelial cells of the oral mucosa (Tzanck cells)
Source: authors' photo

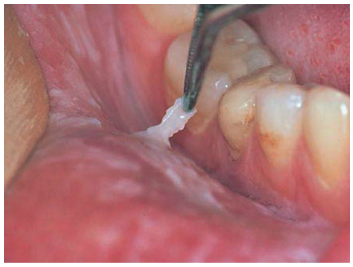

Figure 3. Nikolsky sign on the oral mucosa
Source: authors' photo

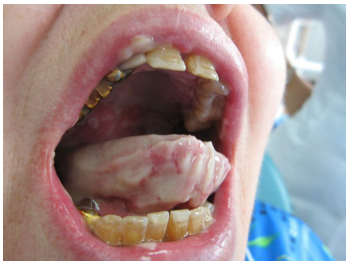

Figure 4. Tongue – macerated epithelium on the dorsal, lateral, and ventral surfaces
Source: authors' photo

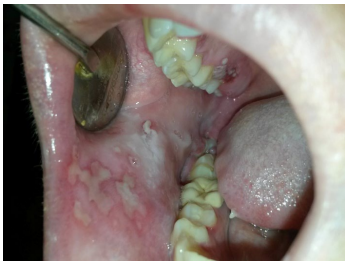

Figure 5. Buccal mucosa – erosions covered with detached macerated epithelial flaps
Source: authors' photo

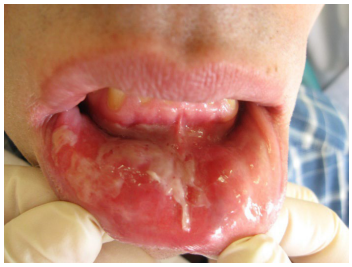

Figure 6. Lower lip – sheets of detached epithelium and fragments of blister roofs
Source: authors' photo

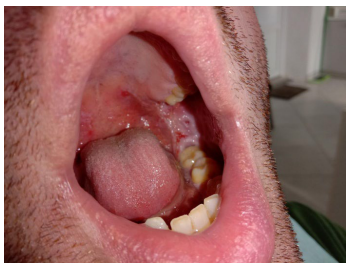

Figure 7. Retromolar area – red superficial erosions without bleeding or surrounding inflammatory reaction
Source: authors' photo

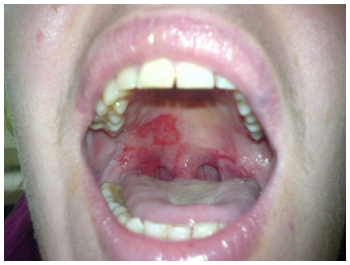

Figure 8. Soft palate and palatal arches – erythematous erosions surrounded by non-reactive mucosa
Source: authors' photo

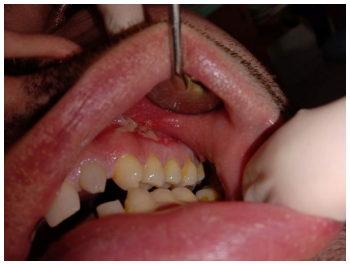

Figure 9. Macerated epithelium covering an erosive lesion surface
Source: authors' photo

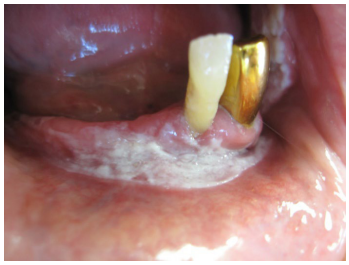

Figure 10. Gingiva of the mandible – detached (macerated) epithelium in the anterior region without inflammatory response
Source: authors' photo

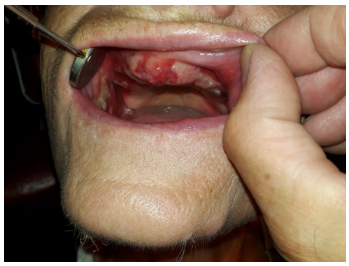

Figure 11. Maxillary alveolar ridge and buccal mucosa – erythematous erosions partially covered by macerated epithelium, without reactive changes in surrounding tissues
Source: authors' photo

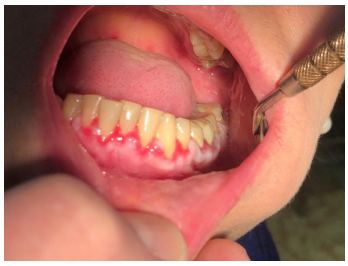

Figure 12. Mandibular gingiva – erosions of the papillary and marginal areas without inflammatory changes in adjacent tissues
Source: authors' photo

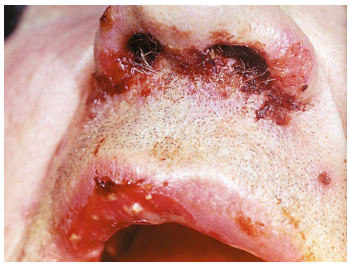

Figure 13. Generalised form of PV – involvement of the oral mucosa, vermilion border of the lips, nasal mucosa, and skin of the nose
Source: authors' photo

The cytological hallmark – acantholytic Tzanck cells (Fig. 2) – and the Nikolsky sign (Fig. 3) are presented. Typical erosive–bullous lesions of the oral mucosa are demonstrated across different anatomical sites: the tongue (Fig. 4), buccal mucosa (Fig. 5), lip (Fig. 6), retromolar region (Fig. 7), soft palate and palatal arches (Fig. 8), gingiva (Figs. 10, 12), and alveolar process (Fig. 11). The maceration of the epithelium on the surface of erosions is represented by Figures 4-6, 10-12. Figure 13 shows an example of the generalised form of PV involving the oral mucosa, vermilion border of the lips, nasal mucosa, and nasal skin. The illustrative part shows the characteristic manifestations and the clinical heterogeneity of PV manifestations in the oral mucosa.

The initial clinical manifestations of the PV disease are difficult to diagnose, especially if it is manifested solely by lesions of the oral mucosa. In this case, they are disguised by other more common diseases, which leads to mistakes in diagnosing the disease and delays in the visit to a dermatologist. The results obtained coincide with literature data on the low clinical suspicion of the general practitioners and the insufficient use of special diagnostic methods [13]. The occurrence of isolated lesions in the oral mucosa in most cases (83.3%) is the main clue to the diagnosis. The average diagnostic delay of 3.5 ± 0.6 months indicates an error in differential diagnosis, as in most patients, the initial diagnosis is often incorrect. According to V.A. Litvinov [14], in the case of oral manifestations, the PV is often confused with erythema multiforme, candidiasis, recurrent aphthous stomatitis and recurrent herpes simplex infection. This highlights the need to increase clinical awareness among primary care physicians, otorhinolaryngologists, and dentists. The delay in diagnosis causes clinical, psycho-emotional and organisational problems. The delay causes the progression of the lesion of the mucous membrane of the oral mucosa and its generalisation. From a psycho-emotional perspective, it is associated with increased discomfort, social maladjustment, and emotional exhaustion, as reflected in high DLQI scores reported by O. Segal *et al.* [15]. From an organisational standpoint, the delay causes an increase in the workload of the medical personnel of specialised outpatient care and increases the cost of medical assistance, as noted by D. Didona *et al.* [16]. The method of Tzanck was also shown to be effective. Acantholytic cells were revealed in 47.9% of cases in the initial period of observation and in 100% in the second study. The advantage of the method is its speed, accessibility, and minimal invasiveness. However, this approach has its limitations: it requires expertise, it does not exclude false negative results in

cases of minimal lesions, and it is not useful in determining subtype. A significant practical significance and high specificity were observed when determining the antibodies to Dsg1 and Dsg3 by the ELISA technique. Antibodies to Dsg3 were recorded with lesions localised on the oral mucosa, and the presence of antibodies to Dsg1 was associated with generalised forms; this matches the international data. It was also determined that it was a serological investigation that had the decisive impact on establishing the diagnosis in cases of false-negative results in cytological examination, in confirming the correctness of the initial diagnosis [17]. This confirms the hypothesis of the "molecular profile" in PV proposed by J. Wang *et al.* [18], which is important to predict generalisation and to monitor treatment. Thus, the combination of cytological and serological methods is the most acceptable option for diagnostics. This technique shortens diagnostic delay, allows for timely distinction between forms of PV and improves the prognosis. These data coincide with the results of previous studies by R. Czerninski *et al*. [19] regarding the significant negative effect of PV on physical and psychoemotional spheres of life. Patients with concomitant lesions of the oral mucosa and the skin showed high DLQI scores, which is likely due to the severity of the generalised form of the disease. The relationship between diagnostic delay and quality of life deterioration confirms the necessity of early diagnostic verification, as suggested by the results of J.Y. Sun *et al.* [20]. The diagnostic algorithm developed in this study for use in cases of suspected PV may serve as a practical guide in patients presenting with erosive and ulcerative oral mucosal lesions that are unresponsive to standard therapy (Table 2).

Table 2. Clinical decision-making algorithm in suspected PV

Stage	Actions	Aim
1. Initial examination	Identification of non-healing erosions; assessment of medical history	Increase clinical suspicion
2. Exclusion of common conditions	Candidiasis, erythema multiforme, recurrent aphthous stomatitis, oral lichen planus, bullous pemphigoid, recurrent herpes simplex infection, leukoplakia	Reduce risk of misdiagnosis
3. Detection of Tzanck cells	Smears taken from the base of a "fresh" erosion	Identification of acantholytic cells
4. Referral for serological testing	Determination of anti-Dsg3 and anti-Dsg1 antibodies	Diagnostic confirmation and prognosis assessment
5. Quality of life assessment	Use of DLQI or SF-36v2	Evaluation of patients' psycho-emotional and physical status
6. Dermatology consultation	Referral of the patient to a dermatologist	Timely and appropriate treatment and follow-up

Source: developed by the authors

The use of the proposed sequence of tests for suspected PV allows reduction of the time until diagnosis and timely referral to an expert. Early diagnosis of PV is very important as it is a precondition for effective treatment that today involves modern immunosuppressive or targeted therapeutic options.

CONCLUSIONS

1. PV more often involves the oral mucosa than skin, but the isolated oral form of the disease is the most common reason for incorrect and delayed diagnosis.

2. The clinical presentation in 83.3% of the PV cases was limited to oral mucosal lesions. This fact complicated differential diagnostics, resulting in misdiagnoses such as oral candidiasis, oral erythema multiforme, herpes simplex recurrent infection and others. The time between the onset of symptoms and the correct diagnosis of the disease in the current observation was 3.5 months; this period was longer in males than in females. These data confirm the significance of the time factor on prognosis and quality of life.

3. At first, when the disease begins, the pain for patients with PV is not pronounced; only mild pain or a feeling of soreness is observed. In the future, the larger the size of erosions, the stronger the pain that arises, interfering with chewing, talking, and affecting the general condition of patients.

4. At the very first examination, acantholytic cells were identified in 47.6% cases by cytological testing with the Tzanck method; repeat cytology showed a 100% confirmation of the diagnosis. Serological testing for antibodies against desmoglein 1 and 3 demonstrated a relatively high sensitivity: anti-Dsg3 antibodies were detected in all patients, and anti-Dsg1 antibodies in 41.7%, which correlates with the phenotypes of isolated and generalised forms of PV. This again proves that the combined use of cytology and serology will significantly improve the rate of diagnosing disease and shorten its delay.

5. There is a positive correlation between the length of delay in diagnosis and the deterioration of the patients' quality of life ($\rho = 0.62$; $p < 0.01$). Patients reported a gradual decline in emotional and social functioning as well as an escalating pain syndrome.

6. Early detection of the initial isolated oral mucosal lesions, enhanced clinical alertness among primary care doctors, and combined diagnostic methods will help prevent the development of this disease,

improve its prognosis and allow for the preservation of patients' quality of life.

7. The importance of the problem's multidisciplinary nature should be emphasised: dentists, otolaryngologists and family physicians should be well acquainted with the typical clinical symptoms of PV to ensure early referral of these patients to a dermatologist. Such an approach will make it possible to shorten the period of diagnosis, avoid inappropriate treatment and enable more accurate therapy.

Study limitations. The relatively small sample size (42 patients) and the descriptive prospective design do not exclude systematic bias and data incompleteness. Serological testing (anti-Dsg1 and anti-Dsg3 antibodies) is only available for a selected few patients. Socio-psychological factors were only partially considered, and standardised scales do not fully capture patients' cultural characteristics. It requires further confirmation and should be continued in a large-scale multicentre prospective study involving more patients and a wider range of diagnostic methodologies.

Further research directions. Multicentre prospective studies with larger patient cohorts, standardised diagnostic protocols, and expanded laboratory methods (ELISA, immunoblotting) are required for a more precise assessment of the antibody profile.

Disclaimer. The authors declare that the views expressed in this article are their own and do not represent the official positions of their affiliated institutions.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Олександр Несин
Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-9197-4983

Костянтин Печковський
Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-5143-2768

Ірина Печковська
Кандидат медичних наук, доцент
Приватний вищий навчальний заклад «Київський медичний університет»
02099, вул. Бориспільська, 2, м. Київ, Україна
https://orcid.org/0000-0003-1795-0566

Сергій Самойленко
Кандидат медичних наук, доцент
Національний університет охорони здоров'я України імені П. Л. Шупика
04112, вул. Дорогожицька, 9, м. Київ, Україна
https://orcid.org/0000-0002-6441-3192

Олексій Куваєв
Кандидат медичних наук, асистент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-0012-333X

Клінічні особливості та діагностичні помилки при проявах *pemphigus vulgaris* у порожнині рота

Анотація
Актуальність. *Pemphigus vulgaris* – орфанне автоімунне бульозне захворювання, що характеризується утворенням внутрішньоепітеліальних пухирів та ерозій. У більшості випадків першими й тривалий час єдиними проявами є ураження слизової оболонки порожнини рота, які нерідко маскуються під поліморфну ексудативну еритему, кандидоз, хронічний рецидивний герпес чи інші поширені патології. Це зумовлює діагностичні помилки, затримку направлення пацієнтів до дерматолога та призначення неадекватної терапії. Вчасне розпізнавання ізольованих уражень слизової оболонки порожнини рота має вирішальне значення для прогнозу та якості життя пацієнтів.
Мета. Систематизувати клінічні прояви *pemphigus vulgaris* у порожнині рота, проаналізувати типові діагностичні помилки на етапі первинного звернення та розробити практичні рекомендації для лікарів щодо послідовності дій при підозрі на *pemphigus vulgaris*.
Матеріали та методи. Проведено проспективний клініко-описовий аналіз 42 пацієнтів із діагнозом *pemphigus vulgaris*, які звернулися до стоматологічного медичного центру Національного медичного

університету імені О. О. Богомольця з 2018 по 2025 р. Використано клінічні, цитологічні (метод Тцанка) та серологічні (ELISA на антиDsg1 та антиDsg3) методи. Якість життя пацієнтів оцінювали за допомогою опитувальників SF36v2 та DLQI. Статистичний аналіз проводили з використанням t-тесту, тесту МаннаУїтні та кореляційного аналізу за Спірменом ($p < 0,05$).

Результати. У 83,3 % пацієнтів первинні прояви були ізольованими ураженнями слизової оболонки порожнини рота, що значно ускладнювало диференційну діагностику. Середній інтервал між появою симптомів і встановленням діагнозу становив 3,5 ± 0,6 місяця, у жінок він був коротшим, ніж у чоловіків. На момент направлення всі пацієнти отримали хибні діагнози (кандидоз, поліморфна ексудативна еритема, хронічний рецидивний герпес тощо) та неадекватне лікування. Акантолітичні клітини виявлено у 47,6 % мазків при першому цитологічному дослідженні та у 100 % при повторних. Серологічне тестування підтвердило наявність антиDsg3 у всіх пацієнтів та антиDsg1 у 41,7 %, що узгоджується з фенотипом ізольованих і генералізованих форм. Встановлено позитивний кореляційний зв'язок між тривалістю діагностичної затримки та погіршенням якості життя ($\rho = 0,62$; $p < 0,01$).

Практичне значення. Раннє розпізнавання ізольованих уражень слизової оболонки порожнини рота та комбіноване застосування цитологічного й серологічного досліджень дозволяють скоротити діагностичну затримку, диференціювати форми *pemphigus vulgaris* та запобігти прогресуванню захворювання. Запропонована послідовність дій лікаря може слугувати практичним орієнтиром для стоматологів та оториноларингологів, підвищуючи настороженість і забезпечуючи своєчасне направлення пацієнтів для спеціалізованої допомоги.

Висновки. *Pemphigus vulgaris* у порожнині рота часто маскується під інші патології, що призводить до діагностичних помилок і затримки встановлення діагнозу. Цитологічне дослідження за методом Тцанка залишається простим і доступним інструментом, але потребує доповнення серологічними методами. Поєднання цих підходів забезпечує більш точну діагностику, покращує прогноз та якість життя пацієнтів.

Ключові слова: *pemphigus vulgaris*, диференційна діагностика; цитологічне обстеження; серологічне дослідження; якість життя.

STOMATOLOGY

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.314.15:004.852
DOI: https://doi.org/10.32345/2664-4738.2.2026.08

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 21.12.2025 Revised: 20.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Iryna Zabolotna*

PhD in Medical Sciences, Associate Professor
Donetsk National Medical University
25031, 4-A Yuri Kovalenko Str., Kropyvnytskyi, Ukraine
https://orcid.org/0000-0002-3284-0392

Tatiana Bohdanova

PhD in Pedagogical Sciences, Associate Professor
National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"
03056, 37 Beresteyskyi Ave., Kyiv, Ukraine
https://orcid.org/0000-0001-5501-132X

Determination of predictors of non-carious cervical lesions of teeth using logistic regression analysis

Abstract

Relevance. Non-carious cervical lesions of teeth remain the second reason for contacting the dentist after tooth decay and its complications.

Aim. To determine predictors of the occurrence and progression of wedge-shaped defect (WSD) and erosion (E) of tooth enamel in young patients.

Materials and methods. 272 patients (mean age 24.3 ± 6.9 years) were examined, in which potential predictors were collected during the examination and questionnaire method. To analyse the strength of the association between the factors and the outcome, the odds ratio (OR) was used within a 95% confidence interval (CI). Univariate and multivariate logistic regression analysis was used to determine the predictors.

Results. Independent predictors of WSD were salivation rate less than 0.5 mL/min, hygiene habit of applying pressure to the toothbrush, age of 25 and older, the presence of gingival recession and tooth extraction. Latent predictors of WSD development were oral fluid pH (OF) values less than 6.9 C.U., behavioural factors, clinical markers. Potentially protective variables were variables with OR < 1: duration of brushing teeth for three minutes or more, consumption of yoghurt and bananas. Confounding was identified for the "fruit consumption" predictor. Independent predictors of the occurrence of enamel E were the presence of occlusal tooth wear and enamel cracks; modifier factors – OF pH values less than 6.9 C.U., and the habit of brushing teeth before breakfast. However, the broad CI determined for all predictors of the appearance of enamel E in univariate logistic regression analysis, and a small number of observations, indicate the prematurity of the results and the need for their confirmation. Most predictors of the progression of non-carious cervical lesions of teeth were latent and had broad CI in univariate logistic regression analysis, indicating evaluation instability and requiring further studies in larger samples.

Conclusions. The use of the logistic regression analysis method determined statistically independent and hidden predictors that are recommended to be considered in the diagnosis and preparation of a treatment plan for non-carious cervical lesions lesions of teeth in young patients.

Keywords: erosion; wedge-shaped defect; dietary and hygiene habits; oral fluid, cracks.

INTRODUCTION

Non-carious dental pathology in 55% of cases is diagnosed in the cervical region (CR). These are lesions that form in the area of the enamel-cement junction: wedge-shaped defects (WSD) and enamel erosion (E) [1]. Their aetiology is multifactorial, and prevention is difficult in the absence of a clear understanding

Suggested Citation:
Zabolotna I, Bohdanova T. Determination of predictors of non-carious cervical lesions of teeth using logistic regression analysis. Med Sci Ukr. 2026;22(2):66–75. DOI: https://doi.org/10.32345/2664-4738.2.2026.08

*Corresponding author (*myhelp200@gmail.com*)

of predictors [2]. Detailed review of aetiopathogenetic factors of non-carious cervical dental pathology, conducted by M. Dioguardi *et al.* [3], showed that they have differences from tooth decay. The occurrence of WSD and E is increasingly associated with the demineralising effect of acids that dissolve enamel minerals. Acids can have different similarities. This refers both to dietary acids found in food and drinks and to acids produced by bacteria. Together, additional conditions are created in the oral cavity (OC) to lower the OF pH. However, according to C.J. Goodacre *et al.* [4], regardless of the mechanism of development of non-carious cervical dental pathology, demineralisation represents the opposite process. Enamel is capable of reversible isomorphic replacement of its ions with saliva ions without destroying the crystal structure and dramatically changing its properties. This minimises its demineralisation and enhances remineralisation, which is carried out by OF, which is oversaturated with ions in relation to tooth enamel [5]. Therefore, saliva is considered as one of the important biological factors that has an intraoral neutralising effect on the action of acid. But this requires favourable conditions in the OC. First of all, the norm should be biophysical indicators of OF: salivation rate (SR), pH, and buffer capacity [6]. The role of other local aetiological factors is actively discussed in contemporary discourse. Increasing attention is being paid to the link between dental occlusion, temporomandibular disorders, parafunctional habits, and non-carious cervical lesions of the teeth. But research findings are sometimes contradictory. Thus, G.A. Fontelle *et al.* [7] did not determine the existence of a significant association between the presence of parafunctional habits (bruxism), stress, and the occurrence of dental pathology in young patients.

The influence of common factors on the appearance of cervical lesions of the teeth has also been proven. Special attention should be paid to the socio-economic and behavioural characteristics of the patient [8-9]. Other variables, such as the region of residence, are likely to influence the occurrence of WSD and E of tooth enamel [10]. Therefore, only a combination of various local and general factors can be crucial in the aetiopathogenesis of non-carious cervical dental pathology. Therefore, timely identification of individual predictors that have a significant impact on the occurrence of dental lesions will minimise their negative impact and include specific measures in a personalised prevention plan. However, this requires a detailed analysis of potential predictors. Most of them have specific consequences in different age groups. The most vulnerable, according to G.A. Fontelle *et al*. [7], are patients over the age of 30. This makes it relevant to determine predictors in young patients and separately consider the factors of their occurrence and progression for WSD and E of tooth enamel. The purpose of the study was to identify predictors of the occurrence and progression of WSD and E of tooth enamel in young patients, their detailing, and further analysis.

MATERIALS AND METHODS

Prim.ary data on potential predictors were collected during a survey of 272 patients (174 women and 98 men) with an average age of 24.3 ± 6.9 years, which included: review of the OC, assessment of the state of hard tissues of teeth, periodontal and hygiene levels, diagnosis of clinical symptoms of musculoskeletal dysfunction of the temporomandibular joint (TMJ) according to the Helkimo Clinical Dysfunction Index (HCDI) [11]; determination of biophysical indicators unstimulated OF (pH and buffer capacity using pH meter AZ-8689 in C.U., SR in mL/min) [12]. The psychoemotional state of the subjects was determined by the level of personal anxiety according to questionnaire by C.D. Spielberger *et al.* in the adaptation of Yu.L. Khanin [13]. A questionnaire was also conducted on the developed "Patient questionnaire/survey", which contained information on self-assessment of parafunctional, dietary, and hygienic habits; the most common complaints about systemic health and the list of diseases according to the International Classification of Diseases, 10th Revision. The criteria for inclusion in the study were young age according to the WHO classification (2016), absence of alcohol and drug addiction, neoplasms, tuberculosis, HIV/AIDS, hepatitis C, mental disorders, pregnancy and lactation, occupational hazards, and written informed consent to participate.

Statistical processing of the source data was performed using Microsoft Excel 2016 spreadsheets (Microsoft Corp., USA) and the Python 3.12 programming language. Univariate analysis (2x2 conjugacy tables) and logistic regression with L1 regularisation (LASSO) were used to determine predictors as the main method of multivariate analysis and the most effective machine learning model according to contemporary researchers [14-15]. LASSO regression models included all variables that had clinical substantiation for inclusion (n = 84). Calculations in Python 3.12 were performed using the pandas libraries for data processing, numpy for numerical calculations, statsmodels for evaluating univariate associations, and scikit-learn for building a LASSO logistic regression model. For each factor, two methods were used to calculate the odds ratio (OR) with the determination of 95% confidence intervals (95% CI) based on the standard error. A factor was considered significant if the CI did not include 1. Multicollinearity control between selected predictors was performed using variance inflation factor (VIF). Values VIF < 5 were considered acceptable. CI for OR in LASSO models was determined by bootstrap resampling (1,000 iterations, percentile method). The stability of variable selection was estimated as the proportion of bootstrap iterations in which the predictor received a

non-zero coefficient and was considered stable under the condition ≥80%.

When analysing the primary data, the presence or absence of a variable and its individual characteristics were taken into consideration. For quantitative indicators, the average values among all respondents were taken as the limit values (n = 272). No additional threshold setting was performed for binary variables (0/1). Analysis of potential predictors of dental pathology progression was performed separately on a subset of patients with WSD (n = 60) and E of tooth enamel (n = 15). Signs that characterise the progression of non-carious cervical lesions of the teeth included an increase in their number and depth in one patient, the appearance of symptoms of dentin hypersensitivity, which indirectly suggests the presence of a pathological process. Interpretation of the results obtained was carried out by the size of the OR, the width of the CI, and the direction of their change during the introduction of the control. The identified predictors were divided into independent (primary aetiological, which is significant in both logistic regression analyses with a change in OR of less than 20%) and latent (modifier factors, which are significant only in LASSO, their effect is manifested after confounder control) [16]. Change in OR of more than 20% was the threshold for establishing confounding [17]. The use of univariate and multi-factor regression analysis helped to simultaneously select the most informative predictors, reducing the coefficients of insignificant variables in the optimisation process to zero. Factors with fewer than 10 observations were excluded from the analysis. The quality of the models was determined by the area under the Receiver Operating Characteristic (ROC)-curve and sensitivity (recall) calculated by stratified cross-validation (CV). It was this approach that provided an unbiased assessment of data that was not used in training the model. For comparison, the Area under the curve (AUC)-ROC values in the training sample were additionally provided. The study was conducted in accordance with the ethical requirements, principles of the Declaration of Helsinki [18], and completely ruled out any compromise of the patient's interests or harm to their health (conclusion of the Bioethics Committee of Donetsk National Medical University No. 43 of 21.01.2021).

RESULTS AND DISCUSSION

The prevalence of cervical dental pathology was 43.3%. 22.1% of those examined (60 people) were diagnosed with WSD, and 5.5% (15 people) – tooth enamel erosion [19]. The restored teeth were not taken into consideration in the CR. Predictors of the occurrence of dental WSD determined by univariate and multivariate analyses are shown in Tables 1 and 2. Independent variables were SR less than 0.5 mL/min, hygienic habit of applying pressure to the toothbrush, and clinical markers: patient age of 25 and older, gingival recession, and impaired dentition integrity due to tooth extraction (Table 1).

The applying of pressure on a toothbrush was determined by the patient's self-assessment and confirmed by the history of its premature renewal due to changes in the appearance of the work surface: less than 30 days for medium bristle roughness and 45 days for stiff bristles [20]. Modifier factors were OF pH values less than 6.9 C.U., the hygienic habit of brushing teeth for three minutes or more, diet features, parafunctional habits (clenching teeth against the background of emotional stress and biting and/or licking the lip mucosa) and clinical markers (Table 2).

Table 1. Independent factors of dental WSD occurrence

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
OF indicators					
SR	30/50.0	2.12	1.18-3.79	1.23	1.09-1.38
Hygiene habits					
Applying pressure on the toothbrush	19/31.7	2.34	1.22-4.51	1.31	1.16-1.47
Clinical markers					
Age	27/45.0	4.0	2.15-7.45	2.95	2.62-3.32
Gingival recession	20/33.3	5.74	2.76-11.91	6.51	5.78-7.33
Extracted teeth	32/53.3	2.22	1.24-3.97	1.31	1.16-1.48

Note: n/% – number of patients with the corresponding variable and their percentage of the total number of patients with dental WSD
Source: compiled by the authors

Table 2. Hidden factors of dental WSD occurrence

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
OF indicators					
pH	40/66.7	1.50	0.82-2.75	1.48	1.31-1.67
Hygiene habits					
Duration of brushing teeth	25/41.7	0.90	0.50-1.60	0.86	0.77-0.97

Table 2. *Continued*

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
Dietary habits					
Consumption of yoghurt	10/16.7	0.76	0.36-1.63	0.89	0.79-1.00
Consumption of bananas	19/31.7	0.65	0.36-1.20	0.56	0.49-0.63
Consumption of tangerines	10/16.7	2.29	0.99-5.32	2.45	2.17-2.76
Fruit consumption	24/40.0	0.92	0.51-1.65	1.43	2.89-3.67
Parafunctional habits					
Habit of clenching teeth tightly	12/20.0	2.05	0.95-4.42	3.26	1.27-1.61
Biting and/or licking lips	11/18.3	1.18	0.56-2.49	1.65	1.46-1.85
Clinical markers					
TMJ musculoskeletal dysfunction	19/31.7	1.54	0.82–2.90	1.43	1.27-1.61
Occlusal tooth wear	39/65.0	1.75	0.97-3.18	1.41	1.25-1.58
History of teeth whitening	12/20.0	1.52	0.72-3.18	1.50	1.34-1.69

Source: ompiled by the authors

Among dietary preferences, the predictors were determined by the consumption of yoghurt, bananas, tangerines, fruits (citrus fruits, apples, kiwis in a total of 2.5 units or more). Clinical markers of the occurrence of dental WSD were musculo-articular dysfunction of the temporomandibular joint lasting more than a year, the presence of occlusal wear facets on the teeth, and a history of teeth whitening. The hygiene habit of "duration of brushing", and dietary features such as consumption of yoghurt and bananas, had OR < 1, indicating their potential protective role in the development of dental WSD. When all fruits were combined in the variable "fruit consumption", the univariate analysis determined OR = 0.92, which corresponds to a negative association with the study result. But in multivariate analysis, OR = 1.43, which indicates a predictor of the occurrence of dental WSD. A change in the direction of association after correction for other variables indicates the existence of confounding. Assessment of the quality of the LASSO model of the occurrence of WSD showed signs of overfitting: AUC-ROC in the training sample was 0.882, while in CV – 0.594 (95% CI (0.506-0.674)), indicating moderate discriminative ability (Table 3). Analysis of the stability of predictor selection by bootstrap resampling (1,000 iterations) confirmed the reliability of key factors: gingival recession was selected in 100% of iterations, patient age ≥25 years – in 97.4%, violation of the dentition integrity – in 79.8%. The hygienic habit of applying excessive pressure to the toothbrush had moderate stability (62.7%), and the OF values (pH – 75.0%, SR – 71.7%) corresponded to a moderate level of reproducibility of selection. Thus, independent predictors of dental WSD occurrence (Table 1) were confirmed as stable associations, while some modifier factors (Table 2) required verification in a larger sample.

Table 3. Quality indicators of LASSO models

Model	n	AUC-ROC training	AUC-ROC cross-validation (95% CI)	Recall
Occurrence of WSD	272	0.882	0.594 (0.506-0.674)	0.183
Increase in the number of WSD	60	0.977	0.662 (0.526-0.805)	0.600
Increase in the depth of WSD	60	0.947	0.404 (0.198-0.642)	0.959
Active WSD progression	60	0.935	0.317 (0.177-0.465)	0.419

Source: compiled by the authors

Factors of tooth enamel erosion were also identified. Independent variables were clinical markers: the presence of occlusal tooth wear and enamel cracks, which are diagnosed during visual examination of the vestibular surface of the teeth under natural and/or artificial lighting and drying. It was found that occlusal tooth wear in univariate analysis increased lice by 5.87 times (95% CI (1.30-26.56)), in multivariate analysis – by 1.24 times (95% CI (1.10-1.39)); enamel cracks on the vestibular surface of teeth increased OR by 5.87 (95% CI (1.30-26.56)) and 1.69 times (95% CI (1.50-1.90)), respectively. Modifier factors were OF pH values and the patient's medical history of brushing teeth before breakfast. Saliva pH values are less than 6.9 C.U. in the univariate analysis increased OR by 2.90 times (95% CI (0.80-10.52)), in the multivariate analysis – by 1.22 times (95% CI (1.08-1.37)); brushing teeth in the morning before meals increased OR by 2.05 (95% CI (0.68-6.16)) and 1.23 times (95% CI (1.09-1.38)), respectively. However, the broad CI determined for all predictors of enamel E occurrence in univariate logistic regression analysis, and the small number of examined teeth with this pathology (n = 15), are direct evidence of instability in the assessment. At the next stage of the study, predictors of dental WSD progression were considered. Only the factors of increasing the number of lesions were independent: age of 25 and older, male gender, and the presence of gum recession (Table 4).

Table 4. Predictors of an increase in the number of WSD

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
Independent					
Clinical markers					
Age	19/31.7	4.53	1.51-13.65	5.44	4.22-7.02
Gender	15/25.0	3.14	1.03-9.56	1.57	1.22-2.03
Gingival recession	16/26.7	7.14	1.99-25.59	4.25	3.29-5.49
Hidden					
Dietary habits					
Drinking green tea	11/18.3	1.29	0.44-3.80	1.58	1.23-2.04
Drinking black tea	10/16.7	0.54	0.19-1.53	0.51	0.40-0.66
Anatomical features					
Crowding of teeth	17/28.3	0.80	0.28-2.26	0.66	0.51-0.85

Source: compiled by the authors

Hidden factors for increasing the number, depth, and active progression of WSD were diet characteristics, the presence of crowding teeth, the hygienic habit of applying pressure to the toothbrush, and clinical markers. Some of them corresponded to predictors of the occurrence of WSD (the patient's age was 25 years and older, the presence of gingival recession and extracted teeth, applying of pressure on the toothbrush). Age and male gender were factors that simultaneously significantly affected both the increase in the number and depth of lesions in CR. The average daily consumption of green tea more than one cup was variable, which simultaneously increased the number of teeth with WSD and contributed to the active progression of pathology. Both hidden factors of increasing depth of WSD in teeth (Table 5), in univariate analysis, had wide confidence intervals crossing unity, and were not statistically significant. This is a consequence of limited statistical power.

A sub-sample of patients with WSD (n = 60), among whom only a fraction had a progression of lesion depth, was insufficient to identify predictors with moderate effect (OR ~ 1.5-3.0) in a univariate analysis. The multi-factor LASSO model, which simultaneously considers all variables, has a higher sensitivity to such effects, which helped to identify an independent contribution of age and gender. This is why these predictors were classified as hidden rather than independent. Among the hidden factors of the active WSD progression, such a dietary habit as "consuming sour foods" in a daily amount of more than 0.25 of the average serving size was identified (Table 6).

Table 5. Hidden factors of increasing the depth of dental WSD

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
Clinical markers					
Age	25/41.7	4.17	0.80-21.64	2.74	2.12-3.54
Gender	20/33.3	2.76	0.53-14.38	1.51	1.17-1.95

Source: compiled by the authors

Table 6. Hidden factors of the active WSD progression

Variables	n/%	OR	(95% CI)	OR	(95% CI)
		univariate analysis		multivariate analysis	
Hygiene habits					
Applying pressure on the toothbrush	12/20.0	1.89	0.62-5.81	1.68	1.30-2.17
Dietary habits					
Drinking green tea	14/23.3	3.02	0.96-9.51	2.13	1.65-2.76
Drinking tea with lemon	10/16.7	3.97	0.96-16.33	1.64	1.27-2.12
Consumption of sour foods	15/16.7	2.34	0.80-6.91	1.67	1.29-2.16

Note: foods containing vinegar were considered "sour"
Source: compiled by the authors

Variables such as black tea consumption of more than one cup per day and the presence of crowding teeth had OR < 1, indicating their potential protective role in the progression of dental WSD. Among the identified hidden predictors of the active WSD progression, the greatest effect was demonstrated by the consumption of green tea (OR = 2.13). Applying pressure to the toothbrush (OR = 1.68), drinking lemon tea, and

sour foods (OR = 1.64 and OR = 1.67, respectively) had approximately the same OR values. The difference between the hidden factors of the active WSD progression (Table 6) was that they contained one within the CI interval in univariate analysis, while they did not include one in multivariate CI. This is conditioned by the fact that in a subset of patients with dental WSD, the influence of dietary preferences and the hygiene habit of applying pressure to the toothbrush is masked by stronger predictors and only becomes statistically significant after including a control variable in the LASSO model. The small absolute size of the variables in the sub-sample (patients who consumed green tea had n = 14, lemon tea – n = 10) limited the statistical significance of the univariate analysis. That is why these factors were classified as hidden. The conducted study determined that saliva pH values less than 6.9 C.U. as an independent predictor of the active course of tooth enamel E: in univariate analysis, they increase OR by 29.4 times (95% CI (1.12-772.42)), in multivariate analysis – by 2.47 times (95% CI (1.49-4.10)). Broad CI in univariate analysis indicates instability of the estimate. Other variables that were determined by predictors of the progression of tooth enamel erosion in the subjects were excluded from the analysis, since the number of observations was less than 10. The analysis of factors of occurrence and active course of e enamel due to the small size of the sub-sample (n = 15) is pilot in nature; the corresponding models showed signs of retraining (AUC-ROC training 0.961 and 1.000, respectively) at zero sensitivity and CV, which makes it impossible to interpret them meaningfully. Therefore, the resulting OR and CI reflect associations in the sub-sample under study and can be considered as research hypotheses rather than final prognostic estimates. The results of the study complement the information on the multifactorial aetiopathogenesis of non-carious cervical lesions of teeth [21-22].

The patient's age determined as an independent factor in the occurrence of dental WSD corresponds to the observations of G.A. Fontelle *et al.* [7], L. Sakhabutdinova *et al.* [10] and V. Kolak *et al.* [23]. The results also highlight the significant role of the biophysical properties of OF in the development and progression of non-carious cervical dental pathology. According to V. Kolak *et al.* [23], lower saliva pH values are observed in patients with multiple (≥3) non-carious cervical lesions of teeth. It is known that individual OF characteristics can change the relationship between dietary characteristics and wear of hard tooth tissues [24]. D.W. Bartlett *et al.* [21] and M. Nascimento *et al.* [25] proved the effect of fresh fruit on the appearance of non-carious cervical dental pathology in young patients. According to V. Kolak *et al.* [23], special attention should be paid to the excessive consumption of citrus fruits. The study found that the addition of tangerines to the diet is a hidden predictor of the occurrence of WSD. It is impossible to confirm or refute the potential protective role of banana consumption, as the authors were unable to find any studies in the available literature that examined the effect of this dietary habit on the development of non-carious cervical lesions of the teeth. Therefore, direct comparison of the results obtained is limited. When citrus fruits, apples, and kiwis were combined into the "fruit consumption" variable, it ceased to be a significant factor in the occurrence of WSD in the univariate analysis. However, after recording other variables with higher OR scores in the multivariate logistic model (patient age, presence of gingival recession), a significant association with increased risk was determined. Therefore, these confounders simultaneously affect both the frequency of fruit consumption and the risk of dental WSD. This is probably conditioned by the fact that the relationship between dietary characteristics and the severity of tooth wear is not direct and is influenced by many other variables [24]. The use of yoghurt containing probiotics helps to reduce the number of pathogens in OC, and thus its addition to the diet prevents enamel demineralisation [26]. Research conducted by H. Aidi *et al.* [27] showed that yoghurt consumption was negatively associated with the frequency of erosive tooth wear. This may well explain the protective effect that this dietary factor has on the development of dental WSD. In addition to food preferences, the habit of brushing teeth plays an important role in the appearance, distribution, and structure of cervical dental pathology. Simultaneously, the technique of brushing teeth has a greater impact [22]. B. Hamza *et al.* [28] also drew attention to the application of pressure on the toothbrush as a potential predictor of non-carious cervical lesions of the teeth, which was confirmed by the conducted study. Mechanical injury to the hard tissues of the teeth during brushing, according to M. Dioguardi *et al.* [3], determines the pathological picture of non-carious lesions, which is clinically manifested by wear. According to V. Grover *et al.* [29], manual brushes have a greater negative effect on teeth compared to electric brushes. In addition, the traumatic technique of brushing teeth can become one of the reasons for a certain other independent factor in the occurrence of dental WSD – gingival recession, which was confirmed in the paper by M.A. Cassini *et al.* [30]. According to F.F. Demarco *et al.* [31], gingival recession is a significant clinical indicator of the presence of non-carious cervical lesions of the teeth, as shown by the conducted study.

One of the hidden predictors of the development of tooth enamel erosion was the patient's history of brushing teeth before breakfast. The authors are only aware of one study by D.W. Bartlett *et al.* [21], in which waiting after breakfast before brushing did not significantly affect the degree of tooth wear. But the specifics of dietary and hygienic habits can explain

only a part of cases of non-carious cervical lesions of the teeth [24]. The significant role of parafunctions (clenching teeth tightly and biting nails) and TMJ musculoskeletal dysfunction in their aetiopathogenesis has been proven [32]. The researchers also identified the habit of clenching teeth strongly against the background of emotional stress as hidden predictors of the occurrence of WSD, in addition – biting and/or licking the lip mucosa. But there are also studies that have not revealed the existence of such a relationship [25]. Non-carious cervical pathology of teeth is clinically manifested by facets of occlusal wear, which are significantly more often detected in patients with hyperfunction of the masticatory muscles. This was confirmed in the study by T.S. Carvalho *et al.* [33], which showed that tooth wear and gingival recession are the result of the combined action of many different factors on hard tissues. Enamel cracks are also considered precursors of non-carious pathology [20, 34]. Occlusal wear and cracks are clinical markers of occlusal stress for both WSD and E of tooth enamel [2]. In the case when all occlusal factors were combined, their presence increased the OR of the occurrence of non-carious cervical dental pathology by 4.38 times [35]. M. Giller *et al.* [36] confirmed the existence of a link between occlusal wear and the size of non-carious cervical lesions of the teeth. But clinical practice shows that not all patients with non-carious cervical dental pathology are diagnosed with occlusal wear and vice versa [7, 25]. Using the logistic regression method, R.D. Werneck *et al.* [37] found no correlation between the appearance of WSD and E of tooth enamel and occlusal strength, and with aspects related to brushing and bad habits. But it is important to distinguish physiological changes in the hard tissues of teeth from pathological processes [33]. This distinction should be the basis for making a decision on dynamic monitoring of a patient with non-carious dental lesions. The study found that the presence of extracted teeth is an independent predictor of the occurrence of dental WSD. This was confirmed in the study by D.S. Ramsay *et al.* [24], in which subjects with fewer teeth had a higher chance of hard tissue wear in CR. According to D.C. Penoni *et al.* [38], the average number of non-carious cervical lesions was higher in those individuals with fewer teeth in the OC. As a therapeutic and preventive measure, it was proposed to monitor the condition of CR teeth for at least six months before planning invasive procedures [25]. It is during this period that the OC health of young patients and their quality of life in general can be improved by making significant changes in behavioural habits and treating gingival recession [39]. Restoration of teeth with non-carious pathology should not be considered as a preventive measure to stop the progression of the lesion. Thus, the development of non-carious cervical lesions of the teeth is a multifactorial process due to the interaction of occlusal, behavioural, and hygienic factors, parafunctions and the number of teeth in the oral cavity. Preventing their progression requires a comprehensive risk assessment and dynamic monitoring.

CONCLUSIONS

1. Combination of methods of single- and multivariate logistic regression analysis determined statistically independent and hidden predictors of the occurrence and progression of WSD and E of tooth enamel, and potentially protective factors and a factor with confounding.

2. Independent predictors of WSD occurrence were SR less than 0.5 mL/min, hygienic habit of applying pressure to the toothbrush, age of 25 and older, the presence of gingival recession and extracted teeth. Hidden predictors of WSD development were OF pH values less than 6.9 C.U., dietary, hygienic, and parafunctional habits, clinical markers (duration of temporomandibular joint musculoskeletal dysfunction exceeding one year, presence of occlusal tooth wear, and a history of tooth whitening). Potentially protective variables were variables with OR < 1: brushing teeth for three minutes or more, consumption of yoghurt and bananas. Confounding was identified for the "fruit consumption" predictor. A larger number of dental WSD progression factors were hidden and had broad CI in univariate logistic regression analysis.

3. Pilot analysis of predictors of the occurrence of enamel E identified as independent factors the presence of occlusal tooth wear and enamel cracks, which are diagnosed during visual examination of the vestibular surface under natural and/or artificial lighting and drying; modifier factors – OF pH values of less than 6.9 C.U. and the habit of brushing teeth before breakfast. Saliva pH values are less than 6.9 C.U. were the only detectable predictor of enamel erosion progression that was independent in the number of observations greater than 10. However, broad CI in univariate regression analysis indicates instability in the assessment and prematurity of the results for E of tooth enamel and the need for their confirmation in studies on larger samples.

Limitations of the study. A methodological limitation was the insufficient number of cases of enamel E (n = 15) for multivariate analysis. The inclusion of a significant number of variables (n = 84) in relatively small sub-samples (60 cases of WSD and 15 cases of enamel E) created conditions for retraining LASSO models, which was confirmed by comparing AUC-ROC in the training sample and in CV. There were also limitations in the accuracy of information collected by the questionnaire method. Some differences between the results obtained and the well-known ones were related to the age of the subjects, their socio-economic characteristics, region of residence, etc.

Prospects for further research. In order to provide personalised dental care to patients with non-carious cervical lesions of teeth and a more complete

analysis of the predictors of their occurrence and progression in the future, it is planned to use combined approaches that integrate classical statistical methods with nonlinear machine learning algorithms on a reduced set of primary aetiological predictors with verification on an independent sample. A separate task is to increase the subsample of patients with tooth enamel erosion to confirm the experimental results obtained.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Ірина Заболотна

Кандидат медичних наук, доцент
Донецький національний медичний університет
25031, вул. Юрія Коваленка, 4-А, м. Кропивницький, Україна
https://orcid.org/0000-0002-3284-0392

Тетяна Богданова

Кандидат педагогічних наук, доцент
Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського»
03056, просп. Берестейський, 37, м. Київ, Україна
https://orcid.org/0000-0001-5501-132X

Визначення предикторів некаріозних пришийкових уражень зубів методом логістичного регресійного аналізу

Анотація

Актуальність. Некаріозні пришийкові ураження зубів залишаються другою після карієсу та його ускладнень причиною звернення до стоматолога.

Мета. Визначення предикторів виникнення і прогресування клиновидного дефекту (КД) та ерозії (Е) емалі зубів у пацієнтів молодого віку.

Матеріали та методи. Були обстежені 272 пацієнта (середній вік 24,3 ± 6,9 роки), в яких потенційні предиктори були зібрані під час огляду та методом анкетування. Для аналізу сили асоціації між чинниками та наслідком був використаний показник відношення шансів (ВШ) у межах 95 % довірчого інтервалу (ДІ). Для встановлення предикторів був застосований однофакторний і багатофакторний логістичний регресійний аналіз.

Результати. Незалежними предикторами виникнення КД були швидкість слиновиділення менша за 0,5 мл/хв, гігієнічна звичка прикладати тиск на зубну щітку, вік 25 років і старше, наявність рецесії ясен і видалених зубів. Прихованими предикторами розвитку КД були показники pH ротової рідини (РР) менші за 6,9 ум. од., поведінкові фактори, клінічні маркери. Потенційно захисними були змінні з ВШ < 1: тривалість чищення зубів протягом трьох хвилин і більше, вживання йогурту та бананів. Для предиктору «вживання фруктів» було визначено існування конфаундингу. Незалежними предикторами виникнення Е емалі були наявність оклюзійної стертості зубів і тріщин емалі; факторами-модифікаторами – показники pH РР менші за 6,9 ум. од. і звичка чистити зуби до сніданку. Але широкі ДІ, визначені для усіх предикторів появи Е емалі при однофакторному логістичному регресійному аналізі, а також незначна кількість спостережень вказують на попередність результатів та необхідність їх підтвердження. Більшість предикторів прогресування некаріозних пришийкових уражень зубів були прихованими та мали широкі ДІ при однофакторному логістичному регресійному аналізі, що свідчить про нестабільність оцінки та потребує подальших досліджень на більших вибірках.

Висновки. Використання методу логістичного регресійного аналізу дозволило визначити статистично незалежні та приховані предиктори, які рекомендовано враховувати при діагностиці та складанні плану лікування некаріозних пришийкових уражень зубів у пацієнтів молодого віку.

Ключові слова: ерозія; клиновидний дефект; дієтичні та гігієнічні звички; ротова рідина; тріщини.

THERAPY AND REHABILITATION

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 615.8:616.711.6-007.43-057.36-036.82
DOI: https://doi.org/10.32345/2664-4738.2.2026.09

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 18.12.2025 Revised: 21.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Vitalii Visych
Student
National University of Pharmacy
61002, 53 Hryhoriy Skovorodf Str., Kharkiv, Ukraine
https://orcid.org/0009-0009-0447-6210

Ganna Tamozhanska
PhD in Pedagogical Sciences, Associate Professor
National University of Pharmacy
61002, 53 Hryhoriy Skovorodf Str., Kharkiv, Ukraine
https://orcid.org/0000-0003-2430-8467

Nataliia Seliukova*
Doctor of Biological Sciences, Associate Professor, Senior Researcher
National University of Pharmacy
61002, 53 Hryhoriy Skovoroda Str., Kharkiv, Ukraine
https://orcid.org/0000-0001-9657-6888

Olha Svierchkova
PhD in Physical Education and Sports Sciences, Senior Lecturer
Kharkiv State Academy of Physical Culture
61058, 99 Klochkivska Str., Kharkiv, Ukraine
https://orcid.org/0000-0001-9987-6405

Vitalii Ivanov
Lecturer
National University of Pharmacy
61002, 53 Hryhoriy Skovoroda Str., Kharkiv, Ukraine
https://orcid.org/0009-0002-4442-8001

Features of physical therapy for lumbar hernias in military personnel during the late stage of rehabilitation

Abstract

Relevance. This study addresses the issue of rehabilitation for military personnel with lumbar disc herniation, which poses a critical challenge due to high levels of physical exertion and combat stress.

Aim. To investigate the effectiveness of manual therapy as a means of correcting the psychoemotional state and improving the quality of life of such patients within a long rehabilitation cycle.

Materials and methods. The study involved 30 military personnel (23 men and 7 women), randomised into two groups: basic (manual therapy + exercise (MT)) and control (exercise only + sham mobilisation (EX)). The assessment was performed using a number of tools: the McGill-Melzack Pain Questionnaire (pain), the HADS (anxiety/depression), the Tampa Scale of Kinesiophobia (kinesiophobia), the PCS (pain catastrophisation), and the Nottingham Health Profile (quality of life). Patients' condition was assessed in three stages: before treatment (T1), after a 5-week course (T2), and after three months of follow-up (T3).

Results. At baseline, the groups were homogeneous, although the MT group had higher levels of pain and catastrophisation. After the course (T2), both cohorts showed significant progress: in the MT group, pain intensity halved and quality of life improved by 64.1% (compared to 36.8% in EX). Only the MT group had a statistically significant reduction in anxiety and depression (49.2%) with a high effect size (0.432). Furthermore,

Suggested Citation:
Visych V, Tamozhanska G, Seliukova N, Svierchkova O, Ivanov V. Features of physical therapy for lumbar hernias in military personnel during the late stage of rehabilitation. Med Sci Ukr. 2026;22(2):76–87. DOI: https://doi.org/10.32345/2664-4738.2.2026.09

*Corresponding author (*selyk3@gmail.com*)

in this group, the effect size for reducing pain catastrophisation (0.571) was twice that of the EX group (0.256). However, at the T3 stage, different trajectories were found: in the MT group, partial regression of results occurred, while the EX group showed a prolongation of the effect with a stable improvement in quality of life by 54.8%. Therefore, manual therapy is effective for rapid psychoemotional stabilisation, and physical exercises are effective for maintaining a long-lasting analgesic result.

Conclusions. Manual therapy is an effective tool in the comprehensive rehabilitation of service personnel, as it not only helps to reduce the intensity of pain but also successfully overcomes psychological barriers, such as fear of movement and depressive states. To achieve the most sustainable functional well-being, it is recommended to integrate manual techniques into long-term physical training programmes.

Keywords: kinesiotherapy; functional recovery; combatants; herniated disc; manual therapy; quality of life; kinesiophobia; psychoemotional state.

INTRODUCTION

In the context of a full-scale war in Ukraine, the rehabilitation of military personnel with lumbar hernias is a strategic challenge for the healthcare system. Combat-related factors – carrying heavy equipment, vibrations in armoured vehicles, and blast waves – contribute to the development of complex spinal pathologies, where intense pain is combined with profound psycho-emotional exhaustion, thereby threatening the combat readiness of personnel. Limited access to long-term inpatient treatment and the need for rapid recovery of personnel require the introduction of effective, mobile, and evidence-based physical therapy protocols. Of particular importance are integrated methods that allow simultaneously restoring the biomechanical integrity of the spine and levelling cognitive barriers to rehabilitation (kinesiophobia, post-traumatic stress), which is critical for preserving the human potential of the Defence Forces of Ukraine.

Contemporary scientific periodicals define lumbar hernias as a critical medical and social challenge that causes somatic deficits and a decrease in the quality of life of patients. J. Xu *et al*. [1] proved that the combination of manual manipulation with musculoskeletal modelling effectively restores the biomechanics of the spine. T. Ranger *et al*. [2] emphasised the inextricable link between chronic pain and psychological comorbidity, noting that ignoring mental disorders negates the results of physical therapy. Confirming this, D. Yi *et al*. [3] indicated that anxiety and depressive symptoms are a direct consequence of chronic pain syndrome. Such psychoemotional deviations create a pathological circle that significantly slows down the process of functional recovery. In the context of ongoing military operations, this issue is becoming an extremely pressing one for Ukraine's Defence Forces. Constant excessive axial loading, prolonged maintenance of antalgic or non-physiological postures, and mine-blast injuries and concussions, significantly contribute to the development of intervertebral disc herniation. For a serviceman, this pathology is transformed into a complex destructive factor: it not only limits combat capability, but also synergistically interacts with combat stress and post-traumatic stress disorder (PTSD). This leads to a high risk of chronic pain and depressive states, which dictates the need to implement integrated rehabilitation strategies aimed at simultaneously correcting physical and psychoemotional status.

The phenomenon of kinesiophobia, manifested as an irrational fear of physical activity, is a common comorbid condition in chronic low back pain, which in clinical practice is regarded as an unfavourable predictor that impedes the trajectory of recovery. C. de Freitas *et al*. [4] in their study proved that targeted physical therapy has a significant effect on the reduction of kinesiophobia; they concluded that overcoming this psychological barrier is a key condition for restoring motor functions. For military personnel, this task is strategically important, since their professional fitness directly correlates with successful integration into physical activity. According to the principles of the biopsychosocial model, pain intensity and the degree of disability are viewed as the outcome of a non-linear interaction between somatic and mental factors. In particular, W. Lu *et al*. [5], analysing risk factors in lumbar pathologies, showed that psychosocial determinants and structural features of spinal lesions have a dominant effect on the transformation of acute pain into chronic pain. Their data confirmed that a high level of psychological distress acts as a barrier that significantly limits the therapeutic potential of any analgesic measures.

The contemporary therapeutic strategy for lumbar hernias is differentiated into surgical intervention and conservative correction, which aims to restrain degenerative processes and improve the patient's quality of life. Analysing the structure and demand for such non-surgical measures, W.-J. Lee *et al*. [6] in their paper, based on large-scale surveys, demonstrated that the multimodal approach (which includes physical therapy, counselling, pharmacotherapy, and hardware treatment) is an economically and clinically justified basis for recovery, allowing most patients to avoid invasive surgery. Manual therapy occupies a special place amongst these treatments, as it is aimed at relieving pain, optimising myofascial tone and restoring joint mobility. Specifically, in their randomised clinical trial, B. Taşkaya *et al*. [7] concluded that the use of targeted manual techniques (such as high-speed impulse manipulation and soft rhythmic mobilisation) has a

powerful positive effect not only on somatic indicators, but also on psychological factors and the quality of life of patients with herniated discs, providing rapid improvement in joint play and reducing the level of distress.

Current scientific data show a clear correlation between the presence of hernias in the lumbar spine, the intensity of pain, and the development of anxiety and depressive states. In particular, Y.-C. Kao *et al*. [8] in their study confirmed a direct link between depressive disorders and chronic lower back pain resulting from disc degeneration, and pointed out that this pathology acts as a powerful destructive factor. In turn, M. Roiha *et al*. [9] concluded that the development of a hernia significantly limits the quality of life of patients, but timely elimination of the compression factor allows achieving favourable long-term results in restoring their overall well-being. In addition to the proven effect on pain intensity and functional state, manual therapy is highly effective in stabilising the psychological status of patients. Thus, in a randomised clinical trial, M. Danazumi *et al*. [10] proved that the use of spinal manipulation and mobilisation as an adjunctive treatment significantly accelerates the relief of radicular pain and improves the psychological and emotional well-being of patients with lumbar hernias. This opinion is shared by B. Cao *et al*. [11], who in their study indicated that the integration of conventional manual techniques has a pronounced therapeutic effect on alleviating the symptoms of depression and optimising the subjective assessment of quality of life due to the effective elimination of spinal dysfunctions. Additionally, C. Gong *et al*. [12], comparing different concepts of spinal mobilisation, concluded that targeted manual treatment provides a stable analgesic effect and improves the psychosomatic status of patients with chronic lumbalgia.

In the contemporary scientific literature, there is a certain shortage of comprehensive studies analysing the effectiveness of manual techniques in the context of psychological rehabilitation and improving the quality of life in spinal pathologies. Since the consequences of a herniated disc in the lumbar spine go beyond purely physical discomfort, affecting the emotional and social spheres, recovery strategies should be multi-modal in nature. Effective rehabilitation of patients with low back pain should focus on systemic correction of the state of health according to the biopsychosocial model, ensuring comprehensive functional restoration. The purpose of the study was to investigate the effectiveness of manual therapy as a means of improving the psychological and emotional well-being and quality of life of military personnel with lumbar disc herniation as part of a prolonged rehabilitation programme.

MATERIALS AND METHODS

To achieve this goal, a comprehensive methodological approach was applied, including theoretical analysis of professional literature and systematic collection of anamnestic data. The functional status was assessed in accordance with the principles of the International Classification of Functioning, Disability, and Health (ICF). The sensory-discriminatory and emotional-affective characteristics of the pain syndrome were assessed using the McGill Pain Questionnaire (SF-MPQ-2) [13]. The respondents' psychoemotional state was analysed on the Hospital Anxiety and Depression Scale (HADS) [14]. The degree of motor limitations and cognitive distortions was assessed using the Tampa Kinesiophobia Scale (TKS) and the Pain Catastrophisation Scale (PCS), respectively [15, 16]. The level of subjective well-being and integral quality of life indicators were determined using the Nottingham Health Profile (NHP) [17].

The study design involved the collection of demographic data and a multi-faceted assessment of the respondents' pain status, psycho-emotional profile, and overall quality of life. Dynamic monitoring of parameters was carried out at three time points: pre-test before the start of the intervention (T1), post-test immediately after completion of the therapeutic course (T2), and follow-up assessment after a three-month interval (T3). The initial phase included verification of clinical diagnoses and recording of anthropometric characteristics (gender, age, height, weight), followed by calculation of body mass index (BMI). Randomisation of the sample into two equivalent groups was performed on a 1:1 basis using the closed opaque envelope method. In order to minimise the subjective impact on the results, a "blind" distribution method was used, in which participants were not informed about belonging to a specific group.

The study sample was differentiated into the main group where manual therapy (MT) was used, and the control group with exercise (EX). Participants in the EX group performed a programme of stabilising gymnastics in combination with sham (placebo) mobilisation, while in the MT group, an identical set of exercises was supplemented with authentic techniques of manual spinal correction. The physical therapy programme applied for both groups lasted 5 weeks, included 10 practical sessions conducted under the direct supervision of a specialist with a frequency of twice per week (each session lasting 45-60 minutes). After completing the active phase (point T2), participants in both cohorts switched to the mode of self-performing regulated complexes at home (lasting 30 minutes daily) until the final cut (point T3). Continuous monitoring of patients' adherence to the therapeutic programme and correction of motor mode were provided by weekly remote telephone assistance and self-monitoring diaries. The total number of respondents who completed the full cycle according to the inclusion criteria was 30 (23 men and 7 women). The strict study protocol provided for the complete refusal of participants to use analgesic drugs during the entire period of therapeutic exposure.

The study was conducted at the rehabilitation units in Kharkiv in 2025. The study group was formed according to the following inclusion criteria: MRI-confirmed diagnosis of hernias established by a specialist; chronic lumbalgia (lasting >8 weeks) with an intensity of 3 points for VAS; lack of physical therapy courses during the last 6 months; age range 18-65 years. The exclusion criteria were: a history of spinal surgery; systemic autoimmune, oncological, or inflammatory diseases; structural deformities (spondylolisthesis, fractures); severe concomitant pathologies (cardiovascular disorders, stroke); specific neurological complications (ponytail syndrome), and pregnancy status.

The study protocol, experimental design, participant selection criteria, and patient information sheets and written informed consent forms, were reviewed in advance, expert evaluated, and officially approved by the Bioethics Commission of the National University of Pharmacy (Protocol No. 4, dated 15 October 2025). The study was conducted in accordance with the ethical principles of the WMA Declaration of Helsinki and Law of Ukraine No. 2801-XII [18, 19]. All participants were thoroughly acquainted with the terms of the programme in written and oral forms, after which they confirmed their participation by signing an informed consent. The questionnaire was completed by the patients themselves, in accordance with confidentiality guidelines. The study was conducted in accordance with the ethical standards of the American Sociological Association's Code of Ethics [20]. Mathematical and statistical processing of the obtained results was carried out using the SPSS v. 25 software suite. In the previous stage, the data distribution was tested for compliance with the normal distribution by calculating the skewness and kurtosis coefficients (considering a reference interval of ±1.5). Intergroup comparison of nominal (demographic) indicators was performed using Pearson's χ^2 criterion, while Student's t-test for independent samples was used to analyse quantitative values on the MMPQ, HADS, TKS, PCS, and NHP scales. Estimation of the time transformation of parameters at three observation stages (T1, T2, T3) was performed by the method of variance analysis (ANOVA) with repeated measurements. To clarify the nature of the changes observed, a post-hoc comparison procedure was applied using the least significant difference (LSD) criterion. Results were considered statistically significant at a significance level of $p < 0.05$ and a 95% confidence interval.

The authors state that the opinions expressed in the submitted paper are their own, and do not represent the official positions of their institution.

RESULTS

The basis for developing a personalised physical therapy strategy was the development of a categorical profile of each participant. The latter was structured in accordance with the ICF methodology using a unified basic set of domains (Fig. 1). The model used not only identified the existing physical deficit, but also ensured a comprehensive approach to all components of the patient's biopsychosocial status throughout the long-term rehabilitation period.

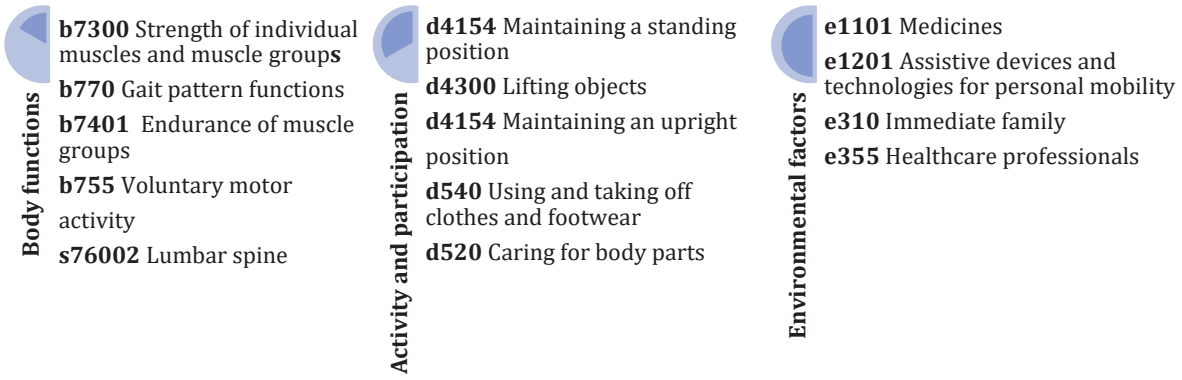

Figure 1. Categorical profile of ICF patients

Source: compiled by the authors

The use of the ICF categorical profile helped to implement the SMART goal strategy through a multimodal programme that combined manual spinal mobilisation and progressive strength training. In the short-term stage (1-2 weeks), efforts focused on pain relief, eliminating protective muscle spasms, and overcoming kinesiophobia through training in safe biomechanics of movement. Long-term goals (4-8 weeks) included restoring walking tolerance, forming a stable muscular corset to stabilise the spine, and gradually returning to military professional duties in compliance with ergonomic standards to compensate for structural changes.

The rehabilitation protocol for the EX group included a combination of stabilisation gymnastics with sham mobilisation, while in the MT group, a similar set of exercises was supplemented with authentic manual techniques. The course lasted five weeks and consisted of 10 sessions (twice a week), after which patients

switched to independent home exercises until a three-month catamnestic examination. To ensure adherence to therapy and monitor exercise performance, the researchers conducted weekly remote monitoring by telephone assistance.

The stabilisation training system was aimed at restoring the muscular corset and ensuring long-term stabilisation of the spine by maintaining the functional capacity of the "neutral zone". The main focus shifted to isolated and synergistic activation of the deep core muscles – the transverse abdominis muscle (m. *transversus abdominis*) and multi-split muscles (mm. *multifidi*). The programme was implemented in three stages with a progressive level of difficulty (Table 1), where the transition to the next phase took place only under the condition of full technical control over the movements of the previous level, the absence of pain, and maintaining a neutral position of the spine.

Table 1. Stabilisation training exercises

Phase	Purpose and functional tasks	Composition of exercises
Phase 1 Cognitive (local)	Activation of deep stabilisers in a neutral position, differentiation of local and global muscles	⬡ Local muscle activation ⬡ Stretching of the piriformis muscle ⬡ Torso rotation left/right ⬡ Correction of the neutral position of the lower back
Phase 2 Dynamic stabilisation	Strengthening stabilisers during limb movements, developing coordination between local and global muscle groups	⬡ Hip and knee flexion while lying down ⬡ One-legged bridge ⬡ Diagonal lifts of the limbs lying on the stomach ⬡ "Bird-Dog" exercise (diagonal limb lifts in quadruped position)
Phase 3 Functional (progressive)	Improving balance, stability, and proprioception when integrated into complex functional movements on unstable supports	⬡ Mini squats in a vertical stance ⬡ Fitball leg extension ⬡ Side bridge using a ball ⬡ Knee extension with resistance (expander) in a quadropedal position

Source: compiled by the authors

Within the manual therapy block, techniques of grade 4 passive mobilisation according to the Maitland concept were applied. Manipulations were performed with a series of low-amplitude rhythmic movements at the limit of the available activity range, observing the individual threshold of pain sensitivity of the patient (Table 2).

Table 2. Manual therapy practices

Mobilisation techniques	Patient's position	Dosage	Execution technique and manual contact
1	2	4	3
Anterior-posterior mobilisation	Lying on the stomach (prone)	Each lumbar vertebra: 20 repetitions	The ulnar border of the hand is placed over the spinous process of the vertebra, while the other hand reinforces the grip. Pressure is applied vertically downwards with straight elbows (low-speed rhythmic presses)
Rotary mobilisation	Lying on the side (painful side up)	20 repetitions for each side	Hip and knee are bent at 90°, the lower leg is straightened. One arm stabilises the shoulder, the other on the wing of the ilium. Rotational force is created by pressure on the pelvis in the direction of the therapist
Mobilisation in the flexion position	Lying on the side in the lower back flexion position	Each lumbar vertebra: 20 repetitions	One hand on the sacrum, the other on the lower thoracic region. Caudal arm shifts the lower vertebra in the transverse plane, and the cranial arm pushes the upper vertebra up (distraction effect)
Sham (placebo) mobilisation	Similar to the above techniques	Similar to active groups	Physiotherapist performs manual contact in the appropriate areas, but does not apply any mechanical force or pressure

Source: compiled by the authors

To implement sham (placebo) mobilisation, the specialist was limited exclusively to passive tactile contact of the hands with the patient's body. The procedure simulated a therapeutic position, but any active manipulations aimed at dislocating the vertebrae, mobilising joints, or overcoming tissue resistance were completely excluded. At the initial stage, a comparative analysis of the anthropometric and demographic characteristics of respondents was carried out. The results of statistical processing confirmed that there were no significant differences between the groups by age, body weight, height, and BMI ($p > 0.05$). The uniformity of the sample ensured high internal validity of the experiment, minimising the influence of interventional factors on rehabilitation results. The initial data of patients in the MT and EX groups are systematised in Table 3.

Table 3. Distribution of demographic information by group

Continuous variables	MT (n = 15)	EX (n = 15)	t	p*
Age (years)	38.80 ± 9.44	37.30 ± 9.11	0.454	0.653
Weight (kg)	88.61 ± 12.95	81.74 ± 11.54	2.043	0.050
Height (cm)	174.93 ± 9.43	171.50 ± 7.01	1.848	0.074
BMI (kg/m^2)	29.06 ± 4.22	26.69 ± 2.81	0.988	0.330

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group
Source: compiled by the authors

The gender distribution of the sample was 76.6% male and 23.3% female. Statistical analysis confirmed the equivalence of MT and EX groups by demographic characteristics ($p > 0.05$), which indicates their comparability at the initial stage. Below are the results of a comparative analysis of the health indicators of military personnel with lumbar herniated discs, in particular, according to the McGill-Melzack Pain Questionnaire (MMPQ) (Table 4). The results obtained indicate a pronounced positive dynamics of pain intensity reduction in both groups, but with a different trajectory of changes. At baseline (T1), the MT group had significantly higher levels of pain compared to the EX group ($p = 0.000$). After the end of therapy (T2), both methods showed high effectiveness: the MT group scores decreased by more than half, and the EX group – up to 22.43 points, which levelled the statistical difference between them ($p = 0.196$) and confirmed a similar short-term effect of interventions. However, during the follow-up assessment (T3), the EX group showed greater stability in their results compared with the MT group, which again resulted in a statistically significant difference in favour of exercise ($p = 0.036$).

Table 4. Intra-group and inter-group comparisons of the McGill-Melzack Pain Questionnaire

Variables	MT (n = 15)	EX (n = 15)	p*
T1	57.56 ± 11.18	41.62 ± 9.85	t: 4.814 p: 0.000
T2	27.62 ± 10.73	22.43 ± 12.51	t: 1.317 p: 0.196
T3	32.02 ± 14.68	20.31 ± 11.70	t: 2.182 p: 0.036
Effect size	0.754	0.588	

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group; T1 – before treatment; T2 – after treatment; T3 – 3-month follow-u
Source: compiled by the authors

Analysis of the results using the McGill-Melzack questionnaire confirmed the high effectiveness of both rehabilitation approaches. It was found that both methods have a significant effect size, while in the MT group this indicator was slightly higher – 0.754 against 0.588 in the EX group. This discrepancy is probably conditioned by a more pronounced primary dynamics of pain reduction in the MT group, whose participants had significantly higher baseline pain levels at T1 point. Analysis of long-term results indicates a higher effectiveness of physical exercises to stabilise the achieved effect. Whilst the MT group showed regression after three months (T3), with a slight increase in pain intensity – from 27.62 to 32.02 points – the EX group recorded a continued positive trend, with the score falling from 22.43 to 20.31. This confirms that the stabilisation exercise programme provides a longer and more stable analgesic effect in military personnel with lumbar spine hernias compared to manual exposure. The results of assessing the psychoemotional status of military personnel on the HADS scale confirm the positive impact of both rehabilitation strategies, although the intensity of dynamics of indicators in the groups had certain discrepancies (Table 5).

Table 5. Hospital Anxiety and Depression Scale

Variables	MT (n = 15)	EX (n = 15)	p*
T1	12.83 ± 6.12	10.58 ± 6.64	t: 0.991 p: 0.333
T2	6.52 ± 5	9.33 ± 5.66	t: −1.474 p: 0.151
T3	9.16 ± 5.25	9.28 ± 6.13	t: −0.062 p: 0.951
Effect size	0.432	0.127	

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group; T1 – before treatment; T2 – after treatment; T3 – 3-month follow-up
Source: compiled by the authors

Immediately after the end of the intervention (T2), the MT group showed the most pronounced positive dynamics: the average score on the HADS Scale decreased by 49.2% from the initial level, while in the EX

group the improvement was moderate – 11.8%. During the catamnestic examination (T3), partial regression of symptoms was observed in the MT group, but the final indicator remained 28.6% lower than the initial one. The EX group at the T3 stage showed high stability, maintaining an improvement of 12.3%. Despite the absence of a statistically significant difference between the groups at all stages of monitoring ($p > 0.05$), the effect size in the MT group (0.432) significantly exceeded the same indicator in the EX group (0.127), which indicates a stronger short-term clinical effect of manual therapy on the psychoemotional state of patients. The results of assessing the level of Kinesiophobia on the Tampa Scale (TSK) confirm that both rehabilitation approaches contributed to the reduction of fear of movement in military personnel with lumbar herniated discs (Table 6).

Table 6. Tampa Scale of Kinesiophobia

Variables	MT (n = 15)	EX (n = 15)	p*
T1	40.52 ± 7.57	37.58 ± 7.11	t: 1.114 p: 0.264
T2	34.43 ± 6.31	31.71 ± 9.66	t: 1.268 p: 0.201
T3	35.83 ± 7.01	34.66 ± 6.12	t: 0.580 p: 0.550
Effect size	0.238	0.133	

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group; T1 – before treatment; T2 – after treatment; T3 – 3-month follow-up

Source: compiled by the authors

At the T2 stage, the MT group showed a decrease in the level of kinesiophobia by 15.0%, and in the EX group – by 15.6%. During the follow-up assessment (T3), both groups maintained the stability of the result, despite a slight regression: the indicator remained lower than the initial one by 11.6% in the MT group and by 7.8% in the EX group. There was no statistically significant difference between the groups at all stages ($p > 0.05$), but a higher effect size in the MT group (0.238 vs. 0.133) indicates a more significant clinical effect of manual techniques on reducing fear of movement. Results on the Pain Catastrophisation Scale (PCS) confirm a significant reduction in cognitive-emotional stress in pain perception in both groups of military personnel (Table 7).

Table 7. Pain Catastrophisation Scale

Variables	MT (n = 15)	EX (n = 15)	p*
T1	26.22 ± 10.74	14.33 ± 12.52	t: 2.709 p: 0.009
T2	12.83 ± 11.06	8.20 ± 9.98	t: 1.350 p: 0.183
T3	10.33 ± 8.35	8.28 ± 12.00	t: 0.623 p: 0.544
Effect size	0.571	0.256	

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group; T1 – before treatment; T2 – after treatment; T3 – 3-month follow-up

Source: compiled by the authors

In the MT group, which had a higher initial level of catastrophisation ($p = 0.009$), after treatment (T2), a decrease of 51.1% was recorded, and after three months (T3) – by 60.6%. In the EX group, the improvement was 42.8% at T2 stage and stabilised at 42.2% at T3 stage. Despite the absence of a statistically significant difference between the groups in the long-term period ($p > 0.05$), a significantly higher effect size in the MT group (0.571 vs. 0.256) indicates a more intense effect of manual techniques on reducing patients' negative psychological attitudes towards pain. Analysis of the results for the Nottingham Health Profile (NHP) confirms the pronounced positive dynamics of indicators of the quality of life of military personnel in both groups (Table 8).

Table 8. Nottingham Health Profile

Variables	MT (n = 15)	EX (n = 15)	p*
T1	186.13 ± 116.55	144.27 ± 107.71	t: 1.100 p: 0.270
T2	66.79 ± 63.65	91.22 ± 82.66	t: −0.914 p: 0.362
T3	82.44 ± 89.40	65.23 ± 76.28	t: 0.622 p: 0.532
Effect size	0.403	0.413	

Note: * – independent selective t-test; MT – manual therapy group; EX – exercise group; T1 – before treatment; T2 – after treatment; T3 – 3-month follow-up

Source: compiled by the authors

At the initial stage (T1), the groups were statistically homogeneous ($p = 0.270$). After completing the course (T2), the MT group showed an improvement of 64.1%, while the EX group showed an improvement of

36.8%. During the follow-up assessment (T3), the EX group showed a prolongation of the effect (an additional decrease in indicators by 28.5% relative to T2, a total of 54.8%), while in the MT group there was a regression with an increase in the score by 23.4% relative to the T2 result. Despite the absence of a statistically significant difference between the groups ($p > 0.05$), the slightly higher effect size in the EX group (0.413 vs. 0.403) confirmed the high therapeutic value of both methods with a long-term benefit from exercise.

Thus, at the initial stage, the MT and EX groups were identical in terms of kinesiophobia and indicators of the hospital anxiety and depression scale ($p > 0.05$), which confirms the uniformity of the sample. However, after completing the therapeutic course, statistically significant positive dynamics in these parameters was observed mainly in the MT group, which led to the appearance of a likely intergroup difference ($p < 0.05$). As for the pain catastrophisation scale, the initial values of the MT group significantly exceeded similar data of the exercise group ($p < 0.05$). Although after treatment, the intensity of catastrophisation significantly decreased in both cohorts ($p < 0.05$), the effect size in patients in the MT group was more than double that observed in the EX group. Simultaneously, analysis of the McGill-Melzack questionnaire and the Nottingham Health Profile showed pronounced positive changes in both groups ($p < 0.05$). A post hoc analysis showed that overall statistical differences in pain intensity and quality of life parameters were determined by the respondents' significant progress relative to their primary condition (T1).

This study was devoted to the clinical analysis of the impact of manual techniques on the psychoemotional status and quality of life of patients with lumbar herniated discs. It was found that the integration of manual therapy into the rehabilitation process provides a pronounced positive trend in overcoming kinesiophobia, and symptoms of anxiety and depression. Both follow-up groups showed a significant reduction in pain syndrome, a decrease in the level of pain catastrophisation, and an overall improvement in quality of life indicators. The obtained results confirm that manual intervention is an effective tool for the correction of pain manifestations, stabilisation of the psychological state, and restoration of patients' functional well-being.

DISCUSSION

Recent evidence-based studies confirm the high clinical significance of conservative treatment for lumbar hernias. In particular, a large-scale systematic review and meta-analysis published by S. Thavarajasingam *et al*. [21] has shown that the differentiated use of manual manipulation, traction therapy, and targeted physical exercises provides statistically and clinically significant reduction of pain syndrome and is a financially justified basis for first-line therapy, which allows most patients to avoid invasive surgical intervention. The importance of combining manual techniques with advanced hardware techniques for rapid relief of neurological deficits was investigated by D. Lytras *et al*. [22] in their randomised clinical trial. The researchers concluded that the integration of manual therapy enables a rapid short-term analgesic effect, significantly reduces radicular pain intensity, and effectively alleviates functional limitations in chronic conditions. Active kinesiotherapy remains critical for maintaining a long-term result and regenerating the spinal muscular corset. As demonstrated in the meta-analysis by S. Du *et al*. [23], regular exercise programmes targeting deep stabilising muscles (in particular the transversus abdominis and multifidus muscles) not only restore spinal stability and locomotor biomechanics, but also exert a strong positive effect on patients' mental health, significantly improving overall quality of life indicators.

The results obtained in the course of the clinical study confirm the complex, multi-vector and non-linear biopsychosocial nature of the course of lumbar spine pathology in military personnel of the Defence Forces of Ukraine. It was established that in the context of combat operations, the development of intervertebral disc herniations is determined by the aggressive synergy of somatic and extreme environmental factors (carrying heavy personal equipment, prolonged exposure to vibrations in armoured vehicles, the effects of mine and explosive shock waves, and prolonged periods spent in forced, non-physiological postures). As noted by J. Xu *et al*. [1], degenerative and dystrophic lesions of the spine and directly herniated discs are a critical medical and social problem, accompanied by somatic deficits and a sharp decrease in the quality of life of patients. According to W. Lu *et al*. [5], psychosocial determinants combined with structural features of tissue destruction have a dominant effect on the transformation of acute pain syndrome into chronic, creating a stable barrier to successful rehabilitation.

The analysis of the initial data (point T1) is fully consistent with the current literature on the presence of deep comorbidity between chronic vertebrogenic pain and psychoemotional disorders of patients. Military personnel in both groups showed marked levels of distress, anxiety, depressive states, kinesiophobia, and pain catastrophisation at the time of inclusion in the programme. This is confirmed by the conclusions of B. Taşkaya *et al*. [7] on the indissoluble connection of chronic pain with mental pathology. This problem is particularly acute for combatants, whose intense pain interacts synergistically with combat stress and post-traumatic stress disorder.

The key theoretical and practical conclusion of the conducted study is the demonstration that manual therapy according to the Maitland concept (grade 4 passive mobilisation) acts as a powerful and rapid catalyst for the reduction of cognitive and emotional

distortions and the stabilisation of psycho-emotional state in patients in the short-term perspective (T2). Immediately after completing the 5-week course, the MT group showed a 49.2% reduction in anxiety and depression on the HADS Scale, while the isolated exercise (EX) group showed only 11.8% improvement. A significant advantage in effect size in the MT group (0.432 vs. 0.127 in EX) demonstrates a pronounced clinical effect of targeted manual techniques. This effect correlates with conclusions of B. Taşkaya *et al*. [7] that high-speed and soft rhythmic manual manipulations optimise myofascial tone, provide rapid improvement in the articular play of the spine, and have a powerful regulatory effect on the psychological factors of patients. Similar data was provided by M. Danazumi *et al*. [10], emphasising that spinal mobilisation as an adjunctive method can significantly improve the psychoemotional background and stop radicular pain.

Special attention was paid to the dynamics of overcoming mental barriers to rehabilitation, in particular kinesiophobia and pain catastrophisation. The phenomenon of irrational fear of movement is considered an unfavourable predictor of recovery. C. de Freitas *et al*. [4] emphasised that the reduction of kinesiophobia is a basic condition for the restoration of motor functions. According to the data, although both approaches reduced the level of fear of activity, the effect size in the MT group was twice as high (0.238 vs. 0.133 in EX). A similar pattern was found on the Pain Catastrophisation Scale (PCS), where the effect size in the MT group reached 0.571 compared to 0.256 in the EX group. This indicates that manual exposure by immediately eliminating mechanical irritation and decompression creates a positive sensory experience, destroying negative cognitive attitudes about own motor ability, which is fully consistent with the provisions of papers by B. Cao *et al*. [11] and C. Gong *et al*. [12].

Analysis of long-term results (catamnestic point T3 after three months of follow-up) revealed fundamentally different trajectories of long-term adaptation in the groups. In patients of the MT group, after discontinuation of direct supervision by a specialist, a partial regression of results occurred: the intensity of pain in MMPQ slightly increased (from 27.62 to 32.02 points), and the quality of life in NHP worsened by 23.4% compared to the T2 stage. In contrast, the EX group (which performed progressive stabilisation exercises targeting the deep core muscles, namely the transversus abdominis and multifidus muscles) demonstrated a more pronounced persistence of the treatment effect. In the control group at the T3 stage, a stable improvement in quality of life was recorded by 54.8% with a subsequent reduction in pain, which led to a statistically significant intergroup difference in favour of active exercise ($p = 0.036$).

This phenomenon of long-term stabilisation due to the active kinesiotherapy component confirmed the principles of the multimodal approach described by W.-J. Lee *et al*. [6], as the most clinically and economically justified basis for recovery. The observed long-term trajectories are also consistent with the findings of M. Roiha *et al.* [9], who noted that sustained maintenance of high quality of life and complete elimination of somatic deficits are only possible under the condition of forming long-term adaptive mechanisms of the musculoskeletal system. Manual techniques are indispensable for the initial "breakthrough" through acute pain syndrome and psychological distress, but stable long-term remission and restoration of professional combat capability of military personnel depend entirely on the development of a muscular corset during regular training. Thus, in the controversial field of physical rehabilitation of combatants with herniated discs, the study substantiated the feasibility of introducing an integrated rehabilitation model. It should combine passive manual manipulations in the initial stages (for elimination of protective muscle spasm, rapid psycho-emotional stabilisation, and reduction of kinesiophobia) with a mandatory subsequent transition to long-term individualised programmes of stabilisation and strength exercises to ensure sustained functional well-being.

CONCLUSIONS

1. Patients in both groups had high levels of anxiety, depression, kinesiophobia, and pain catastrophisation at the start (especially in the MT group, $p < 0.05$). This confirms the need for a comprehensive impact on both somatic and psychoemotional factors.

2. Developed protocol combined physical exercises with manual therapy techniques. The programme was aimed at biomechanical correction, decompression of nerve structures, and reduction of sensory perception of pain, which created conditions for effective functional recovery.

3. Both approaches showed positive dynamics of pain intensity and quality of life ($p < 0.05$). However, only the MT group achieved statistically significant correction for anxiety, depression, and kinesiophobia. The effect on pain reduction in the MT group was more than twice that of the control group.

4. Manual therapy was highly effective in the long-term rehabilitation of military personnel. It provided not only physical recovery, but also acts as a powerful factor in correcting the psychoemotional state, helping to overcome the fear of movement ($d = 0.238$ vs. $d = 0.133$ in the control group).

The main limiting factors of this study were the relatively small sample size (30 people), pronounced gender asymmetry with a predominance of men (76.6%), and a short three-month period of catamnestic follow-up. In addition, the effectiveness assessment was based mainly on subjective scales and questionnaires of patients without the use of instrumental

control methods (repeated MRI, electromyography or goniometry), and rehabilitation in a full-scale war imposed additional uncontrolled psychoemotional stress on the participants.

Prospects for further research include scaling up the experiment to involve a larger number of combatants (in particular, women) and extending the monitoring period to 6-12 months to assess the recurrence rate. Given the identified different temporal dynamics of effects, it is critically important to create and investigate a consistently integrated rehabilitation model, where manual therapy will serve as a quick tool for relieving distress and pain at the initial stage, with the obligatory subsequent transition to long-term stabilisation training for long-term retention of the result in under combat conditions. It is also advisable to supplement the methodology with objective biomechanical metrics of the spine and an assessment of the impact of physical therapy on patients with concomitant PTSD.

ACKNOWLEDGEMENTS

The authors express sincere gratitude to the command and medical staff of the rehabilitation units in Kharkiv for their comprehensive support in organising the study, and to all military personnel who participated in the research for their courage, trust, and resilience.

FUNDING

The implementation of this study and the preparation of the manuscript were carried out without external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Віталій Вісич

Студент
Національний фармацевтичний університет
61002, вул. Григорія Сковороди, 53, м. Харків, Україна
https://orcid.org/0009-0009-0447-6210

Ганна Таможанська

Кандидат педагогічних наук, доцент
Національний фармацевтичний університет
61002, вул. Григорія Сковороди, 53, м. Харків, Україна
https://orcid.org/0000-0003-2430-8467

Наталія Селюкова

Доктор біологічних наук, доцент, старший дослідник
Національний фармацевтичний університет
61002, вул. Григорія Сковороди, 53, м. Харків, Україна
https://orcid.org/0000-0001-9657-6888

Ольга Свєрчкова

Кандидат наук з фізичного виховання і спорту, старший викладач
Харківська державна академія фізичної культури
61058, вул. Клочківська, 99, м. Харків, Україна
https://orcid.org/0000-0001-9987-6405

Віталій Іванов

Викладач
Національний фармацевтичний університет
61002, вул. Григорія Сковороди, 53, м. Харків, Україна
https://orcid.org/0009-0002-4442-8001

Особливості фізичної терапії при поперекових грижах у військовослужбовців на віддаленому етапі реабілітації

Анотація

Актуальність. Робота присвячена проблемі реабілітації військовослужбовців із грижами міжхребцевих дисків поперекового відділу, що є критичним викликом через високі фізичні навантаження та бойовий стрес.

Мета. Вивчення ефективності мануальної терапії як засобу корекції психоемоційного стану та підвищення якості життя таких пацієнтів у межах тривалого реабілітаційного циклу.

Матеріали та методи. У дослідженні взяли участь 30 військовослужбовців (23 чоловіки та 7 жінок), рандомізованих на дві групи: основну (мануальна терапія + вправи (МТ)) та контрольну (тільки вправи + плацебо-мобілізація (ФВ)). Оцінка проводилася за допомогою низки інструментів: опитувальника Макгілла-Мелзака (біль), шкали HADS (тривога/депресія), шкали Тампи (кінезіофобія), шкали PCS (катастрофізація болю) та Ноттінгемського профілю здоров'я (якість життя). Оцінка стану пацієнтів проводилася у три етапи: до початку лікування (Т1), після 5-тижневого курсу (Т2) та через три місяці спостереження (Т3).

Результати. На вихідному етапі групи були однорідними, хоча в групі МТ спостерігався вищий рівень болю та катастрофізації. Після курсу (Т2) обидві когорти продемонстрували значний прогрес: у групі МТ інтенсивність болю знизилася вдвічі, а якість життя покращилася на 64,1 % (проти 36,8 % у ФВ). Тільки в групі МТ зафіксовано статистично значущу редукцію тривоги та депресії (49,2 %) з високим розміром ефекту (0,432). Також у цій групі розмір ефекту щодо зниження катастрофізації болю (0,571) удвічі перевищив показники групи ФВ (0,256). Однак на етапі Т3 було виявлено різні траєкторії: у групі МТ відбулася часткова регресія результатів, тоді як група ФВ продемонструвала пролонгацію ефекту зі стабільним покращенням якості життя на 54,8 %. Отже, мануальна терапія є ефективною для швидкої психоемоційної стабілізації, а фізичні вправи – для утримання тривалого анальгетичного результату.

Висновки. Мануальна терапія є ефективним інструментом комплексної реабілітації військовослужбовців, оскільки вона дозволяє не лише знизити інтенсивність болю, а й успішно долати психологічні бар'єри, такі як страх перед рухом та депресивні стани. Для досягнення максимально стійкого функціонального благополуччя рекомендовано інтегрувати мануальні техніки в довготривалі програми фізичних тренувань.

Ключові слова: кінезіотерапія; функціональне відновлення; комбатанти; грижа міжхребцевого диска; мануальна терапія; якість життя; кінезіофобія; психоемоційний стан.

THERAPY AND REHABILITATION

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.127-005.8-085.825:615.825:004.738.5
DOI: https://doi.org/10.32345/2664-4738.2.2026.10

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 14.01.2026 Revised: 05.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Ihor Savchuk

Senior Lecturer
Academy of Recreation Technologies and Law
43023, 2 Promyslova Str., Lutsk, Ukraine
https://orcid.org/0000-0002-5724-0078

Andrii Sitovskyi

PhD in Physical Education and Sports
Academy of Recreation Technologies and Law
43023, 2 Promyslova Str., Lutsk, Ukraine
https://orcid.org/0000-0002-7434-7475

Olena Yakobson

PhD in Medical Sciences, Associate Professor
Lesya Ukrainka Volyn National University
43025, 13 Voli Ave., Lutsk, Ukraine
https://orcid.org/0000-0002-7340-2014

Iana Ushko*

PhD in Biological Sciences, Associate Professor
Academy of Recreation Technologies and Law
43023, 2 Promyslova Str., Lutsk, Ukraine
https://orcid.org/0000-0003-3017-7766

Home-based cardiac rehabilitation after myocardial infarction in the long-term rehabilitation period: Evidence base and prospects for development

Abstract

Relevance. Myocardial infarction is accompanied by long-term functional, clinical, and psycho-emotional consequences, whereas insufficient accessibility of traditional centre-based cardiac rehabilitation programmes determines the need for evidence-based home-based, hybrid, and telerehabilitation models capable of supporting safe physical activity, self-management, and secondary prevention in the long-term rehabilitation period.

Aim. To summarise the current evidence base on home-based cardiac rehabilitation after myocardial infarction and determine its effectiveness, safety, and prospects for use in the long-term rehabilitation period.

Materials and methods. The study was prepared as an analytical narrative review with elements of a systematised search. Systematic reviews, meta-analyses, randomised controlled trials, cohort studies, scientific statements of professional societies, and clinical guidelines on exercise-based cardiac rehabilitation, home-based cardiac rehabilitation, cardiac telerehabilitation, mobile health technologies (mHealth), the maintenance phase, adherence to home-based physical exercises, kinesiophobia, psychological distress, and long-term self-management in patients after myocardial infarction were analysed.

Results. Current evidences indicate that home-based cardiac rehabilitation can achieve outcomes comparable to those of centre-based cardiac rehabilitation programmes in clinically stable patients at low or moderate risk following myocardial infarction. The safety of the home-based model depends on appropriate patient selection, risk stratification, individualised exercise prescription, self-management training, regular professional feedback, and symptom-response algorithms – that is, structured rules for stopping or modifying physical exercise, contacting a specialist, or seeking emergency care when clinical signs of exercise intolerance appear.

Suggested Citation:
Savchuk I, Sitovskyi A, Yakobson O, Ushko I. Home-based cardiac rehabilitation after myocardial infarction in the long-term rehabilitation period: Evidence base and prospects for development. Med Sci Ukr. 2026;22(2):88–103. DOI: https://doi.org/10.32345/2664-4738.2.2026.10

*Corresponding author (*ianaushko21@gmail.com*)

Telerehabilitation and mobile digital health technologies can improve accessibility, support self-management, and facilitate the monitoring of symptoms and physical activity. However, they should complement rather than replace a clinically structured cardiac rehabilitation programme. The greatest gap remains the long-term rehabilitation period, in which the maintenance of movement behaviour, adherence, psychological adaptation, overcoming kinesiophobia, self-efficacy, and social support become decisive.

Conclusions. Home-based cardiac rehabilitation after myocardial infarction is a promising secondary prevention model for selected clinically stable patients, but its long-term effectiveness requires structured professional supervision, risk stratification, psychological-behavioural support, telerehabilitation or analogue self-management tools, and standardised assessment of functional, clinical, and behavioural outcomes.

Keywords: physical therapy; secondary prevention; adherence; risk factors; cardiovascular diseases.

INTRODUCTION

Myocardial infarction remains one of the key clinical forms of ischaemic heart disease, causing a considerable burden of mortality, recurrent cardiovascular events, hospitalisations, disability, and long-term decline in functioning. Current global epidemiological data indicate that cardiovascular diseases continue to occupy a leading place among the causes of years of life lost, and ischaemic heart disease remains one of the most important components of this burden. As G.A. Roth *et al.* [1] noted, after completion of acute treatment, a patient after myocardial infarction does not automatically return to the previous level of functioning, since detraining, restrictions in everyday activity, fear of physical exertion, the need to control risk factors, and the necessity of long-term adherence to secondary prevention persist. Exercise-based cardiac rehabilitation is one of the most substantiated components of post-infarction recovery, as it combines physical training, risk-factor control, patient education, psychosocial support, and the formation of self-management skills.

In the contemporary understanding, cardiac rehabilitation is not an isolated set of exercises but, as M. Ambrosetti *et al.* [2] and R.S. Taylor *et al.* [3] emphasised, a multicomponent model of secondary prevention directed towards reducing residual cardiovascular risk, improving functional capacity, increasing quality of life, and returning the patient to active participation in everyday life. Accordingly, the availability of a rehabilitation programme alone is insufficient. Its accessibility, continuity, personalisation, and capacity to support behavioural change after completion of the early stage of recovery also become relevant. Despite the proven clinical importance of cardiac rehabilitation, its actual use remains insufficient in many countries. Low coverage of patients by cardiac rehabilitation programmes is connected not only with an insufficient number of centres but also with low referral rates, geographical distance, transport barriers, cost, employment, family responsibilities, comorbidities, and insufficient patient awareness. For this reason, international initiatives of the last decade have focused not only on the evidence base of cardiac rehabilitation but also on strategies for increasing its accessibility and patient participation, specifically through automated referral, flexible formats, home-based models, and self-management [4-5]. Research on the structure and accessibility of cardiac rehabilitation by M. Supervia *et al.* [6] and K. Turk-Adawi *et al.* [7] showed that programme provision differs considerably between countries and regions, while access to rehabilitation care is especially limited in healthcare systems with an insufficient number of specialised centres or uneven territorial distribution of services. These data are directly relevant to post-myocardial infarction rehabilitation, as patients requiring long-term professional support often face the greatest barriers to participation in centre-based cardiac rehabilitation programmes. These barriers include older age, multimorbidity, reduced mobility, residence in remote areas, and limited social support.

In response to these limitations, home-based, hybrid, and telerehabilitation models of cardiac rehabilitation are actively being developed. Home-based cardiac rehabilitation should be considered not as unsupervised independent exercise, but rather as a structured programme that includes preliminary clinical and functional assessment, individualised physical exercise, self-management training, symptom control, professional feedback, and periodic reassessment of outcomes. As S.T. McDonagh *et al.* [8] stated, telerehabilitation and digital technologies acquire particular importance, as they partly compensate for the lack of face-to-face contact and support the monitoring of physical activity, symptoms, heart rate, blood pressure, and adherence to the programme. However, the digitalisation of cardiac rehabilitation should not be equated with an automatic increase in its effectiveness. Mobile applications, wearable devices, video consultations, and electronic diaries are only support tools, the effectiveness of which depends on integration into a clinically structured programme, availability of professional feedback, the patient's digital literacy, and the presence of symptom-response algorithms. A systematic review of digital interventions in cardiac rehabilitation by S. Wongvibulsin *et al.* [9] stressed the potential of such solutions to improve accessibility and maintain physical activity, while indicating the need for standardisation, assessment of acceptability, and consideration of the digital divide. The long-term rehabilitation period remains the most problematic, because the main task is not only recovery after the acute event but also

maintenance of the achieved level of functional capacity, physical activity, self-management, and secondary prevention. After completion of centre-based cardiac rehabilitation, the patient often loses regular contact with specialists, which increases the risk of returning to sedentary behaviour, reduced adherence, and loss of the results achieved. In this context, not only the parameters of physical exercise become important, but also the patient's ability for self-management, symptom recognition, maintenance of motivation, and adaptation of physical activity to the real-life environment [3, 10].

Thus, the relevance of the study is determined by the combination of three interrelated problems: the high burden of the consequences of myocardial infarction, insufficient coverage of patients by traditional centre-based cardiac rehabilitation programmes, and the need for long-term supervision models capable of maintaining physical activity, adherence, and self-management Thus, the relevance of the study is determined by the combination of three interrelated problems: the high burden of the consequences of myocardial infarction, insufficient coverage of patients by traditional centre-based cardiac rehabilitation programmes, and the need for long-term supervision models capable of maintaining physical activity, adherence, and self-management after completion of the early stage of recovery. The unresolved issue is the determination of the conditions under which home-based cardiac rehabilitation after myocardial infarction can be not only an accessible alternative to a centre-based programme but also a safe, structured, and long-term effective physical therapy model integrated with telerehabilitation, digital or analogue self-management tools, and periodic professional reassessment. The study aimed to evaluate current scientific data on home-based cardiac rehabilitation after myocardial infarction, determine its impact on patient recovery and safety, and assess the possibilities for its integration into a long-term rehabilitation programme. This goal required the following analytical tasks: to characterise exercise-based cardiac rehabilitation as an evidence-based standard of secondary prevention after myocardial infarction (MI); to determine the content, key components, and limits of use of home-based cardiac rehabilitation; to compare different cardiac rehabilitation models and identify the main gaps in the evidence base concerning the long-term rehabilitation period after MI.

MATERIALS AND METHODS

The object of the study was home-based cardiac rehabilitation of patients after myocardial infarction in the long-term rehabilitation period. The subject was the evidence base on the effectiveness, safety, organisational conditions, telerehabilitation support, and psychological-behavioural factors of home-based cardiac rehabilitation after myocardial infarction. The theoretical basis of the study consisted of the works by G.O. Dibben *et al.* [11] and T.M. Brown *et al.* [12] on the multicomponent structure of contemporary cardiac rehabilitation, and by R.J. Thomas *et al.* [13] on the definition and principles of home-based cardiac rehabilitation. These publications formed the conceptual framework of the analysis: evidence-based cardiac rehabilitation – home-based cardiac rehabilitation – long-term maintenance of activity – psychological-behavioural barriers – digital or analogue support. The selected format of an analytical narrative review with elements of a systematised search corresponds to the purpose of the study. It provides a conceptual synthesis of the current evidence base and identifies key directions for the development of home-based cardiac rehabilitation after myocardial infarction, rather than quantitatively summarising all available studies. The search for sources was performed in the electronic databases PubMed, Cochrane Library, Scopus, Web of Science, PEDro, and Google Scholar. The review focused mainly on publications from 2019 to 2025, as they reflect the current state of the evidence base on home-based cardiac rehabilitation, telerehabilitation, mobile digital health technologies (mHealth), and long-term supervision models. Earlier sources could be considered only if they had conceptual importance for defining basic approaches to cardiac rehabilitation or the methodology for its assessment.

The following keywords and their combinations were used during the search: "home-based cardiac rehabilitation", "centre-based cardiac rehabilitation", "centre-based cardiac rehabilitation", "hybrid cardiac rehabilitation", "myocardial infarction", "exercise-based cardiac rehabilitation", "cardiac telerehabilitation", "mHealth cardiac rehabilitation", "maintenance phase", "long-term rehabilitation", "long-term adherence", "exercise adherence", "kinesiophobia", "psychological distress", "post-myocardial infarction psychological distress", "exercise self-efficacy", and "cost-effectiveness". The Boolean operators AND and OR were used to refine the results, along with manual screening of reference lists in key systematic reviews, meta-analyses, and scientific statements. Source selection was performed using the PRISMA approach. At the identification stage, 330 records were selected, including 312 through the electronic databases PubMed, Cochrane Library, Scopus, Web of Science, PEDro, and Google Scholar, and 18 through manual screening of reference lists of relevant systematic reviews, meta-analyses, and scientific statements After the removal of 96 duplicates, 234 records remained for title and abstract screening. Of these, 176 were excluded because they did not meet the eligibility criteria with respect to the study topic, target population, or intervention. Full-text assessment was performed for 58 sources; after excluding publications due to non-compliance with the inclusion criteria, absence of a home-based or remote component, insufficient coverage of the long-term period, absence of physical

therapy, or duplication of content, 25 sources were included in the final analytical synthesis.

RESULTS AND DISCUSSION

Exercise-based cardiac rehabilitation is one of the key components of contemporary management of patients after myocardial infarction. Its importance extends beyond restoring exercise capacity, as it is considered a component of comprehensive secondary prevention aimed at minimising the risk of recurrent cardiovascular events, reducing hospitalisations, improving functional status and quality of life, and supporting a safe return to everyday activities. For this reason, cardiac rehabilitation after MI should be interpreted as an evidence-based standard of long-term patient management, instead of an additional stage of post-hospital recovery [11]. Participation of patients with ischaemic heart disease in exercise-based cardiac rehabilitation programmes is associated with reduced cardiovascular mortality, recurrent cardiac events, and hospitalisations, and improved quality of life. These data have fundamental importance for post-infarction rehabilitation because they prove that structured physical training is not only a means of functional recovery but also an instrument for influencing clinically meaningful consequences of the disease. Accordingly, the contemporary scientific discussion shifts from the question "is cardiac rehabilitation effective?" to the question "how can its accessibility, safety, personalisation, and long-term implementation be ensured?" [11]. After MI, the patient often faces detraining, reduced aerobic capacity, limitations in everyday physical activity, fear of exertion, psycho-emotional instability, and difficulties returning to usual social and professional functioning. Exercise-based cardiac rehabilitation is directed towards overcoming these consequences through gradual, controlled, and individualised increases in physical exercise. The clinical value of such a programme lies not only in improving functional capacity, as reflected by measures such as peak oxygen uptake (VO_2peak) and Six-Minute Walk Test (6MWT) distance, but also in promoting safe exercise behaviours that patients can maintain after completing the early structured phase of rehabilitation. Cardiac rehabilitation should not be considered as an isolated block of physical training. The guidelines of the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation define cardiac rehabilitation as a multicomponent programme that includes patient assessment, individual exercise prescription, physical-activity counselling, control of blood pressure, lipid profile, glycaemia, and body weight, correction of behavioural risk factors, psychosocial support, patient education, and evaluation of programme quality [12]. Physical training within the structure of exercise-based cardiac rehabilitation should be dosed, progressive, and adapted to the patient's clinical condition, level of functional capacity, concomitant pathology, medication therapy, and individual risk of complications. A typical programme includes a combination of aerobic exercise, strength exercises, flexibility training, and a gradual increase in everyday movement activity. However, the effectiveness of such a programme is determined not only by the parameters of intensity, frequency, and duration of sessions but also by regular performance, quality of self-management, timely adjustment of exercise load, and the patient's ability to integrate physical activity into everyday life [12].

Its multidisciplinary character is one of its key features. The rehabilitation process should involve a physician, physical therapist, nurse, psychologist, and, when necessary – a dietitian and other specialists. Such a team model provides not only for exercise prescription but also assessment of barriers to performance, setting realistic goals, symptom control, teaching the patient the principles of self-observation, and support for adherence to secondary prevention. For patients after MI, this has particular importance, as the risk of recurrent events is closely connected with behavioural factors, insufficient physical activity, low adherence to treatment, and psychosocial difficulties [12]. Exercise-based cardiac rehabilitation affects several levels of recovery simultaneously. At the physiological level, it improves cardiorespiratory endurance, muscle function, control of metabolic risk factors, and general exercise tolerance. At the functional level, it helps the patient increase the amount of everyday activity, improve tolerance to daily loads, and reduce dependence on external assistance. At the behavioural level, it forms skills of self-management, prevention, safe dosing of exercise, symptom recognition, and maintenance of physical activity as a stable component of lifestyle [11-12]. Nevertheless, recognition of exercise-based cardiac rehabilitation as the standard after MI does not eliminate the problem of its practical implementation. Even with a convincing evidence base, some patients do not participate in cardiac rehabilitation programmes or discontinue participation before a stable effect is achieved. The reasons may include logistical difficulties, remoteness of rehabilitation centres, employment, financial and transport barriers, insufficient motivation, fear of physical exertion, comorbidity, and a low level of understanding of the importance of rehabilitation [12]. Thus, the further development of post-infarction cardiac rehabilitation should be connected not only with confirmation of the effectiveness of exercise-based cardiac rehabilitation but also with the development of models that ensure its actual accessibility for different groups of patients. In this context, exercise-based cardiac rehabilitation is the evidence-based foundation for the development of home-based, hybrid, and telerehabilitation models. Home-based cardiac rehabilitation does not deny the importance of physical exercises as the central component of the programme but transfers them into the

patient's living environment, provided that preliminary assessment, risk stratification, individual exercise prescription, self-management training, and professional feedback are ensured. Therefore, further analysis of home-based cardiac rehabilitation after MI should be based on an understanding of exercise-based cardiac rehabilitation as the basic standard that requires adaptation to the long-term rehabilitation period, the patient's real living conditions, and the possibilities of the healthcare system [11-12].

Home-based cardiac rehabilitation was developed as a response to the limited coverage of patients by traditional centre-based cardiac rehabilitation programmes. Its development does not mean abandonment of the principles of exercise-based cardiac rehabilitation but involves another way of organising the rehabilitation process – mainly outside a specialised centre, in the patient's home or usual living environment. In scientific statements of the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology, home-based cardiac rehabilitation is defined as a structured programme implemented fully or mainly outside a centre, but involving professional assessment, individual exercise prescription, education, monitoring, risk-factor management, and regular feedback from a specialist [13]. It is fundamentally important to distinguish between home-based cardiac rehabilitation and uncontrolled independent physical exercise. Home-based cardiac rehabilitation is not simply a recommendation to "move more" or a set of general advice after inpatient rehabilitation. It is an organised model of rehabilitation care that should include clinical risk stratification, assessment of functional capacity, determination of a safe level of physical exercise, patient training in self-management, periodic contact with a physical therapist or another specialist of the multidisciplinary team, and, when necessary, psychosocial support. The presence of these components distinguishes evidence-based home-based cardiac rehabilitation from everyday physical activity without clinical supervision [12-13]. The main advantage of home-based cardiac rehabilitation is its capacity to overcome barriers that restrict patient participation in centre-based cardiac rehabilitation programmes. Such barriers include distance to the rehabilitation centre, transport difficulties, employment, the need to provide family care, financial costs, limited mobility, comorbidity, residence in a rural or remote area, and psychological factors, specifically anxiety, fear of physical exertion, and low motivation. The home-based format can increase the accessibility of rehabilitation, provide a more flexible schedule of sessions, involve the family, and transfer acquired skills directly into the patient's everyday life [13].

The evidence base on the effectiveness of home-based cardiac rehabilitation has been considerably strengthened by systematic reviews and meta-analyses comparing home-based and centre-based programmes. The updated Cochrane review devoted to comparison of home-based and centre-based cardiac rehabilitation provided no convincing evidence of a substantial difference between these models for a number of key outcomes, including mortality, cardiovascular events, functional capacity, quality of life, risk factors, and costs during follow-up of up to 12 months. This enables home-based cardiac rehabilitation to be considered an evidence-supported alternative to centre-based cardiac rehabilitation for clinically stable patients at low or moderate risk [14]. More recent comparative reviews confirm this position and indicate that home-based cardiac rehabilitation can achieve results comparable to centre-based cardiac rehabilitation in terms of functional capacity, adherence to the programme, quality of life, and control of individual cardiovascular risk factors. Specifically, the recent comparative systematic review by P. Karisa *et al.* [15] demonstrated that home-based models may have small advantages for certain indicators of functional capacity and adherence, although the clinical meaning of these differences depends on programme structure, method of monitoring, duration of supervision, and patient characteristics [15]. Thus, contemporary literature is gradually moving from evaluating home-based cardiac rehabilitation as a "reserve" model to considering it as an independent format of cardiac rehabilitation capable of scaling rehabilitation care without loss of the main clinical outcomes. Digital technologies acquire particular importance in contemporary home-based programmes. Mobile applications, wearable devices, telemonitoring, electronic diaries, video consultations, and remote feedback systems can partly compensate for the absence of constant face-to-face control. The meta-analysis by L. Li *et al.* [16] presented that such interventions can improve functional capacity and support the patient's participation in the rehabilitation process, especially when digital tools are combined with professional supervision, individualised exercise prescription, and regular symptom monitoring. Nonetheless, digital support should be considered not as a replacement for clinical reasoning but as an instrument for implementing a structured programme.

The safety of home-based cardiac rehabilitation is a key issue, especially after myocardial infarction. The systematic review by M. Stefanakis *et al.* [17] showed that the risk of adverse events during home-based cardiac rehabilitation is low if appropriate patient selection, risk stratification, preliminary training, symptom control, and clear criteria for stopping or modifying exercise are provided. This means that the safety of the home-based model is determined not by the place where exercises are performed, but by the quality of the clinical protocol, initial assessment, instruction,

monitoring, and availability of professional feedback. Cohort studies also support the possibility of wider use of home-based cardiac rehabilitation in real clinical practice. In the study by C. Nkonde-Price *et al.* [18], patients who participated in home-based and centre-based cardiac rehabilitation were compared in terms of hospitalisations, adherence to medication therapy, and control of risk factors. In this demographically diverse cohort, participation in home-based cardiac rehabilitation was associated with fewer hospitalisations over 12 months compared to centre-based cardiac rehabilitation, which highlights the potential of the home-based model not only to increase accessibility but also to support clinically meaningful outcomes in real practice. However, the cohort design of the study requires cautious interpretation of causal inferences. Despite its considerable advantages, home-based cardiac rehabilitation also has important limitations. It is most suitable for clinically stable patients after MI at low or moderate risk who have undergone initial clinical assessment, have a clear individual physical therapy plan, are capable of self-management, and can maintain contact with a specialist. By contrast, patients with unstable angina, decompensated heart failure, uncontrolled arrhythmias, pronounced symptoms during minimal exertion, severe comorbid conditions, or high risk of complications require more intensive face-to-face supervision, at least at the initial stage. For such groups, centre-based cardiac rehabilitation or a hybrid model with a gradual transition to a home-based format after stabilisation may be more appropriate [13, 17].

A separate limitation of home-based cardiac rehabilitation is the dependence of its effectiveness on behavioural and social factors. In home conditions, the patient has more freedom but less external control. This may reduce adherence to the programme, especially in the presence of kinesiophobia, anxiety, depressive symptoms, low self-efficacy, weak family support, or insufficient understanding of rehabilitation goals. Therefore, a home-based programme should not be limited to the transfer of a set of exercises; it should contain elements of motivational counselling, education, gradual formation of confidence in the safety of movement, family involvement, and regular feedback [12-13]. Another important limitation is the digital divide. Although mobile digital health technologies and telerehabilitation substantially expand the possibilities of home-based cardiac rehabilitation, not all patients have sufficient access to technical devices, stable internet, or skills in using digital platforms. This is especially relevant for older patients, persons with a lower level of education, residents of remote areas, and patients with cognitive or sensory limitations. In such cases, digital tools should be supplemented with analogue means: printed instructions, self-management diaries, telephone consultations, family involvement, and periodic face-to-face visits [13, 16]. Thus, home-based cardiac rehabilitation after MI is an evidence-based model that can provide results at the same level a as centre-based cardiac rehabilitation in stable patients at low or moderate risk. Its strengths are accessibility, flexibility, integration into everyday life, the possibility of family involvement, and the use of digital technologies. However, its effectiveness and safety depend on correct patient selection, risk stratification, individualisation of physical exercise, quality of self-management, psychological support, a digital or analogue feedback system, and professional supervision. Therefore, within long-term post-infarction management, home-based cardiac rehabilitation should be considered not as a universal model for all patients but as a structured format of rehabilitation that requires adaptation to clinical risk, functional capacity, psychological profile, and the patient's real living environment [13, 18]. A synthesis of the current evidence indicates that cardiac rehabilitation following myocardial infarction should not be viewed simply as a choice between centre-based rehabilitation and home-based exercise. Rather, these approaches represent a continuum of care models that differ in the level of professional supervision, accessibility, support for self-management, and suitability for different patient groups. A comparative characteristic of the main models of cardiac rehabilitation after myocardial infarction is presented in Table 1.

Table 1. Comparative characteristics of cardiac rehabilitation models after myocardial infarction

Organisational characteristic	Main advantages	Main limitations	Most appropriate use
Centre-based cardiac rehabilitation model			
The programme is performed in a specialised institution under direct supervision of specialists from a multidisciplinary team.	Face-to-face monitoring of the patient's condition, possibility of functional testing, rapid adjustment of exercise load, control of exercise technique, and higher safety for patients at increased risk.	Lower accessibility due to transport, geographical, time, financial, and organisational barriers; need for regular visits to the centre; limited patient coverage.	Patients after myocardial infarction with high or uncertain clinical risk, complex comorbidity, low ability for self-management, or need for initial face-to-face supervision.

Table 1. *Continued*

Organisational characteristic	Main advantages	Main limitations	Most appropriate use
Home-based cardiac rehabilitation model			
A structured programme is performed mainly in the home environment after initial assessment, risk stratification, individualised exercise prescription, and self-management training.	Higher accessibility, flexible schedule of sessions, integration of physical activity into everyday life, possibility of family involvement, and reduction of logistical barriers.	Requires sufficient clinical stability, ability for self-management, skills in responding to symptoms, and regular professional feedback.	Clinically stable patients at low or moderate risk who are able to follow instructions, keep self-management records, and maintain contact with a specialist.
Hybrid cardiac rehabilitation model			
Combines face-to-face visits, initial assessment, or control consultations with subsequent home-based performance of the programme and remote supervision.	Balance between the safety of face-to-face control and the accessibility of the home-based format; possibility of gradual transition from intensive supervision to self-management.	Requires coordination between face-to-face and remote stages, a clear patient pathway, definition of contact frequency, and criteria for transition between formats.	Patients at moderate risk, persons with unstable adherence, partial digital readiness, moderate kinesiophobia, or need for periodic face-to-face control.
Home-based cardiac rehabilitation model with telerehabilitation support			
The home-based programme is supplemented by video consultations, telephone support, electronic or paper diaries, mobile digital health technologies, wearable devices, or remote monitoring.	Supports self-management, regular feedback, monitoring of physical activity and symptoms; may increase adherence and accessibility in the long-term period.	Depends on digital literacy, technical accessibility, data confidentiality, quality of professional response, and availability of alternatives for patients without digital skills.	Patients who need long-term supervision after the inpatient stage of rehabilitation, especially when territorial or transport barriers are present, provided that professional control is maintained.

Source: compiled by the authors

The data in Table 1 indicate that comparison of different models of cardiac rehabilitation after myocardial infarction has fundamental importance for determining the optimal format of care in the long-term rehabilitation period. Contemporary literature most often considers three organisational models: centre-based cardiac rehabilitation, home-based cardiac rehabilitation, and hybrid cardiac rehabilitation. They should not be contrasted as mutually exclusive options since each model has its own clinical indications, advantages, limitations, and requirements for professional supervision. Telerehabilitation and mobile digital health technologies can supplement the home-based cardiac rehabilitation model with structure, control, and clinical manageability [12-13]. Centre-based cardiac rehabilitation has historically remained the basic model for organising cardiac rehabilitation. Its main advantage is direct face-to-face control by specialists, the possibility of functional testing, rapid adjustment of exercise load, observation of exercise technique, and involvement of a multidisciplinary team. This format is especially important for patients with higher clinical risk, comorbidity, low ability for self-management, or a need for more intensive observation. However, the centre-based rehabilitation model is the one most often limited by transport, time, geographical, financial, and organisational barriers, which reduces actual patient participation in cardiac rehabilitation programmes [11, 13]. Home-based cardiac rehabilitation emerged as a response to the limitations of the centre-based cardiac rehabilitation model. Its advantage lies in transferring the rehabilitation process to the patient's home or usual living environment, which increases accessibility, schedule flexibility, the possibility of family involvement, and integration of physical activity into everyday life. For stable patients at low or moderate risk, home-based cardiac rehabilitation is not inferior to centre-based cardiac rehabilitation in key outcomes, including functional capacity, quality of life, risk factors, and costs during follow-up of up to 12 months [14]. Nevertheless, home-based cardiac rehabilitation is not simple independent performance of exercises at home. Its evidence-based effectiveness presupposes a structured programme: preliminary assessment, risk stratification, individualised exercise prescription, self-management training, symptom monitoring, professional feedback, and clear safety criteria. Without these components, the home-based model loses clinical manageability and may turn into non-specific recommendations on physical activity [13, 17].

Hybrid cardiac rehabilitation combines the advantages of both approaches: initial face-to-face assessment, education, and primary adjustment of exercise load with subsequent home-based performance of the programme and remote or periodic face-to-face supervision. This format is particularly promising for patients at moderate risk, persons with a partial need for face-to-face control, patients with unstable adherence, moderate

kinesiophobia, or different levels of digital literacy. The hybrid model also has advantages for the long-term period, as it enables the intensity of professional control to be gradually reduced without complete termination of feedback [12]. Telerehabilitation and mobile digital health technologies have a separate role in the comparison of models. In home-based and hybrid models, they can provide monitoring of symptoms, heart rate, physical activity, adherence to the programme, and regular professional feedback. However, digital tools do not eliminate the need for a clinical protocol, risk stratification, and specialist participation. Their effectiveness depends on the patient's digital literacy, the quality of professional supervision, and the presence of symptom-response algorithms [16, 19, 20]. Comparison of the three models indicates that centre-based cardiac rehabilitation retains leading importance for patients who need intensive face-to-face control and multidisciplinary supervision. Home-based cardiac rehabilitation is an evidence-supported alternative for clinically stable patients at low or moderate risk, especially when logistical, geographical, or time barriers are present. Hybrid cardiac rehabilitation occupies an intermediate position and is promising for patients who need initial face-to-face assessment but can subsequently perform the programme at home with remote or periodic face-to-face supervision [14, 16, 20]. Thus, the choice of a cardiac rehabilitation model after MI should be determined not only by the accessibility of a centre or the availability of digital technologies, but primarily by clinical risk, functional capacity, psychological profile, ability for self-management, and the need for professional feedback. In the long-term rehabilitation period, the most promising approach is not the opposition of centre-based, home-based, and hybrid cardiac rehabilitation models, but their rational combination according to the patient's condition, rehabilitation goals, and the intensity of supervision required.

Telerehabilitation and mobile digital health technologies are key instruments that enable home-based cardiac rehabilitation to be transformed from a format of independent implementation of recommendations into a structured, controlled, and clinically managed model of care. In patients after myocardial infarction, these technologies have particular importance, as long-term recovery requires not only exercise prescription but also regular monitoring of symptoms, maintenance of adherence, adjustment of exercise load, self-management training, and timely contact with a specialist. Thus, digital support in home-based cardiac rehabilitation should be considered not as a technical addition but as an organisational mechanism for ensuring continuity of the rehabilitation process [12-13]. In the cardiological context, telerehabilitation should be understood as remote provision or support of rehabilitation care using telecommunication technologies. Such a format may include video consultations, telephone contact, transmission of self-management data, remote education, electronic diaries, reminders, professional feedback, and, where possible, monitoring of physiological indicators. Unlike a standard home-based programme, in which the patient mainly performs prescribed exercises independently, telerehabilitation preserves professional control and brings the home-based model closer to centre-based cardiac rehabilitation in terms of the supervision level, but without the need for regular physical attendance at a rehabilitation centre [13, 19]. The systematic review and meta-analysis by W. Zhong *et al.* [19], devoted to the long-term effects of cardiac telerehabilitation in patients with ischaemic heart disease, showed that telerehabilitation programmes can be effective for improving cardiorespiratory fitness and quality of life during long-term follow-up. The authors reported a positive effect of telerehabilitation on peak oxygen consumption and quality of life, while the completion rate of telerehabilitation interventions remained high. However, a stable long-term effect on control of cardiovascular risk factors, anxiety, or depressive symptoms was not convincingly demonstrated, which indicates the need to strengthen behavioural and psychosocial components in digitally supported programmes [19]. The practical importance of these data lies in the fact that telerehabilitation can partly compensate for one of the main weaknesses of home-based cardiac rehabilitation – the limitation of direct face-to-face professional control. Remote contact with a specialist allows for the assessment of exercise tolerance, detection of overload symptoms, correction of exercise intensity, maintenance of motivation, and gradual formation of safe independent training skills in the patient. It is especially important that the telerehabilitation format can be used in the long-term rehabilitation period, when the frequency of face-to-face contacts with the medical system decreases and the risk of losing achieved functional results increases [19-20].

A separate direction is represented by electronic health technologies and mobile digital health technologies oriented towards the maintenance phase of cardiac rehabilitation. The systematic review and meta-analysis by M. Heimer *et al.* [20] was specifically directed towards assessing electronic health technologies in the maintenance phase, where the main task is not functional recovery to the initial level but maintenance of physical activity, exercise tolerance, quality of life, self-management, and behavioural changes. The authors underlined that electronic health technologies can contribute to increased physical activity, improved exercise tolerance and quality of life, and improvement in individual indicators of cardiovascular risk compared with usual care. However, data on the impact on morbidity, mortality, and hard clinical endpoints remain limited [20]. For home-based cardiac rehabilitation after myocardial infarction, this has fundamental importance because it shifts the emphasis from

short-term performance of exercises to maintenance of behavioural changes in the long-term period. The most clinically meaningful components of electronic health technologies are behavioural self-management, goal setting, regular feedback, reminders, visualisation of progress, and professional reinforcement of activity. These components can prevent a gradual decline in physical activity after completion of the intensive phase of rehabilitation, when the patient is no longer under constant supervision [20]. Mobile digital health technologies are the most flexible and potentially scalable segment of digitally supported home-based cardiac rehabilitation. They include smartphone applications, wearable devices, heart-rate monitors, fitness trackers, electronic diaries, SMS reminders, chat communication with a specialist, and remote transmission of indicators of physical activity, heart rate, blood pressure, symptoms, and subjective exercise tolerance. The meta-analysis by L. Li *et al.* [16] was concentrated specifically on the effectiveness of home-based cardiac rehabilitation interventions delivered through mobile digital health technologies. Such interventions can increase rehabilitation accessibility, improve the regularity of the patient's contact with the programme, and create conditions for more objective self-management compared with traditional paper diaries. The clinical value of mobile digital health technologies lies not in the mere fact of using an application or wearable device, but in the feedback these instruments create between the patient and the specialist. The patient receives an opportunity to see personal progress, record symptoms, monitor heart rate, mark completed exercises, and receive reminders. The physical therapist or another member of the multidisciplinary team, in turn, can assess adherence, exercise tolerance, the need to adjust intensity, and detect signs of deterioration in a timely manner. Thus, mobile digital health technologies transfer the home-based programme from the passive format of "the patient has received recommendations" to the dynamic format of "the patient performs the programme under remote supervision" [12, 16].

In the long-term rehabilitation period, digital components that support behavioural stability are especially important. Such components include personalised physical-activity goals, regular feedback, automated reminders, visualisation of progress, brief educational modules, remote consultations, messages on achievement of intermediate goals, and the possibility of quick contact with a specialist when symptoms appear. These elements should be combined with the clinical logic of exercise dosing and should not function as isolated technological services. Without a clearly defined rehabilitation protocol, digital tools may increase the volume of data but do not guarantee improved clinical outcomes [16, 20]. Remote cardiac rehabilitation after myocardial infarction may also include an educational component implemented through e-learning platforms. The review by D. Trache *et al.* [21] emphasised the importance of combining remote learning, monitoring of cardiovascular risk factors, control of physical activity, and maintenance of adherence after a heart attack. Such an approach allows both monitoring of exercise performance and support for the broader process of secondary prevention, which includes lifestyle modification, blood pressure control, nutritional correction, smoking cessation, medication adherence, and patient self-management. Firstly, digital models depend on access to a smartphone, stable internet, wearable devices, or other technical means. Secondly, older patients and persons with a lower level of education or cognitive or sensory limitations may have difficulties using applications and platforms. Thirdly, some patients do not trust digital tools or are not ready to interpret indicators independently. Fourthly, issues arise concerning confidentiality of medical data, responsibility for responding to warning signals, and standardisation of remote monitoring algorithms [12, 20].

For this reason, digital support for home-based cardiac rehabilitation should not have a universal character. For patients with sufficient digital literacy, the use of smartphone applications, wearable devices, electronic diaries, and video consultations may be appropriate. For patients with a lower level of digital literacy, analogue instruments should be provided: telephone support, printed instructions, paper self-management diaries, periodic face-to-face contacts, and family assistance. This approach prevents a situation in which digitalisation increases rehabilitation accessibility for some patients but creates additional barriers for others [13, 16]. The optimal structure of digitally supported home-based cardiac rehabilitation after myocardial infarction should include several mandatory elements. The first is initial clinical and functional assessment and risk stratification, without which a remote format may be unsafe. The second is individual exercise prescription with clear parameters of frequency, intensity, duration, and type of exercise. The third is patient training in self-management: assessment of symptoms, heart rate, level of dyspnoea, fatigue, and signs requiring exercise to be stopped. The fourth is regular remote feedback. The fifth is psychological-behavioural support directed towards overcoming fear of movement, maintaining motivation, and forming self-efficacy [12, 16, 20]. Thus, telerehabilitation and mobile digital health technologies in home-based cardiac rehabilitation after myocardial infarction perform three interrelated functions: they increase accessibility of rehabilitation care, provide remote professional supervision, and support long-term adherence to physical activity. Available systematic reviews indicate a positive effect of telerehabilitation, electronic health technologies, and mobile digital health technologies on functional capacity, physical activity, and quality of life. However, they also emphasise the limited data on long-term clinical endpoints,

psychological outcomes, protocol standardisation, and the effectiveness of digital models in different patient groups. Therefore, the most substantiated approach is not isolated digitalisation of home-based cardiac rehabilitation but the integration of telerehabilitation and mobile digital technologies into a structured clinical programme with risk assessment, professional supervision, psychological support, and adaptation to the patient's capabilities.

The long-term rehabilitation period after myocardial infarction remains one of the least developed areas of the evidence base on home-based cardiac rehabilitation. Available systematic reviews and meta-analyses quite convincingly confirm the effectiveness of home-based programmes in the short and medium term, but the vast majority of studies assess outcomes within several weeks, 3-6 months, or up to 12 months after the start of the intervention. Over this follow-up period, home-based cardiac rehabilitation provides outcomes comparable to those of centre-based cardiac rehabilitation with respect to functional capacity, quality of life, programme adherence, and control of selected cardiovascular risk factors. However, preservation of these outcomes after completion of the structured programme, especially beyond 12 months, remains less extensively evaluated and methodologically heterogeneous [14-15]. The long-term rehabilitation period cannot be considered as a simple continuation of the acute or post-acute phase of cardiac rehabilitation. While the main tasks at the initial stages are safe mobilisation, restoration of basic exercise tolerance, symptom control, and patient education, in the maintenance phase, the main task becomes preservation of the already achieved functional level, prevention of return to sedentary behaviour, maintenance of adherence to physical activity, and integration of secondary prevention recommendations into everyday life. Thus, long-term cardiac rehabilitation requires not only repetition of the training protocol but also a separate behavioural, educational, and organisational strategy [12, 20].

A critical moment in post-infarction recovery is the transition from a controlled rehabilitation environment to independent implementation of recommendations. During a structured programme, the patient has external control, regular contact with a specialist, a clear schedule of sessions, control of exercise tolerance, and constant motivational reinforcement. After completion of the programme, the frequency of professional contact decreases, and responsibility for maintaining activity is transferred to the patient. In home conditions, this creates a risk of gradual reduction in physical activity, irregular performance of exercises, avoidance of exertion because of fear of symptoms, loss of self-management, and return to the previous sedentary lifestyle [13, 22]. The systematic review by H. Graham *et al.* [21], devoted to interventions for maintaining or increasing physical activity after completion of phase II cardiac rehabilitation, showed that the maintenance phase remains one of the most difficult stages of the rehabilitation process. The authors emphasised that existing programmes differ considerably in duration, intensity of contact with a specialist, behavioural components, forms of self-management, and criteria for outcome assessment. Such heterogeneity complicates comparison of studies and does not allow a single standardised protocol for long-term maintenance of physical activity after cardiac rehabilitation to be formed.

A separate problem is the limited data on hard clinical endpoints in the long-term period. Short- and medium-term outcomes are most commonly assessed using peak oxygen uptake (VO_2peak), Six-Minute Walk Test (6MWT) distance, quality of life, physical activity levels, and programme adherence. By contrast, the long-term effect of home-based cardiac rehabilitation on recurrent myocardial infarction, cardiovascular mortality, repeated hospitalisations, stability of risk-factor control, and healthcare system costs requires further evaluation. This does not deny the effectiveness of the home-based model, but it indicates the need for longer, better standardised, and methodologically stronger studies [14, 20]. The problem of adherence to the programme has particular importance in the long-term period. For patients following myocardial infarction, performing exercise at home requires not only an understanding of the benefits of physical activity but also established exercise habits, confidence in exercising safely, the ability to regulate exercise intensity independently, and readiness to continue the programme with reduced professional supervision. For this reason, short-term improvement in functional indicators does not always mean long-term change in movement behaviour. If the programme does not contain mechanisms for maintaining motivation, self-management, feedback, and social support, the achieved effect may gradually be lost [20, 22]. In this aspect, electronic health technologies and mobile digital health technologies have clear potential, but they do not eliminate the problem automatically. The systematic review and meta-analysis by M. Heimer *et al.* [20], devoted to electronic health technologies for cardiac rehabilitation in the maintenance phase, showed that digital interventions can contribute to increased physical activity, improved exercise capacity, quality of life, and individual indicators of cardiovascular risk compared with usual care. However, the authors indicate that available studies remain heterogeneous in design, technological platforms, duration of follow-up, intensity of professional feedback, and method of assessing behavioural outcomes [20]. Thus, digital technologies in the maintenance phase should be considered not as an independent replacement for a rehabilitation programme but as an instrument for maintaining long-term behavioural change. The most clinically meaningful elements are not applications, wearable devices, or electronic diaries themselves, but

the functions they provide: self-management, setting individual goals, regular feedback, reminders, visualisation of progress, remote adjustment of exercise load, and rapid contact with a specialist if symptoms appear. Without professional supervision, digital tools can record activity but cannot always support stable adherence and correct interpretation by the patient of their own condition [16, 20].

Data on cardiac telerehabilitation also confirm the prospects of remote supervision in the long-term period but also demonstrate the incompleteness of the evidence base. The systematic review and meta-analysis by W. Zhong *et al.* [19] demonstrated a positive effect of cardiac telerehabilitation on long-term functional indicators and quality of life in patients with ischaemic heart disease. However, the effect on control of risk factors, psychological outcomes, and hard clinical endpoints remains less clear. This means that telerehabilitation has high potential as a mechanism for supporting home-based cardiac rehabilitation but requires integration with the behavioural, psychological, and clinical components of the programme [19]. For home-based cardiac rehabilitation after myocardial infarction, the long-term period is especially vulnerable due to the combination of several factors: reduced frequency of contact with the medical system, the patient's return to usual everyday and professional loads, fluctuations in motivation, fear of a recurrent cardiac event, comorbidity, uneven family support, and different levels of digital literacy. In patients with low self-efficacy or kinesiophobia, the home environment may fail to support activity and, conversely, may increase avoidance of physical exercise. Therefore, the maintenance phase requires no less, and in some cases greater, individualisation than the early period of cardiac rehabilitation [12-13, 22]. From a methodological position, the main problem of contemporary studies is the heterogeneity of definitions of the long-term period. In different works, the maintenance phase may be interpreted as the period after completion of phase II cardiac rehabilitation, as follow-up beyond 6 months, beyond 12 months, or as an undefined stage of independent activity maintenance. Differences in definitions mean that results are difficult to compare with each other, while conclusions about the effectiveness of long-term interventions remain less certain. For future research, it is advisable to distinguish clearly between the early, post-acute, and long-term stages, and to indicate the duration of active intervention, duration of follow-up, and intensity of professional supervision [20-21].

Another gap is insufficient standardisation of outcomes assessed in long-term programmes. In addition to traditional functional indicators, it is advisable to measure systematically the level of everyday physical activity, sedentary behaviour, adherence to independent exercises, self-efficacy, kinesiophobia, anxiety, depressive symptoms, health-related quality of life, repeated hospitalisations, and use of medical resources. Without such a multidimensional approach, the long-term effectiveness of home-based cardiac rehabilitation may be assessed incompletely: a programme may improve peak oxygen consumption in the short term but fail to ensure sustained behavioural change or reduced risk of recurrent events [12, 20]. In practical terms, this means that home-based cardiac rehabilitation after myocardial infarction should be designed from the outset as a long-term model rather than a brief instruction after discharge. Its structure should provide for initial clinical and functional assessment, individual exercise prescription, periodic reassessment of goals, self-management training, symptom-response algorithms, psychological screening, gradual reduction in the intensity of professional supervision without complete cessation of contact, and instruments for maintaining motivation after completion of the active phase. This approach shifts the focus from short-term performance of a set of exercises to the formation of stable movement behaviour [13, 22].

Long-term care following myocardial infarction should also be considered within the broader framework of secondary prevention and the long-term management of chronic coronary syndromes. Long-term management of the patient after myocardial infarction should also be considered in the broader context of secondary prevention and management of chronic coronary syndromes. After the acute event, the patient moves to long-term control of residual cardiovascular risk, including lifestyle modification, physical activity, control of blood pressure, lipids, glycaemia, body weight, medication adherence, and structured rules for stopping or modifying physical exercise, contacting a specialist, or seeking emergency care when clinical signs of exercise intolerance appear. Therefore, home-based cardiac rehabilitation in the long-term period should be integrated not only into an exercise programme but also into the general strategy of secondary prevention after myocardial infarction [23-24]. Thus, the long-term rehabilitation period is the main gap in the current evidence base on home-based cardiac rehabilitation after myocardial infarction. Available data confirm the effectiveness of home-based programmes in the short and medium term, but leave open the issues of sustained maintenance of physical activity, long-term adherence, impact on recurrent events, optimal duration of supervision, the role of psychological components, and standardisation of digital support. Accordingly, the further development of home-based cardiac rehabilitation should be directed towards the creation of long-term, personalised, and structured programmes that combine clinical and functional stratification, behavioural support, telerehabilitation, mobile digital health technologies, family involvement, and periodic professional control [16, 19-21].

Psychological and behavioural barriers are another reason why home-based cardiac rehabilitation that

is effective in content may fail to ensure a stable result in the long-term period. Psychological distress, kinesiophobia, low self-efficacy, weak social support, insufficient digital literacy, and unstable motivation directly affect the start of the programme, regularity of exercise performance, self-management, and maintenance of movement behaviour. Therefore, home-based cardiac rehabilitation after myocardial infarction should be not only clinically and functionally individualised but also psychologically and behaviourally supported. The integration of psychological screening, behavioural support, family involvement, mobile digital health technologies, and professional feedback creates the prerequisites for effective long-term supervision of the patient after myocardial infarction [22, 25]. Thus, home-based cardiac rehabilitation after myocardial infarction is a promising, evidence-supported, and potentially scalable model of secondary prevention. However, its long-term effectiveness depends not only on prescribing physical exercises at home, but on the comprehensive organisation of the programme: risk stratification, professional supervision, psychological-behavioural support, telerehabilitation, adapted digital or analogue instruments, and standardised assessment of outcomes. Therefore, the optimal development of cardiac rehabilitation after MI lies not in replacing the centre-based cardiac rehabilitation model with a home-based one, but in the rational combination of centre-based, home-based, and hybrid formats according to clinical risk, functional status, psychological profile, and the needs of long-term patient management [23-24].

The results obtained are consistent with the data of the randomised study by R. Bravo-Escobar *et al.* [26], in which home-based cardiac rehabilitation with mixed supervision in patients with ischaemic heart disease at moderate risk showed effectiveness and safety when preliminary selection and controlled supervision were provided. A common conclusion is that the home-based format cannot be considered as uncontrolled independent exercise, it should include initial assessment, individualisation of exercise load, self-management, and professional contact. The difference of the present study lies in its focus specifically on the long-term period after myocardial infarction, where maintenance of adherence, long-term behavioural change, and prevention of loss of achieved functional outcomes become key. The conclusion on the appropriateness of telerehabilitation supervision partly coincides with the findings of R. Hwang *et al.* [27], who indicated that home-based telerehabilitation for patients with chronic heart failure may produce functional outcomes similar to those of a centre-based programme. Although the population of that study differs from post-infarction patients, its results support the general idea that a remote format can be clinically acceptable when proper monitoring is provided. The present study complements these data by stressing the need for symptom-response algorithms, risk stratification, and a combination of digital and analogue tools for patients with different levels of digital literacy.

The data of E. Piotrowicz *et al.* [28] on hybrid telerehabilitation in patients with heart failure demonstrate that remotely supported programmes can improve functional indicators but do not always convincingly affect hard clinical endpoints. This corresponds to the conclusion obtained that telerehabilitation is not a self-sufficient substitute for a clinically structured programme. It should be considered as an instrument for supporting physical activity, self-management, and feedback, rather than as a separate technological intervention. The results of the international INTERASPIRE survey presented by K. Kotseva *et al.* [29] confirm that, even in the presence of an evidence base, cardiac rehabilitation remains underused in different healthcare systems. This coincides with the above-described emphasis on accessibility as one of the main reasons for the development of home-based and hybrid models. However, this paper specifies that increasing accessibility should be accompanied not by simplification of the programme but by preservation of clinical manageability. The analysis by B. Jug *et al.* [30] of outpatient and residential cardiac rehabilitation after myocardial infarction in Slovenia indicates the importance of the organisational model, routing, and regional accessibility for patient participation and clinical outcomes. Unlike that publication, the present study does not analyse a national registry, but complements available data with a conceptual justification of the home-based format for the long-term period. Its contribution lies in the integration of three components that are often considered separately: evidence-based effectiveness of home-based cardiac rehabilitation, telerehabilitation support, and psychological-behavioural conditions for long-term adherence after myocardial infarction.

CONCLUSIONS

1. Exercise-based cardiac rehabilitation is an evidence-based component of secondary prevention following myocardial infarction. Its clinical value extends beyond improving exercise capacity to reducing cardiovascular mortality, recurrent cardiovascular events, and hospitalisations, while also improving health-related quality of life. Accordingly, post-myocardial infarction cardiac rehabilitation should be regarded as a standard component of long-term patient care rather than as an optional post-discharge intervention.

2. Home-based cardiac rehabilitation is an evidence-supported alternative to centre-based cardiac rehabilitation for clinically stable patients at low or moderate risk after myocardial infarction. Current systematic reviews and comparative studies indicate that home-based programmes can provide results not inferior in effectiveness to centre-based programmes in terms of functional capacity, quality of life, adherence to the programme, and control of individual cardiovascular

risk factors. However, these conclusions should not be automatically applied to all patients after MI without prior risk stratification.

3. The safety and effectiveness of home-based cardiac rehabilitation depend not on the place where exercises are performed itself, but on the quality of clinical organisation of the programme. Mandatory conditions are initial clinical and functional assessment, risk stratification, individualised exercise prescription, self-management training, symptom monitoring, clear criteria for stopping or modifying exercises, and regular professional feedback. For patients at high risk or with an unstable clinical condition, centre-based cardiac rehabilitation or hybrid cardiac rehabilitation may be more appropriate.

4. The greatest gap in the current evidence base remains the long-term rehabilitation period, specifically the maintenance phase. Most studies assess outcomes over 3-12 months, whereas questions of sustained maintenance of physical activity, long-term adherence, preservation of functional outcomes, impact on repeated hospitalisations, recurrent myocardial infarction, and cardiovascular mortality beyond 12-24 months remain insufficiently evaluated. In this period, not only the parameters of physical exercise but also self-management, behavioural support, periodic reassessment of goals, and long-term professional supervision become decisive.

5. Telerehabilitation, electronic technologies, and mobile health technologies can improve the accessibility of home-based cardiac rehabilitation by supporting self-management, monitoring, and adherence to the programme. However, their effectiveness depends on integration into clinically structured rehabilitation, professional supervision, and adaptation to the patient's digital literacy.

6. Psychological and behavioural factors are an integral component of home-based cardiac rehabilitation after myocardial infarction. Psychological distress, kinesiophobia, low self-efficacy, and insufficient social support may reduce adherence to the programme, so an effective model should include psychological screening, behavioural support, motivational counselling, family involvement, and regular professional feedback.

Prospects for further research. Further research on home-based cardiac rehabilitation after myocardial infarction should be directed towards long-term randomised studies, standardisation of programmes and outcome indicators, assessment of safety and psychological and behavioural consequences, and comparison of different supervision formats and their economic feasibility.

Limitations of the study. The study is an analytical narrative review with elements of a systematised search and did not involve a formal systematic review or meta-analysis. The conclusions are based on secondary analysis of home-based, hybrid, and telerehabilitation programmes that are heterogeneous in structure, duration, intensity of supervision, and effectiveness indicators. In addition, most studies include patients at low or moderate risk and short- and medium-term outcomes, whereas long-term effectiveness, safety for high-risk patients, and economic feasibility remain insufficiently evaluated. Therefore, the conclusions presented should be considered as a synthesis of the current evidence base requiring further verification in long-term randomised studies.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Ігор Савчук
Старший викладач
Академія рекреаційних технологій і права
43023, вул. Промислова, 2, м. Луцьк, Україна
https://orcid.org/0000-0002-5724-0078

Андрій Сітовський
Кандидат наук з фізичного виховання та спорту
Академія рекреаційних технологій і права
43023, вул. Промислова, 2, м. Луцьк, Україна
https://orcid.org/0000-0002-7434-7475

Олена Якобсон
Кандидат медичних наук, доцент
Волинський національний університет імені Лесі Українки
43025, просп. Волі, 13, м. Луцьк, Україна
https://orcid.org/0000-0002-7340-2014

Яна Ушко
Кандидат біологічних наук, доцент
Академія рекреаційних технологій і права
43023, вул. Промислова, 2, м. Луцьк, Україна
https://orcid.org/0000-0003-3017-7766

Домашня кардіореабілітація після інфаркту міокарда в довготривалому реабілітаційному періоді: доказова база та перспективи розвитку

Анотація
Актуальність. Інфаркт міокарда супроводжується тривалими функціональними, клінічними та психоемоційними наслідками, тоді як недостатня доступність традиційних програм кардіореабілітації у центрі зумовлює потребу в доказово обґрунтованих домашніх, гібридних і телереабілітаційних моделях, здатних підтримувати безпечну фізичну активність, самоконтроль і вторинну профілактику в довготривалому реабілітаційному періоді.
Мета. Узагальнити сучасну доказову базу щодо домашньої кардіореабілітації після інфаркту міокарда, визначити її ефективність, безпечність та перспективи застосування в довготривалому реабілітаційному періоді.
Матеріали та методи. Стаття виконана у форматі аналітичного наративного огляду з елементами систематизованого пошуку. Проаналізовано систематичні огляди, метааналізи, рандомізовані контрольовані дослідження, когортні дослідження, наукові заяви професійних товариств і клінічні настанови, присвячені кардіореабілітації на основі фізичних вправ, домашній кардіореабілітації, кардіотелереабілітації, мобільним технологіям охорони здоров'я (mHealth), фазі підтримки, прихильності до домашніх фізичних вправ, кінезіофобії, психологічному дистресу та довготривалому самокеруванню пацієнтів після інфаркту міокарда.

Результати. Сучасні дані свідчать, що домашня кардіореабілітація може забезпечувати результати, що не поступаються програмам, які проводяться в лікувально-профілактичних та реабілітаційних закладах, у клінічно стабільних пацієнтів низького або помірного ризику після інфаркту міокарда. Безпечність домашньої моделі залежить від належного відбору пацієнтів, стратифікації ризику, індивідуалізованого призначення фізичного навантаження, навчання самоконтролю, регулярного професійного зворотнього зв'язку, алгоритмів реагування на симптоми – тобто структурованих правил припинення або модифікації фізичного навантаження, контакту з фахівцем чи звернення по невідкладну допомогу при появі клінічних ознак непереносимості навантаження. Телереабілітація та мобільні цифрові технології охорони здоров'я можуть підвищувати доступність, підтримувати самоконтроль, полегшувати моніторинг симптомів і фізичної активності, однак не є самодостатньою заміною клінічно структурованої програми. Найбільшою прогалиною залишається довготривалий реабілітаційний період, у якому вирішальними стають підтримання рухової поведінки, прихильність, психологічна адаптація, подолання кінезіофобії, самоефективність і соціальна підтримка.

Висновки. Домашня кардіореабілітація після інфаркту міокарда є перспективною моделлю вторинної профілактики для відібраних клінічно стабільних пацієнтів, проте її довготривала ефективність потребує структурованого професійного супроводу, стратифікації ризику, психологічно-поведінкової підтримки, телереабілітації або аналогових інструментів самоконтролю та стандартизованої оцінки функціональних, клінічних і поведінкових результатів.

Ключові слова: фізична терапія; вторинна профілактика; прихильність; фактори ризику; серцево-судинні захворювання.

PUBLIC HEALTH

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 614.2:[061.2:614.8]
DOI: https://doi.org/10.32345/2664-4738.2.2026.11

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 24.12.2025 Revised: 24.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Anatoliy Hrynzovskyi*

Doctor of Medical Sciences, Professor, Honoured Worker of Science and Technology of Ukraine
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-8391-5294

Svitlana Kalashchenko

PhD, Associate Professor
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-9942-7607

Ihor Kuzin

Postgraduate Student
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
Ministry of Health of Ukraine
01601, 7 Mykhailo Hrushevskyi Str., Kyiv, Ukraine
https://orcid.org/0000-0002-6418-6567

Dmytro Bondarenko

Postgraduate Student, General Director
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
Odesa Regional Centre for Disease Control and Prevention of the Ministry of Health of Ukraine
65074, 5-A Ivan and Yurii Lypa Str., Odesa, Ukraine
https://orcid.org/0009-0009-9087-4281

Taras Ostapchuk

Postgraduate Student
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0009-0005-1563-6217

System for forming and maintaining the competence of rapid response teams of the Centres for Disease Control and Prevention of the Ministry of Health of Ukraine

Abstract

Relevance. Under modern biological, chemical, radiological, and other threats to public health, improvement of the system for developing and maintaining the competence of rapid response teams of the Centres for Disease Control and Prevention becomes particularly important.

Aim. To identify the main problems in developing and maintaining professional competence and to substantiate directions for its improvement based on an analysis of regulatory support and the results of a survey of specialists from rapid response teams of the Centres for Disease Control and Prevention.

Materials and methods. Bibliosemantic, information-analytical, and sociological methods, together with descriptive statistics, were used in the work. The sociological stage of the study involved an anonymous questionnaire survey of specialists from rapid response teams (RRTs) of the Centres for Disease Control and

Suggested Citation:
Hrynzovskyi A, Kalashchenko S, Kuzin I, Bondarenko, D, Ostapchuk T. System for forming and maintaining the competence of rapid response teams of the Centres for Disease Control and Prevention of the Ministry of Health of Ukraine. Med Sci Ukr. 2026;22(2):104–113. DOI: https://doi.org/10.32345/2664-4738.2.2026.11

*Corresponding author (*grin_am@ukr.net*)

Prevention (CDCPs) to assess the current training system, experience of participation in emergency response, and directions for its improvement. Regulatory documents, educational and certificate programmes, electronic resources, and the results of sociological studies on the training and activity of RRTs of CDCPs were analysed.
Results. It was established that the competence system of RRTs of CDCPs should include cognitive, operational-technological, communicative, digital, and personal-motivational components. The key competences include emergency response, epidemiological investigation, risk assessment, laboratory diagnostics, interagency interaction, and public information. Competence is maintained through continuous learning, training, updating of the regulatory framework, resource provision, readiness monitoring, and international cooperation. According to the results of the questionnaire survey, 47.0% of respondents indicated the need to strengthen practical training, and 48.5% had experience of responding to public health emergencies. The need to develop psychological training, improve the integrated competence-based approach, and train personnel to work with modern material and technical support was also determined.
Conclusions. The results obtained indicate the need to strengthen the practical and psychological components of training for RRT personnel of CDCPs, develop practice-oriented forms of learning, and regularly practise emergency response algorithms. Professional competence should be maintained by combining continuous professional development, readiness monitoring, interagency drills, and international cooperation. The certificate programme "Emergency Preparedness, Response and Management" can be considered an effective instrument of professional development, as it combines a competence-based approach, practical training, training in response to chemical, biological, radiological, and nuclear threats, and the development of interagency interaction skills.
Keywords: emergencies; professional standards; conditions of uncertainty; epidemiological surveillance; martial law.

INTRODUCTION

Current threats to public health, including epidemics of infectious diseases, the consequences of military actions, technogenic accidents, and chemical, biological, and radiological risks, require the creation of effective response mechanisms at both national and regional levels. The COVID-19 pandemic, the full-scale war in Ukraine, and the growing number of emergencies have demonstrated the importance of trained specialists who can rapidly assess risks, conduct epidemiological investigations, and coordinate response measures [1]. One of the key elements in ensuring the preparedness of public health systems for emergencies is the functioning of specialised rapid response teams. Data from the World Health Organization [2] and N.R. Gillon *et al.* [3] indicated that the effectiveness of such teams depends not only on the professional knowledge of their members but also on the level of development of practical skills, interagency interaction, crisis communication, and readiness to work under conditions of uncertainty. Y. Khan *et al.* [4] focused on the development of a competence-based approach, which involves the integration of theoretical training, practical exercises, and continuous professional development. An important direction of current research concerns mechanisms for maintaining the professional competence of personnel involved in emergency response. H. Utunen *et al.* [5] noted that even a high level of basic training requires regular updating of knowledge and skills due to changes in the nature of threats, the introduction of new monitoring and diagnostic technologies, and the development of digital tools in public health. Simulation-based learning, scenario-based training, and intersectoral educational programmes acquire particular importance, as they allow action algorithms to be practised under conditions close to real crisis situations. The work by M.M. Koziar [6] focused attention on the psychological readiness of personnel, as work in emergency sites is accompanied by considerable psycho-emotional strain, the need for rapid decision-making, and a high level of responsibility. In this regard, stress resistance, self-regulation skills, and the ability to work effectively in a team are increasingly included in the structure of professional competence.

In Ukraine, the issue of developing and maintaining the competence of rapid response teams became especially relevant after the adoption of Law of Ukraine No. 2573-IX [7], according to which rapid response teams and operational-dispatch units must function within the structure of the Centres for Disease Control and Prevention. Under martial law, they are assigned tasks related to epidemiological surveillance, risk assessment, response to outbreaks of infectious diseases, participation in eliminating the consequences of emergencies, laboratory monitoring, and interaction with other actors in the civil protection system. The system for developing the competence of rapid response teams (RRTs) of the Centres for Disease Control and Prevention (CDCPs) is based on the principles of continuous professional development and includes training in epidemiological surveillance, sample collection and transportation, risk assessment, biosafety, crisis communication, and response to chemical, biological, radiological, and nuclear threats. However, the practice of RRT functioning indicates the need for further improvement of existing approaches to personnel training, strengthening of the practical component of learning, development of psychological readiness, and improvement of mechanisms for maintaining

professional competence. Educational and certificate programmes aimed at forming modern professional competencies play an important role in this process. The World Health Organization [1] considered competence-oriented education as one of the key mechanisms for strengthening the workforce capacity of healthcare systems. Among the instruments of continuous professional development, specialised certificate programmes occupy an important place, as they combine theoretical learning with practical training and practising emergency response algorithms. One such instrument is the certificate programme "Emergency Preparedness, Response and Management". Despite the presence of regulatory support and individual publications in the field of professional training for public health specialists, the issue of a comprehensive assessment of the system for developing and maintaining the competence of RRTs of CDCPs, together with identification of ways to improve it in view of specialists' practical experience, remains insufficiently examined, which determined the relevance of the present study. The study aimed to assess the features of developing and maintaining the professional competence of specialists from rapid response teams of the Centres for Disease Control and Prevention and to substantiate directions for its improvement based on an analysis of regulatory support and survey results.

MATERIALS AND METHODS

The study was designed as a cross-sectional medical-sociological study aimed at assessing the features of developing and maintaining the professional competence of specialists from RRTs of CDCPs. The object of the study was the system of training and maintenance of professional competence of RRT personnel, and the subject was the professional, organisational, and educational factors that influence specialists' readiness to respond to public health emergencies. Bibliosemantic and information-analytical methods were used to analyse regulatory documents, scientific publications, methodological materials, and electronic resources that regulate RRT activity and the training of specialists for emergency response, including Resolution of the Cabinet of Ministers of Ukraine No. 321/25 [8] and Order of the Ministry of Health of Ukraine No. 2213 [9]. The source base was selected according to the criteria of relevance, correspondence to the subject of the study, and practical importance for the public health system. The sociological stage of the study was conducted during 2023-2024 through an anonymous questionnaire survey of specialists from the Public Health Centre of the Ministry of Health of Ukraine and regional Centres for Disease Control and Prevention. The survey involved 381 respondents who were members of the main or reserve composition of RRTs. Among them, 195 (51.2%) worked in the biological field, 129 (33.9%) – in the chemical field, and 57 (14.9%) –in the radiological/nuclear field of activity. Employees of the Public Health Centre of the Ministry of Health of Ukraine and regional Centres for Disease Control and Prevention who belonged to the main or reserve composition of RRTs and provided written informed consent to participate in the study were included. The exclusion criteria were refusal to participate in the study or incomplete completion of the questionnaire.

The questionnaire included 40 questions grouped into thematic blocks devoted to assessing the conditions of professional activity, health status, readiness to respond to emergencies, psychophysiological characteristics, and needs in professional development. Open, closed, and multiple-choice questions were used to collect information. Closed questions enabled standardised quantitative indicators to be obtained, multiple-choice questions –the range of possible characteristics and influencing factors to be assessed, and open questions –respondents to express their own proposals for improving the system of training and maintaining the competence of RRT personnel. This structure of the questionnaire allowed both quantitative and qualitative data to be obtained for a comprehensive analysis of the problem under study. The questionnaire survey was performed individually using an electronic survey form. The average time for completing the questionnaire was about 15-20 minutes, which supported the collection of complete information without excessive burden on respondents. The questionnaire was developed by the authors of the study in accordance with the purpose and objectives of the work, based on an analysis of regulatory documents, scientific publications, and practical experience of rapid response teams in public health. The content of the questions covered the main components of professional activity, readiness to respond to emergencies, psychophysiological characteristics, and needs in professional development, which ensured the content validity of the instrument.

Nominal and ordinal scales, together with point-based self-assessment scales for individual characteristics, were used to assess most indicators. Closed questions were analysed by calculating absolute and relative indicators. Responses to open questions were subjected to content analysis, followed by grouping into content categories and determining the frequency of mention of individual proposals and problematic aspects. Statistical processing of the results was performed using descriptive statistics. Data analysis used calculation of absolute values, relative indicators (%), synthesis, and comparison of the results obtained between separate groups of respondents. Data processing was performed using Microsoft Excel and IBM SPSS Statistics. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki of the World Medical Association [10]. All respondents participated in the study voluntarily and provided written informed consent. Confidentiality of personal data was ensured

at all stages of the study. The work was approved by the Ethics Committee of the State Institution "Public Health Centre of the Ministry of Health of Ukraine" (IRB2022-80; protocol dated 17.11.2022 No. 241). The opinions expressed in this paper are those of the authors and not the official positions of the institution.

RESULTS AND DISCUSSION

According to the results of the conducted study, regulatory documents, methodological materials, and educational and certificate programmes regulating the activity of RRTs of CDCPs and the formation of their professional competences were analysed. It was established that RRTs are specialised mobile units of the public health system that provide rapid response to biological, chemical, radiological, and other emergencies. Their activity is directed towards performing tasks of epidemiological surveillance, risk assessment, laboratory monitoring, investigation of infectious disease outbreaks, and implementation of anti-epidemic measures directly in the sites where threats arise. Analysis of current regulatory documents allowed the key competences required for effective RRT activity to be identified (Table 1) [11].

Table 1. Key competences of RRTs of CDCPs

Competence	Main content
Rapid response to threats	Immediate response to emergencies related to infectious diseases, mass poisonings, and exposure to hazardous environmental factors
Epidemiological investigation	Identification of sources and routes of transmission of infectious diseases and determination of risk factors
Specialised monitoring	Biological, chemical, and radiological control and localisation of hazard sites
Laboratory diagnostics	Collection, transportation, and testing of samples
Implementation of anti-epidemic measures	Localisation and elimination of infectious disease sites
Interagency interaction	Coordination of activity with the State Emergency Service of Ukraine, healthcare facilities, and authorities
Risk communication and public information	Provision of reliable information and communication during crisis situations

Source: compiled by the authors

The analysis performed indicated that the regulatory framework sufficiently regulates the functions and tasks of RRTs, but gives much less attention to mechanisms for maintaining the competences already formed. Specifically, regulatory documents describe in detail the issues of epidemiological surveillance, laboratory diagnostics, and anti-epidemic measures, whereas regular practising of practical skills, psychological training of personnel, interagency interaction, and assessment of readiness level are covered less systematically. It was established that the modern RRT competence model should include not only professional knowledge but also practical skills required for work directly in emergency sites. Based on the analysis of educational programmes and international approaches, five main components of competence were determined: cognitive, operational-technological, communicative, digital, and personal-motivational. The operational-technological component requires particular attention, as it includes practical practising of response algorithms, use of personal protective equipment, field sample collection, and work under increased risk. This component is the most difficult to maintain through theoretical learning alone and requires regular training and simulation exercises. Thus, the results of the analysis point to a certain gap between the regulatory requirements for RRT activity and the practical mechanisms for maintaining their readiness. This determines the need for further development of the system of continuous professional training, expansion of practice-oriented forms of preparation, and introduction of mechanisms for regular monitoring of the level of formed professional competences.

An anonymous questionnaire survey of employees of the Public Health Centre of the Ministry of Health of Ukraine and regional CDCPs who were members of the main or reserve composition of RRTs was conducted to clarify current problems in developing and maintaining professional competence. The survey results provided for the strengths of the existing training system to be assessed and directions for its further improvement to be determined. One of the most notable results was that 47.0% of respondents indicated the need to strengthen the practical component of learning. Moreover, 48.5% of the respondents reported having personal experience of participating in response to public health emergencies. This highlights that practical training is relevant both for employees without response experience and for those who have already participated in eliminating the consequences of emergencies. Analysis of respondents' open answers showed that most respondents understood "strengthening practical training" not as an increase in the amount of theoretical knowledge but as expansion of the number of practical exercises, simulation-based learning sessions, and interagency drills. The need to practise algorithms for response to biological, chemical, and radiological threats, use of personal protective equipment, organisation of mobile team work, and interaction with other services during emergencies was mentioned most often [12-13]. This tendency is also confirmed by the results of the

analysis of readiness to work in field conditions. Although more than 80% of respondents assessed their general readiness to respond to emergencies as sufficient, the share of those who were fully ready to work directly in field conditions was substantially lower. This suggests that practical readiness for work under real emergency conditions is the most vulnerable component of professional training. Since the study was descriptive, the results identify the main tendencies and needs of RRT personnel, but further confirmation is needed in studies using comparative statistical analysis. Comparison of indicators of general readiness to respond to emergencies and readiness to work directly in field conditions showed certain differences. While the level of general readiness in most groups exceeded 80%, readiness to work in field conditions was lower and was accompanied by an increase in the proportion of respondents who assessed their training as insufficient. The obtained results indicate the presence of a gap between theoretical training and confidence in performing practical tasks under real emergency conditions, which additionally substantiates the need to expand practice-oriented forms of learning. Analysis of respondents' answers showed that the greatest interest was caused by practical classes aimed at practising algorithms for response to biological, chemical, and radiological threats, use of personal protective equipment, organisation of mobile team work, sample collection and transportation, and interagency interaction during emergencies. Respondents paid separate attention to psychological training. The answers obtained indicate awareness of the importance of skills for working under conditions of increased psycho-emotional strain, time pressure, and the need to make decisions under uncertainty. This confirms the appropriateness of including elements of psychological resilience, crisis communication, and team interaction in training programmes.

Alongside practical training, respondents noted the need for regular familiarisation with updated regulatory documents, modern epidemiological surveillance technologies, digital monitoring tools, and new approaches to emergency response. The obtained results stress the need for continuous professional development as an integral component of maintaining the competence of RRT personnel. Given the survey results, the introduction of a system of regular practical training for RRT personnel is appropriate. The optimal approach may be functional exercises at least once per quarter and comprehensive interagency drills at least once a year. Priority scenarios for practising should include outbreaks of particularly dangerous infectious diseases, mass food poisoning, accidents involving the release of hazardous chemical substances, radiological incidents, and response to emergencies under martial law. Thus, the questionnaire results indicated that further improvement of the RRT training system should be directed primarily towards strengthening practice-oriented learning, developing psychological readiness, improving interagency interaction, and ensuring continuous professional development of personnel. Maintenance of the professional competence of RRT personnel is not limited to initial training and requires the functioning of a system of continuous professional development. The results of the analysis of regulatory documents, international recommendations, and the practice of RRT functioning indicate that the effectiveness of emergency response largely depends on regular readiness monitoring, algorithmisation of actions, resource provision, and international cooperation. The main mechanisms for maintaining RRT competence are presented in Table 2.

Table 2. Main mechanisms for maintaining the competence of RRTs of CDCPs

Direction	Practical significance
Regular readiness monitoring	Assessment of the staffing, technical, and organisational capacity of RRTs
Algorithmisation of actions in response to CBRN threats	Standardisation of response and minimisation of the risk of errors
Educational and certificate programmes	Maintenance of continuous professional development of personnel
International cooperation	Access to modern technologies, educational resources, and best practices
External quality assessment of laboratories	Control of correspondence to international standards
Material and technical support	Maintenance of practical readiness for response

Note: CBRN – chemical, biological, radiological, and nuclear threatss
Source: compiled by the authors

One of the main instruments for ensuring readiness is regular monitoring of RRT activity. Analysis of national reports indicated that the overall assessment of the quality of work of units receiving state support (subvention) averaged 4.3 points, compared with 4.0 points in units without such funding. A similar tendency was observed for technical capacity: the corresponding indicators were 6.8 and 5.2 points, respectively. The obtained results present a positive effect of state support on the level of technical equipment and organisational readiness of RRTs and confirm the importance of stable resource provision for maintaining an appropriate level of readiness to respond to emergencies. The differences indicate that the level of readiness of units depends not

only on the professional training of personnel but also on resource provision. Higher indicators of technical capacity in units receiving state support may contribute to more regular practical training, keeping equipment in proper condition, and increasing the overall effectiveness of response. Algorithmisation of actions in the event of biological, chemical, radiological, and nuclear threats is an important component of competence maintenance. The use of standardised algorithms minimises the risk of errors and ensures consistency of personnel actions regardless of the type of emergency [14]. This acquires particular importance under martial law, when decisions have to be made under time pressure and incomplete information.

The most effective training systems are those based on a competence-based approach and continuous professional development. In the USA, RRT training is provided through programmes of the Centres for Disease Control and Prevention (CDC), which combine distance learning, field training, and simulation exercises. In European Union countries, programmes of the European Centre for Disease Prevention and Control (ECDC), directed towards developing competences in epidemiological surveillance and response to cross-border threats, play an important role [15-16]. The OpenWHO educational platform is an additional instrument of professional development, as it provides open access to training courses on emergency preparedness and response, biosafety, risk communication, and management of infectious disease outbreaks. A common feature of most international programmes is the priority of practice-oriented learning over exclusively theoretical training. Specifically, CDC programmes provide regular field training and participation in investigations of real events, while ECDC training modules widely use case methods, simulation exercises, and scenario modelling. This confirms the relevance of strengthening the practical component of training Ukrainian RRTs in accordance with international approaches. International cooperation makes a substantial contribution to maintaining the professional competence of RRT personnel. It provides access to modern educational resources, external laboratory quality assessment programmes, international training, and professional development programmes. Specifically, participation of CDCP laboratories in international external quality assessment (EQA) programmes, including Quality Control for Molecular Diagnostics programmes [17], supports maintenance of the appropriate level of professional competence among laboratory personnel and ensures that testing corresponds to international standards. Participation in international support and modernisation programmes, including EU4Health and other initiatives of the European Union and the World Health Organization, is also an important direction in the development of the public health system of Ukraine [18]. Such programmes support workforce development, improvement of epidemiological surveillance systems, greater readiness for crisis situations, and harmonisation of national approaches with international standards. Thus, maintenance of RRT competence should be viewed as a continuous process combining regular readiness monitoring, practical training, algorithmisation of actions, resource provision, and active involvement in international professional development programmes. Implementation of these approaches will help improve the readiness of the public health system of Ukraine to respond to current emergencies and challenges to population safety.

The results confirm that developing and maintaining the competence of RRTs of CDCPs should be considered as a continuous process that combines regulatory requirements, practical training, psychological readiness, resource provision, and regular updating of professional skills. The analysis performed indicated that the current regulatory framework sufficiently outlines the functions of RRTs, but the mechanisms for maintaining practical readiness, assessing the formation of competences, and providing psychological support for personnel remain less detailed. The obtained data are consistent with modern international approaches to RRT training. M.A. Stoto *et al.* [19] and S. Elnosserry *et al.* [20] emphasised the need for comprehensive training of rapid response team specialists. It should include not only competencies in epidemiological surveillance and laboratory diagnostics but also skills in risk communication, logistical support, team interaction, psychosocial support, and work under conditions of uncertainty. This corresponds to the results of the present study, in which the importance of operational-technological, communicative, digital, and personal-motivational components of competence was determined alongside professional knowledge. Materials of the World Health Organization [21], regarding workforce development for response to public health emergencies, emphasise that traditional theoretical training is insufficient for ensuring personnel readiness for real crisis events. A similar conclusion was reached in the present study: 47.0% of respondents indicated the need to strengthen the practical component of learning, while comparison of general readiness to respond with readiness to work in field conditions showed a gap between declared readiness and confidence in performing practical tasks directly in emergency sites.

The results of the study are also consistent with ECDC approaches, according to which the training of public health specialists for emergencies should be based on clearly defined competences, scenario-based learning, intersectoral interaction, and practising actions in the event of cross-border threats [22]. In this context, the respondents' identified need to practise algorithms for response to biological, chemical, and radiological threats, use of PPE, organisation of mobile team work, and interaction with other services is

entirely logical. The psychological component of training deserves separate attention. M. Puticiu *et al.* [23] and A. Ben Hamida *et al.* [24] noted that personnel involved in emergency response work under conditions of high responsibility, time pressure, information uncertainty, and psycho-emotional strain. This is consistent with the results of this study, in which respondents indicated the importance of psychological readiness, crisis communication, team interaction, and the ability to make decisions under conditions of uncertainty. Thus, psychological training should not be an additional but a mandatory component of professional development programmes for RRTs. International experience also confirms the appropriateness of using blended learning formats. The OpenWHO platform is considered an instrument for rapid dissemination of knowledge among healthcare workers and public health specialists during crisis situations [19]. However, experience of its use demonstrates that online courses are effective for updating knowledge, but they cannot fully replace practical training, field exercises, and simulation exercises. This is in line with the results of the present study, where the key need identified by respondents was precisely the strengthening of the practice-oriented component of training. Resource provision is also important. The study is also consistent with current approaches to public health system preparedness, where logistics, equipment availability, laboratory capacity, and availability of personal protective equipment are considered integral components of effective response [18]. The obtained data on higher assessment of work quality and technical capacity of units receiving state support indicate that RRT readiness depends both on the level of professional training of personnel and stable material-technical support.

CONCLUSIONS

The following is necessary for developing and maintaining the competencies of specialists from RRTs of CDCPs in public health emergencies:

1. The analysis of regulatory support, educational programmes, and organisational approaches to the activity of rapid response teams of CDCPs allowed the key components of personnel professional competence to be determined. These include cognitive, operational-technological, communicative, digital, and personal-motivational components. It was determined that the current training system sufficiently regulates the professional functions of RRTs, but requires further development of mechanisms for maintaining practical readiness, psychological training, and regular monitoring of the formation of competences.

2. According to the results of the questionnaire survey of 381 specialists from the Public Health Centre of the Ministry of Health of Ukraine and regional CDCPs, it was established that 47.0% of respondents considered it necessary to strengthen the practical component of learning, while 48.5% already had experience of responding to public health emergencies. The results obtained highlight the relevance of developing practice-oriented forms of training regardless of the previous professional experience of personnel.

3. It was determined that the most promising directions for improving RRT training are regular functional exercises, interagency drills, practising algorithms for response to biological, chemical, radiological, and nuclear threats, development of crisis communication, psychological resilience, and skills for working in field conditions.

4. Competence of RRT personnel should be maintained by combining continuous professional development, regular readiness monitoring, algorithmisation of actions in response to CBRN threats, appropriate resource provision, and active involvement in international educational and professional programmes. The appropriateness of using certificate programmes, including the programme "Emergency Preparedness, Response and Management", as an instrument for developing and maintaining the professional competences of public health specialists was established.

The limitation of the study is its descriptive nature, which does not allow statistical links between individual indicators to be fully assessed, particularly between the presence of response experience and the assessment of the need for practical training. This determines the perspective of further research, which should include comparative and correlation analysis, together with an assessment of the effectiveness of different training formats for RRT personnel.

The prospects for further research include the development and validation of a system for evaluating the level of formed professional competences among personnel of rapid response teams of CDCPs, in addition to the examination of the relationship between professional experience, level of training, and effectiveness of emergency response. Comparative studies between different categories of RRT specialists, analysis of the influence of practical training and simulation-based learning on the level of personnel readiness, and assessment of the effectiveness of modern digital educational technologies and international professional development programmes are appropriate. Separate attention should be paid to psychophysiological and psychological factors of professional reliability of RRT personnel under prolonged exposure to stress factors and martial law.

ACKNOWLEDGEMENTS

The authors express sincere gratitude to the employees of the Public Health Centre of the Ministry of Health of Ukraine and the regional Centres for Disease Control and Prevention who participated in the study and questionnaire survey.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Анатолій Гринзовський
Доктор медичних наук, професор, заслужений діяч науки і техніки України
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-8391-5294

Світлана Калашченко
Доктор філософії, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-9942-7607

Ігор Кузін
Аспірант
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
Міністерство охорони здоров'я України
01601, вул. Михайла Грушевського, 7, м. Київ, Україна
https://orcid.org/0000-0002-6418-6567

Дмитро Бондаренко
Аспірант, генеральний директор
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
Одеський обласний центр контролю та профілактики хвороб Міністерства охорони здоров'я України
65074, вул. Івана та Юрія Лип, 5-А, м. Одеса, Україна
https://orcid.org/0009-0009-9087-4281

Тарас Остапчук
Аспірант
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0009-0005-1563-6217

Система формування та підтримки компетентності груп оперативного реагування центрів контролю та профілактики хвороб Міністерства охорони здоров'я України

Анотація
Актуальність. В умовах сучасних біологічних, хімічних, радіаційних та інших загроз громадському здоров'ю особливого значення набуває удосконалення системи формування та підтримки компетентності груп оперативного реагування Центрів контролю та профілактики хвороб.
Мета. Визначити основні проблеми формування і підтримки професійної компетентності та обґрунтувати напрями її удосконалення на основі аналізу нормативно-правового забезпечення та результатів опитування фахівців груп оперативного реагування Центрів контролю та профілактики хвороб.
Матеріали та методи. У роботі застосовано бібліосемантичний, інформаційно-аналітичний, соціологічний методи та методи описової статистики. Соціологічний етап дослідження передбачав анонімне анкетування фахівців груп оперативного реагування (ГОР) Центрів контролю та профілактики захворювань (ЦКПХ) щодо оцінки чинної системи підготовки, досвіду участі в реагуванні на надзвичайні ситуації та напрямів її вдосконалення. Проведено аналіз нормативно-правових документів, освітніх і сертифікатних програм, електронних ресурсів та результатів соціологічних досліджень щодо підготовки і діяльності ГОР ЦКПХ.

Результати. Встановлено, що система компетентності ГОР ЦКПХ повинна включати когнітивний, операційно-технологічний, комунікативний, цифровий та особистісно-мотиваційний компоненти. До ключових компетентностей належать оперативне реагування, епідеміологічне розслідування, оцінка ризиків, лабораторна діагностика, міжвідомча взаємодія та інформування населення. Підтримка компетентності забезпечується через безперервне навчання, тренінги, оновлення нормативної бази, ресурсне забезпечення, моніторинг готовності та міжнародну співпрацю. За результатами анкетування 47 % респондентів вказали на необхідність посилення практичної підготовки, а 48,5 % мали досвід реагування на надзвичайні ситуації у сфері громадського здоров'я. Також визначено потребу в розвитку психологічної підготовки, удосконаленні комплексного компетентнісного підходу та навчанні роботі із сучасним матеріально-технічним забезпеченням.
Висновки. Отримані результати свідчать про необхідність посилення практичної та психологічної складових підготовки персоналу ГОР ЦКПХ, розвитку практикоорієнтованих форм навчання та регулярного відпрацювання алгоритмів реагування на надзвичайні ситуації. Підтримка професійної компетентності має здійснюватися шляхом поєднання безперервного професійного розвитку, моніторингу готовності, міжвідомчих тренувань і міжнародної співпраці. Сертифікатна програма «Готовність, реагування та управління надзвичайними ситуаціями» може розглядатися як ефективний інструмент професійного розвитку завдяки поєднанню компетентнісного підходу, практичної підготовки, навчання реагуванню на хімічні, біологічні, радіаційні та ядерні загрози та розвитку навичок міжвідомчої взаємодії.
Ключові слова: надзвичайні ситуації; професійні стандарти; умови невизначеності; епідеміологічний нагляд; воєнний стан.

PUBLIC HEALTH

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 614.7:504.5:546.26
DOI: https://doi.org/10.32345/2664-4738.2.2026.12

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 12.01.2026 Revised: 19.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Ihor Chernychenko

Doctor of Medical Sciences, Professor
SI "Marzieiev Institute for Public Health of the National Academy of Medical Sciences of Ukraine"
02094, 50 Hetman Pavlo Polubotok Str., Kyiv, Ukraine
https://orcid.org/0000-0002-4784-4628

Olha Lytvychenko

Doctor of Biological Sciences
SI "Marzieiev Institute for Public Health of the National Academy of Medical Sciences of Ukraine"
02094, 50 Hetman Pavlo Polubotok Str., Kyiv, Ukraine
https://orcid.org/0000-0003-2039-3318

Diana Hlavachek*

Master's Degree, Research Fellow
SI "Marzieiev Institute for Public Health of the National Academy of Medical Sciences of Ukraine"
02094, 50 Hetman Pavlo Polubotok Str., Kyiv, Ukraine
https://orcid.org/0000-0002-0512-6927

Serhii Harkavyi

Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-7344-1980

Vitalii Babii

Doctor of Medical Sciences, Professor
SI "Marzieiev Institute for Public Health of the National Academy of Medical Sciences of Ukraine"
02094, 50 Hetman Pavlo Polubotok Str., Kyiv, Ukraine
https://orcid.org/0000-0003-2519-1440

Olena Kondratenko

PhD in Biological Sciences
SI "Marzieiev Institute for Public Health of the National Academy of Medical Sciences of Ukraine"
02094, 50 Hetman Pavlo Polubotok Str., Kyiv, Ukraine
https://orcid.org/0000-0002-9504-7228

Substantiation of medical and sanitary standards for permissible levels of carcinogenic substances in ambient air in populated areas, taking into account the experience of EU countries

Abstract

Relevance. Ukraine's integration into the European Union requires the harmonisation of national legislation with European standards. One of the priority areas is the improvement of the system of medical and sanitary standards for hazardous substances in ambient air. Unlike the EU Member States and the United States, where the regulation of carcinogens is based on a risk-oriented approach that allows for an acceptable level of risk and the periodic revision of limits, the maximum permissible concentrations (MPCs) of carcinogens in Ukraine have traditionally been established on the basis of toxicological experiments without mandatory subsequent review.
Aim. To analyse the compliance of the current Ukrainian medical and sanitary (hygienic) standards for carcinogenic substances in the ambient air of populated areas with international standards.

Suggested Citation:
Chernychenko I, Lytvychenko O, Hlavachek D, Harkavyi S, Babii V, Kondratenko O. Substantiation of medical and sanitary standards for permissible levels of carcinogenic substances in ambient air in populated areas, taking into account the experience of EU countries. Med Sci Ukr. 2026;22(2):114–123. DOI: https://doi.org/10.32345/2664-4738.2.2026.12

*Corresponding author (*glavachek@gmail.com*)

Materials and methods. The Ukrainian regulatory framework governing carcinogenic substances in ambient air, EU legislation and directives, US standards, and the recommendations of the International Agency for Research on Cancer were examined.

Results. A comparative assessment of the current Ukrainian standards for carcinogenic substances was carried out to determine their compliance with internationally accepted carcinogenic risk levels (1×10^{-4}) and reference concentrations. Hygienic standards for 45 substances with established carcinogenic potential were analysed. It was found that the current standards for 34 substances do not comply with international requirements. An improved system of standards is proposed, incorporating annual average concentrations for the assessment of chronic exposure and daily average concentrations for the assessment of acute exposure.

Conclusions. The need to harmonise the Ukrainian system of medical and sanitary regulation of carcinogens with international standards has been demonstrated. The introduction of a risk-oriented approach based on an acceptable risk level (1×10^{-4}), the differentiation of standards according to averaging periods (annual average and daily average concentrations), and the regular revision of the regulatory framework in accordance with current toxicological and epidemiological evidence are scientifically substantiated.

Keywords: acceptable risk; system of permissible level indicators; daily average and annual average concentrations; prevention of adverse effects on human health and the environment.

INTRODUCTION

As Ukraine continues its process of state-building, it has chosen the path of European integration and, in doing so, has undertaken to align its legislation with the laws, standards, and practices of the European Union. Despite the considerable resources devoted to countering Russian aggression, the development of preventive medicine continues, with one of its key priorities being the improvement of the Ukrainian system of medical and sanitary standards governing permissible levels of hazardous substances in ambient air and their effects on the environment, in accordance with international best practice [1-3]. An important contribution to the harmonisation of Ukrainian sanitary legislation with European legislation was made by Law of Ukraine No. 2573-IX [4]. Further progress in this area has been facilitated by the introduction of the risk-based approach into sanitary and hygienic practice [5-6]. In particular, I.O. Chernychenko *et al.* [7-8], in previous studies, analysed the compliance of hygienic standards for carcinogenic substances with international standards and identified differences in the criteria and principles underlying hygienic standard-setting in Ukraine compared with those applied in the EU and the United States.

In the United States and EU countries, including France, the United Kingdom, and Germany, the strategy for preventing the adverse effects of carcinogens on human health and the environment follows a stepwise approach. When a hazardous substance is detected in industrial emissions and poses a potential risk of environmental contamination, the primary objective is to eliminate the substance from the production process or replace it with a less hazardous alternative. Only where such measures are not feasible is the issue of establishing hygienic standards for the substance considered, followed by the periodic review and revision of its maximum permissible concentration (MPC) in the light of newly available scientific evidence. In Ukraine, by contrast, once a compound is identified in the air environment, the immediate focus is on establishing a regulatory standard, without any mandatory requirement for the subsequent review of the approved value. Furthermore, the criteria used to establish maximum permissible concentrations of chemical substances differ substantially. In the EU and the United States, separate exposure limits are established for carcinogens and, where appropriate, mutagens [9-11], based on an acceptable level of risk associated with exposure to the hazardous substance. These health-based limits are derived as threshold exposure concentrations. Internationally, the recommended exposure limit for carcinogens in the ambient air of populated areas has traditionally been based on an acceptable lifetime excess cancer risk of one additional case per 10,000 exposed individuals (1×10^{-4}).

In addition to carcinogenic risk assessment, EU countries also apply the concept of a reference concentration (RfC), which is broadly comparable to the Ukrainian daily average concentration but specifically addresses adverse non-carcinogenic effects on human health. In Ukraine, however, the derivation of MPCs for carcinogenic compounds is based primarily on data from acute and subacute laboratory toxicological studies used to establish dose-response relationships for toxic effects, supplemented, where possible, by published evidence concerning other biological effects, including mutagenicity. It is assumed that lifelong exposure to carcinogens at concentrations equal to the MPC should not result in any adverse effects on either human health or the health of future generations. Once established, these MPC values are, in practice, rarely subject to revision. Given these methodological differences in the derivation of permissible concentrations for carcinogenic substances, the aim of the present study was to evaluate the extent to which the current Ukrainian hygienic standards for carcinogenic substances in ambient air are consistent with their international counterparts.

MATERIALS AND METHODS

A systematic analysis was conducted of the regulatory framework governing carcinogenic substances in the ambient air of populated areas in Ukraine and its compliance with the requirements adopted in the European Union and the United States. Analytical and bibliometric methods were employed to evaluate current methodological approaches to the establishment of hazard assessment criteria for carcinogenic substances, as well as published international evidence concerning the averaging periods applied to carcinogen concentrations for the prevention of both acute and chronic health effects. To address these issues, the databases of the US EPA Integrated Risk Information System (IRIS) [12], the World Health Organization (WHO) [13-14], and the classification database of the International Agency for Research on Cancer (IARC) [15] were analysed with respect to exposure levels and their associated health hazards. The analysis included chemical substances classified by IARC as carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), and possibly carcinogenic to humans (Group 2B).

Carcinogenic substances included in the analysis were selected on the basis of the Ukrainian hygienic regulations [6]. From the complete list, 45 substances with established carcinogenic properties were identified for evaluation. The specific carcinogenic hazard associated with these substances in the ambient air of populated areas was assessed using the methodological recommendations "Assessment of Carcinogenic and Non-Carcinogenic Health Risks from Chemical Air Pollution", approved by Order of the Ministry of Health of Ukraine No. 1811 [5]. Risk estimates were calculated across the range from 1×10^{-2} to 1×10^{-2}. The exposure dose was determined using the following equation:

$$LADD_{a.a.} = C \times CR \times EF \times ED/BW \times AT \times 365, \quad (1)$$

where $LADD_{a.a}$ – intake (or lifetime average daily dose), mg/(kg×day); C – concentration of the compound in polluted ambient air, mg/m^3; CR– inhalation rate, m^3/d (20 m^3/d); EF – exposure frequency, days per year; ED – exposure duration, years (70 years for carcinogens); BW – body weight, kg (70 kg); AT – averaging time, years (70 years for carcinogens); 365 – number of days per year.

After applying the relevant abbreviations, the formula takes the form:

$$LADD_{a.a.} = 0.286 \times C. \quad (2)$$

The individual carcinogenic risk from exposure to a compound in ambient air in populated areas ($ICR_{a.a.}$) was calculated on the basis of the lifetime average daily dose of the carcinogen $LADD_{a.a.}$ and the carcinogenic potential factor SF_i [10]:

$$ICR_{a.a} = LADD_{a.a.} \times SF_i, = 0.286 \times C_{.} \times SF_i. \quad (3)$$

The data obtained on the maximum permissible concentrations of carcinogenic substances for risk conditions ranging from 1×10^{-2} to 1×10^{-6} were compared with similar figures for EU countries and the USA, on the basis of which an acceptable risk for Ukrainian conditions for the study period (early 2026) was determined at a level of 1×10^{-4}, and the maximum permissible concentrations calculated at this level were proposed for approval and subsequent use in Ukraine [12].

RESULTS AND DISCUSSION

The integration of Ukrainian approaches to the regulation of carcinogenic substances in the ambient air of populated areas with international experience in establishing environmental quality standards made it possible to identify the key components of a hygienic standard-setting system consistent with the fundamental principles of Law of Ukraine No. 2573-IX [4]. The main provisions of the Law are aimed at regulating public health and ensuring the sanitary and epidemiological well-being of the population. A cornerstone of this framework is the establishment of state medical and sanitary standards, compliance with which should ensure the protection of public health through appropriate scientific research and risk assessment in accordance with requirements for the protection of human life and health. To implement this approach in practice, the principal elements of the hygienic standard-setting system were examined, including the acceptable level of risk, the maximum permissible concentrations corresponding to that risk level, and the appropriate averaging periods for pollutant concentrations.

Acceptable risk is defined as the level of risk considered tolerable in view of the medical, environmental, social, and economic consequences that society is prepared to accept in exchange for the benefits derived from a particular activity. In preventive medicine, the US Environmental Protection Agency (US EPA) has, until recently, recommended an acceptable lifetime excess cancer risk in the range of 1×10^{-4} to 1×10^{-6} for the regulation of carcinogenic substances [12-13]. Depending on their economic, technological, and social circumstances, individual countries establish by legislation the level of acceptable risk deemed appropriate for their populations. In Ukraine, however, no official acceptable risk level has yet been established within the field of preventive medicine. Consequently, the authors relied on international practice and adopted the upper limit of the internationally accepted risk range, namely 1×10^{-4}, as the benchmark for the present study. A comparative assessment was therefore undertaken to evaluate the compliance of the current Ukrainian medical and sanitary (hygienic) standards for carcinogenic substances with international standards, based on the acceptable carcinogenic risk level of 1×10^{-4} and the reference concentrations (RfCs) applied in the European Union and the United States. Medical and sanitary standards, including MPCs and RfCs, were determined for 45 carcinogenic substances for which carcinogenic potency data are available (Table 1).

Table 1. Hazard assessment of carcinogenic substance concentrations in ambient air in populated areas at the maximum permissible concentration (MPC) level based on risk criteria and reference concentrations

Substance	MPC		RfC	
	mg/m³	Risk	mg/m³	Risk
1	2	3	4	5
Benzo/a/pyrene	0.000001	1.1×10^{-6}	0.000001	1.1×10^{-6}
Benzene	0.1	7.7×10^{-4}	0.03	2.3×10^{-4}
Beryllium	–		0.00002	4.8×10^{-5}
1,3-Butadiene	1.0	3.0×10^{-2}	0.002	6.0×10^{-5}
1,2-Dichloropropane	0.18	1.9×10^{-3}	0.004	4.1×10^{-5}
Ethylene oxide	0.03	3.0×10^{-3}	0.005	5.0×10^{-4}
Cadmium	0.0003	5.4×10^{-4}	0.00002	3.6×10^{-5}
Arsenic	0.003	1.3×10^{-2}	0.00003	1.3×10^{-4}
Nickel	0.001	2.4×10^{-4}	0.00005	1.2×10^{-5}
Carbon black	0.05	2.2×10^{-4}	0.05	2.2×10^{-4}
Trichloroethylene	1.0	1.8×10^{-3}	0.04	7.2×10^{-5}
Formaldehyde	0.003	3.9×10^{-5}	0.003	3.9×10^{-5}
Hexavalent chromium (Chromium VI)	0.0015	1.8×10^{-2}	0.0001	1.2×10^{-3}
Aniline	0.03	4.9×10^{-5}	0.001	1.6×10^{-6}
Dibenz/a,h/anthracene	5.0×10^{-6}	4.4×10^{-6}		
Dichloromethane	8.8	4.0×10^{-3}	0.4	1.8×10^{-4}
Epichlorohydrin	0.2	2.4×10^{-4}	0.001	1.2×10^{-6}
2-Mercaptobenzothiazole	0.12	9.9×10^{-4}	0.35	2.9×10^{-3}
N-Nitrosodiethylamine	15×10^{-6}	6.4×10^{-4}		
N-Nitrosodimethylamine	50×10^{-6}	7.0×10^{-4}		
Styrene	0.002	1.1×10^{-6}	1.0	5.7×10^{-4}
Tetrachloroethylene	0.06	3.4×10^{-5}	0.035	2.0×10^{-5}
1,2,3-Trichloropropane	0.05	1.1×10^{-1}	0.021	4.2×10^{-2}
Aziridine (Ethyleneimine)	0.001	1.9×10^{-2}	0.006	1.1×10^{-1}
Acrylonitrile	0.03	2.1×10^{-3}	0.002	1.4×10^{-4}
Acetaldehyde	0.01	2.2×10^{-5}	0.009	2.0×10^{-5}
Petrol (gasoline)	1.5	1.5×10^{-2}	0.071	7.1×10^{-4}
Hexachloroethane	0.05	2.0×10^{-4}	0.08	3.2×10^{-4}
1,2-Dichloroethane	1.0	2.6×10^{-2}	0.4	1.0×10^{-2}
1,3-Dichloropropene	0.01	1.1×10^{-5}	0.02	2.2×10^{-5}
Ethylbenzene	0.02	2.2×10^{-5}	1.0	1.1×10^{-3}
Cobalt and its compounds	0.001	2.8×10^{-3}	0.00002	5.6×10^{-5}
Naphthalene	0.003	1.0×10^{-4}	0.003	1.0×10^{-4}
Nitrobenzene	0.008	3.2×10^{-4}	0.03	3.6×10^{-4}
2-Chloronitrobenzene (ortho-chloronitrobenzene)	0.004	2.9×10^{-5}	0.001	7.2×10^{-6}
3-Chloronitrobenzene (meta-chloronitrobenzene)	0.004	2.1×10^{-5}	0.001	5.1×10^{-6}
4-Chloronitrobenzene (para-chloronitrobenzene)	0.004	2.1×10^{-5}	0.001	5.1×10^{-6}
Propylene oxide	0.08	3.0×10^{-4}	0.03	1.1×10^{-4}
Lead	0.0003	3.6×10^{-6}	0.0005	6.0×10^{-6}
Antimony trioxide	0.02	2.3×10^{-6}	0.0002	2.3×10^{-8}
Tetrahydrofuran	0.2	3.9×10^{-4}	0.3	5.8×10^{-4}
1,1,2,2-Tetrachloroethane	0.06	3.4×10^{-3}	0.2	1.1×10^{-2}
Carbon tetrachloride	0.7	1.1×10^{-2}	0.04	6.1×10^{-4}
p-Chloroaniline	0.01	1.8×10^{-4}	0.014	2.6×10^{-4}
Chloroprene	0.002	6.3×10^{-4}	0.02	6.3×10^{-3}

Source: compiled by the authors based on [5-6]

The data presented in Table 1 clearly demonstrate that the current hygienic standards for 45 carcinogenic substances in the ambient air of populated areas, in the overwhelming majority of cases, do not provide an adequate level of public health protection. They are associated with estimated lifetime cancer risks ranging from approximately 8 cases per 10,000 people (7.7×10^{-4}) to 2 cases per 100 people (1.8×10^{-2}), and even as high as 1 case per 10 people (1.1×10^{-1}), as calculated for the MPCs of benzene, hexavalent chromium (chromium VI), and 1,2,3-trichloropropane, respectively. These findings raise the question of

establishing permissible concentrations for chemical carcinogens corresponding to a level of risk consistent with international requirements, namely 1×10^{-4}. To address this issue, the authors developed dose-response risk scales covering the range from 1×10^{-3} to 1×10^{-6}. For the derivation of the proposed medical and sanitary standards, concentrations corresponding to an excess lifetime cancer risk of 1×10^{-4} were selected (Table 2). This risk level has been adopted and validated in EU countries, although there is currently ongoing discussion within the EU regarding the possible adoption of a more stringent acceptable risk level of 1×10^{-5}, reflecting the increased effectiveness of environmental protection measures in recent years and the resulting reduction in chemical pollution of ambient air.

Table 2. Recommended annual average MPCs of carcinogenic substances in ambient air in populated areas

Concentrations	Substance		Criteria
	Current (daily average), mg/m³	Recommended (annual average), mg/m³	
1	2	3	4
Benzo/a/pyrene	0.000001	0.000001	Carcinogenic risk
Benzene	0.1	0.01	Carcinogenic risk
Beryllium	–	0.00002	Reference concentration / Resorptive effects
1,3-Butadiene	1.0	0.002	Reference concentration / Resorptive effects
1,2-Dichloropropane	0.18	0.004	Reference concentration / Resorptive effects
Ethylene oxide	0.03	0.001	Carcinogenic risk
Cadmium	0.0003	0.00002	Reference concentration / Resorptive effects
Arsenic	0.003	0.00002	Carcinogenic risk
Nickel	0.001	0.00005	Reference concentration / Resorptive effects
Carbon black	0.05	0.023	Carcinogenic risk
Trichloroethylene	1.0	0.04	Reference concentration / Resorptive effects
Formaldehyde	0.003	0.003	Reference concentration / Resorptive effects
Hexavalent chromium (Chromium VI)	0.0015	0.00001	Carcinogenic risk
Aniline	0.03	0.001	Reference concentration / Resorptive effects
Dibenz/a,h/anthracene	5.0×10^{-6}	0.000005	Carcinogenic risk
Dichloromethane	8.8	0.22	Carcinogenic risk
Epichlorohydrin	0.2	0.001	Reference concentration / Resorptive effects
2-Mercaptobenzothiazole	0.12	0.012	Carcinogenic risk
N-Nitrosodiethylamine	15×10^{-6}	0.000015	Carcinogenic risk
N-Nitrosodimethylamine	50×10^{-6}	0.00005	Carcinogenic risk
Styrene	0.002	0.002	Reference concentration / Resorptive effects
Tetrachloroethylene	0.06	0.035	Reference concentration / Resorptive effects
1,2,3-Trichloropropane	0.05	0.00005	Carcinogenic risk
Aziridine (Ethyleneimine)	0.001	0.000005	Carcinogenic risk
Acrylonitrile	0.03	0.0015	Carcinogenic risk
Acetaldehyde	0.01	0.01	Reference concentration / Resorptive effects
Petrol (gasoline)	1.5	0.01	Carcinogenic risk
Hexachloroethane	0.05	0.025	Carcinogenic risk
1,2-Dichloroethane	1.0	0.004	Carcinogenic risk
1,3-Dichloropropene	0.01	0.01	Reference concentration / Resorptive effects
Ethylbenzene	0.02	0.02	Reference concentration / Resorptive effects
Cobalt and its compounds	0.001	0.00002	Reference concentration / Resorptive effects
Naphthalene	0.003	0.003	Reference concentration / Resorptive effects
Nitrobenzene	0.008	0.002	Carcinogenic risk
2-Chloronitrobenzene	0.004	0.001	Reference concentration / Resorptive effects
3-Chloronitrobenzene	0.004	0.001	Reference concentration / Resorptive effects
4-Chloronitrobenzene	0.004	0.001	Reference concentration / Resorptive effects
Propylene oxide	0.08	0.03	Reference concentration / Resorptive effects
Lead	0.0003	0.0003	Reference concentration / Resorptive effects
Antimony trioxide	0.02	0.0002	Reference concentration / Resorptive effects
Tetrahydrofuran	0.2	0.05	Carcinogenic risk
1,1,2,2-Tetrachloroethane	0.06	0.002	Carcinogenic risk
Carbon tetrachloride	0.7	0.007	Carcinogenic risk

Table 2. *Continued*

Concentrations	Substance		Criteria
	Current (daily average), mg/m³	Recommended (annual average), mg/m³	
p-Chloroaniline	0.01	0.005	Carcinogenic risk
Chloroprene	0.002	0.0003	Carcinogenic risk

Source: compiled by the authors based on [5]

The data presented in Table 2 indicate that the EU and the US assume that the effectiveness of environmental protection measures has recently increased in many countries, leading to a reduction in the level of chemical pollution in the atmosphere. To summarise this point, it can be noted that of the 45 chemical carcinogens included in the Ukrainian database of medical and sanitary standards for permissible concentrations in ambient air in populated areas, the MPCs for 11 compounds do not require revision and are at levels of acceptable risk and reference concentrations. At the same time, for 34 compounds, there is a question as to whether permissible concentration limits need to be reduced, as their current standards do not comply with international standards.

To address the issue of setting hygiene standards for carcinogenic substances in line with EU requirements, as provided for by Regulation (EC) No. 1272/2008 [9], another question arises concerning the averaging of MPCs. As of early 2026, Ukraine applies average daily MPCs, which are used to assess both short-term and long-term (chronic) periods of exposure to chemical carcinogens, although MPCs are calculated based on the lifetime exposure dose. Furthermore, international practice already employs annual average concentrations to prevent chronic exposure to carcinogens, whilst daily average levels are recommended to prevent acute exposure. This circumstance necessitates the establishment of two maximum permissible concentrations for each carcinogenic substance – an annual average and a daily average. It is precisely on the basis of these principles that the authors have proposed an improved, modern system of standards for carcinogenic substances in the ambient air of populated areas, taking into account annual average concentrations for the assessment of chronic exposure and daily average concentrations for acute exposure, as set out in Table 2. Thus, the proposed approaches to hygienic standard-setting require amendments to Ukrainian legislation governing medical and sanitary regulation.

To summarise the results obtained, it should be emphasised that they concerned two aspects of the system of hygienic standardisation: the determination of safe concentrations of chemical carcinogens in ambient air and general characteristic indicators of their application in practical activities. This includes, for Ukraine in 2026, the selection of an acceptable level of societal risk associated with environmental factors, taking into account the country's social, economic, technological, and environmental characteristics, as well as the determination of appropriate concentration averaging periods and sampling durations for environmental monitoring. All of these issues were fundamentally new for Ukrainian specialists in preventive medicine at the beginning of 2026, and the proposed hygienic standards are specifically intended for the assessment of the health hazards posed by chemical environmental factors. In the practice of hygiene science, the methodology for setting hygiene standards for harmful environmental factors, which was established in the 1960s, has remained virtually unchanged. Concentrations set at the level of hygiene standards are ideologically regarded as non-toxic, that is, safe for people living under the influence of harmful chemicals at the levels specified by the approved standards. At the same time, similar approaches proposed by experts from EU countries and the USA hold that there are no "non-effect" concentrations of harmful substances; depending on their level, there is a risk of contributing to the development of disease, which, for carcinogenic substances, corresponds to a specific incidence of cancer relative to the size of the population. In global practice, as of early 2026, according to the definition by IARC experts [15] and WHO specialists [13-14], an acceptable risk for ambient air in populated areas is considered to be a risk level of 1×10^{-4}, i.e. where exposure to a specific chemical compound may result in one case of cancer per 10,000 people over a lifetime. Thus, whilst the air pollution levels are assessed and their safety for the population is indirectly assumed on the basis of the chemical substance standards established by Ukrainian experts as of early 2026, under the risk-based approach, hygiene standards directly assess the risk to human health.

Thus, the results obtained in this study are consistent with the findings of international organisations and are in line with current scientific research, which points to the need to adopt a risk-based approach when regulating carcinogenic air pollutants. For instance, the WHO guidelines on air quality state that, for carcinogens, a safe threshold level of exposure cannot be scientifically justified and standards must be determined on the basis of an acceptable level of risk [13-14, 16]. A similar concept underpins the regulatory policy of the US Environmental Protection Agency, which recommends using individual carcinogenic risk indicators as the primary criterion for regulatory decision-making [17]. Based on this, for example, the MPC of benzene in Ukrainian regulations is 7.7×10^{-4},

which is almost eight times higher than the risk level of 1×10^{-4}. Furthermore, WHO experts [14] emphasise that any level of benzene exposure is associated with a certain probability of developing leukaemia; therefore, regulatory decisions should be based on risk assessment rather than on the concept of a safe threshold concentration. Similar conclusions are presented in the work by A. Sekar *et al*. [18], who, after analysing air quality standards in various countries, concluded that a significant proportion of existing standards do not provide adequate protection for public health and need to be revised on the basis of current assessments of carcinogenic risk. The authors of this study reached a similar conclusion.

A significant exceedance of the acceptable risk was also identified in this study for chromium (VI), arsenic, cadmium, cobalt, ethylene oxide and a number of other substances. Particular attention is drawn to the calculated risk values for chromium (VI) and 1,2,3-trichloropropane, which exceeded the level of 10^{-4} by several orders of magnitude. Similar results were obtained by D.M. Proctor *et al*. [19], who demonstrated that even at low concentrations of Cr(VI), risk levels may exceed those recommended by regulatory authorities. The authors emphasise the need for periodic review of regulatory standards, taking into account new data and approaches to carcinogenic risk assessment. It is also important to note that the list of substances for which the authors of this article propose a review of regulatory limits largely coincides with the list of priority atmospheric carcinogens identified by the International Agency for Research on Cancer [15], including benzene, benzo(a)pyrene, cadmium, arsenic, nickel, formaldehyde, and hexavalent chromium compounds, all of which are classified as carcinogenic to humans (IARC Group 1).

The second aspect of the study concerns the advisability of revising approaches to the averaging of concentrations of carcinogenic substances. The results obtained confirm the need to review approaches to averaging the concentrations of carcinogenic substances. Unlike the current Ukrainian system, where the daily average concentration is predominantly used to assess both acute and chronic effects, international practice involves the use of annual average concentrations to assess long-term carcinogenic effects, whilst daily average concentrations are used to prevent acute toxic reactions [13, 20]. This approach is considered to be more scientifically sound, as the development of malignant tumours is primarily associated with prolonged exposure to low concentrations of carcinogenic agents. The lifetime exposure dose used in risk assessments is also relevant. Furthermore, the List of Air Quality Standards for the Protection of Public Health, as recommended in the EU Directives, clearly stipulates the need to average concentrations over the course of a year (annual concentrations) for substances such as benzo(a)pyrene, benzene, lead, arsenic, cadmium, nickel, chromium other priority pollutants [21].

Finally, in summarising their work, the authors emphasise the need to establish, for the social, economic and technological conditions prevailing in Ukraine in 2026, a level of acceptable risk of 1×10^{-4}, which has been tested in EU countries and the USA and is recommended by the International Agency for Research on Cancer [15]. Not only will this serve as a national indicator of the danger posed by existing actual pollution, but it will also be the single benchmark against which all chemical compounds will be assessed. It is important to note that the results of this study are consistent with the European Union's current environmental policy, according to which the priority approach to preventing carcinogenic effects is not only the establishment of standards but also the maximum reduction or elimination of sources of carcinogens entering the environment [9, 22]. It is precisely this approach that is gradually replacing the traditional concept of hygiene standardisation in Ukraine. Thus, the results of this study confirm the need to harmonise the Ukrainian system of medical and sanitary standardisation of carcinogenic substances with international standards. The implementation of a risk-based approach is scientifically sound and, in the long term, should be developed through legislative measures and the refinement of Ukrainian principles for establishing permissible medical and sanitary standards; the application of these standards will enhance the effectiveness of preventing the adverse effects of environmental factors on the health the population and the formulation of practical steps for management decisions aimed at improving the environment and preventing environmentally-induced morbidity among the population.

CONCLUSIONS

1. The studies conducted show that the standards currently in force in Ukraine for carcinogenic substances in the ambient air of populated areas, in the vast majority of cases, exceed the level of permissible or acceptable risk of probable cancer development in the population.

2. When comparing these standards with the requirements of the EU and the USA, the question arises as to the need to revise Ukraine's regulatory framework for carcinogenic substances in line with international legislation, which provides for the determination at national level of an acceptable risk of exposure to harmful factors affecting the human body and the development of medical and sanitary standards for different levels of concentration: annual averages to prevent chronic exposure and daily averages to prevent acute exposure. This approach to justifying medical and sanitary standards focuses them on preventing the harmful effects of environmental factors on the human body and ensuring an acceptable state of the environment.

3. In view of Ukraine's current economic conditions, the existing technological capabilities of industrial pollution sources, and the social pressures associated with ongoing military conflict, an acceptable lifetime excess cancer risk of 1×10^{-4} is recommended as the basis for establishing medical and sanitary standards. This benchmark has already been formally recognised in countries with higher levels of human development, including the EU and the USA.

4. Continuing scientific research on this topic will enable Ukrainian health legislation to be brought into line with EU legislation, thereby ensuring that medical and health standards for the permissible concentration of carcinogenic substances in the ambient air of populated areas in Ukraine comply with European standards.

ACKNOWLEDGEMENTS

None.

FUNDING

This study was funded by the State Budget of Ukraine (National Academy of Medical Sciences of Ukraine).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Ігор Черниченко
Доктор медичних наук, професор
ДУ «Інститут громадського здоров'я ім. О. М. Марзєєва НАМН України»
02094, вул. Гетьмана Павла Полуботка, 50, м. Київ, Україна
https://orcid.org/0000-0002-4784-4628

Ольга Литвиченко
Доктор біологічних наук
ДУ «Інститут громадського здоров'я ім. О. М. Марзєєва НАМН України»
02094, вул. Гетьмана Павла Полуботка, 50, м. Київ, Україна
https://orcid.org/0000-0003-2039-3318

Діана Главачек
Магістр, науковий співробітник
ДУ «Інститут громадського здоров'я ім. О. М. Марзєєва НАМН України»
02094, вул. Гетьмана Павла Полуботка, 50, м. Київ, Україна
https://orcid.org/0000-0002-0512-6927

Сергій Гаркавий
Доктор медичних наук, професор
Національний медичний університет ім. О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-7344-1980

Віталій Бабій
Доктор медичних наук, професор
ДУ «Інститут громадського здоров'я ім. О. М. Марзєєва НАМН України»
02094, вул. Гетьмана Павла Полуботка, 50, м. Київ, Україна
https://orcid.org/0000-0003-2519-1440

Олена Кондратенко
Кандидат біологічних наук
ДУ «Інститут громадського здоров'я ім. О. М. Марзєєва НАМН України»
02094, вул. Гетьмана Павла Полуботка, 50, м. Київ, Україна
https://orcid.org/0000-0002-9504-7228

Обґрунтування медико-санітарних нормативів допустимого вмісту канцерогенних речовин в атмосферному повітрі населених місць з урахуванням досвіду країн ЄС

Анотація

Актуальність. Інтеграція України до Європейського Союзу вимагає гармонізації національного законодавства з європейськими стандартами. Одним із пріоритетних напрямів є вдосконалення системи медико-санітарних нормативів шкідливих речовин в атмосферному повітрі. На відміну від країн ЄС та США, де нормування

канцерогенів базується на ризик-орієнтованому підході з допущенням прийнятного рівня ризику та можливістю регулярного перегляду лімітів, в Україні гранично допустимі концентрації (ГДК) канцерогенів традиційно встановлюються на основі токсикологічних експериментів без обов'язкового подальшого перегляду величин.

Мета. Провести аналіз відповідності чинних медико-санітарних (гігієнічних) нормативів канцерогенних речовин в атмосферному повітрі населених місць України міжнародним стандартам.

Матеріали та методи. Було досліджено українську нормативну базу канцерогенних речовин в атмосферному повітрі, законодавство і директиви ЄС, стандарти США та рекомендації Міжнародної агенції з вивчення раку.

Результати. Проведено порівняльну оцінку чинних українських нормативів канцерогенних речовин щодо їх відповідності міжнародним рівням прийнятного канцерогенного рику ($1 \times 10^{-}4$) та референтних концентрацій. Проаналізовано показники гігієнічних нормативів для 45 канцерогенних речовин із визначеним канцерогенним потенціалом. Установлено, що діючі нормативи для 34 речовин не відповідають міжнародним стандартам. Запропоновано удосконалену систему нормативів із впровадженням середньорічних концентрацій для оцінки хронічного впливу та середньодобових – для гострого.

Висновки. Доведена необхідність гармонізації української системи медико-санітарного нормування канцерогенів із міжнародними стандартами. Науково обґрунтовано впровадження ризик-орієнтованого підходу на основі прийнятного рівня ризику (1 × 10-4), диференціації нормативів за періодами осереднення (середньорічні та середньодобові) та регулярного перегляду нормативної бази відповідно до сучасних токсикологічних й епідеміологічних даних.

Ключові слова: прийнятний ризик; система показників допустимого рівня; середньодобові та середньорічні концентрації; попередження шкідливого впливу на здоров'я людини та стан довкілля.

PUBLIC HEALTH

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.345-006.6-085.277.3:614.253.8:330.567:[314+316] Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.13 Received: 07.01.2026 Revised: 02.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Andrii Maranov*

Postgraduate Student
Bogomolets National Medical University
01601, 34 Beresteysky Ave., Kyiv, Ukraine
https://orcid.org/0009-0001-3938-6305

Tetiana Vezhnovets

Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 34 Beresteysky Ave., Kyiv, Ukraine
https://orcid.org/0000-0003-1156-8614

The association between patients' sociodemographic characteristics and out-of-pocket payments during chemotherapy for colorectal cancer

Abstract

Relevance. Colorectal cancer (CRC) is one of the three most prevalent malignancies in terms of incidence and mortality, both in Ukraine and worldwide. Despite Ukraine's healthcare financing reform, out-of-pocket payments by patients remain a significant concern.

Aim. To compare the sociodemographic characteristics of patients receiving chemotherapy for CRC. This comparison was made according to whether they made OOPPs.

Materials and methods. A total of 459 people took part in this cross-sectional study. Their sociodemographic characteristics, subjective assessments of healthcare accessibility, awareness and satisfaction were analysed. Respondents who made OOPPs were compared with those who did not using the χ^2 test and the Cochran-Armitage trend test in R with the EZR graphical user interface.

Results. A statistically significant linear trend towards an increased frequency of OOPPs was observed. This was with increasing age ($p = 0.026$) and increasing settlement size ($p = 0.029$). However, the groups did not differ significantly in terms of sex, educational attainment, or income ($p > 0.05$). The likelihood of family members acknowledging payments was significantly higher than that of patients themselves ($p = 0.001$). Patients who made OOPPs were significantly more likely to postpone diagnosis or treatment than those who did not (21.8% versus 8.4%, $p < 0.001$). Patients who were better informed about services that were free of charge were less likely to make payments ($p < 0.001$), as shown by a strong linear trend. Patients who did not make OOPPs also reported a significantly higher level of satisfaction with the quality of care ($p = 0.001$).

Conclusions. The study identified several factors that could potentially be used to prevent out-of-pocket payments (OOPPs). Respondents who received chemotherapy and incurred OOPPs were more likely to be aged 60 years or older, retired and living in a regional capital. They were significantly more likely to postpone a cancer diagnosis or treatment due to anticipated financial costs, which suggests that healthcare services are not easily accessible. These patients did not know that they could get chemotherapy for free and were less satisfied with its quality. No differences were identified in relation to sex, educational attainment, or income level.

Keywords: healthcare financing; oncology; colon and rectal cancer; patient awareness; patient satisfaction; quality of healthcare services; accessibility of healthcare services.

Suggested Citation:
Maranov A, Vezhnovets T. The association between patients' sociodemographic characteristics and out-of-pocket payments during chemotherapy for colorectal cancer. Med Sci Ukr. 2026;22(2):124–132. DOI: https://doi.org/10.32345/2664-4738.2.2026.13

*Corresponding author (*aomaranov@gmail.com*)

INTRODUCTION

The third most common cancer worldwide is colorectal cancer (CRC), according to Global Cancer Statistics 2022. It accounts for 9.6% of all cancers, with 1.9 million new cases. Furthermore, CRC is the second leading cause of cancer-related mortality, accounting for 904,000 deaths (9.3% of all cancer deaths) [1-2]. In Ukraine, CRC is also among the three most prevalent cancers in terms of both incidence and mortality. In 2023, 12,152 new cases were recorded. This accounted for 9.9% of all newly diagnosed cancers. This corresponds to the global proportion. A total of 6,395 deaths were recorded, accounting for 14.4% of all cancer-related deaths – a higher proportion than the global figure. Furthermore, depending on tumour location, the proportion of newly diagnosed CRC patients who did not survive the first year after diagnosis ranged from 20.9% to 25.9% [3]. These statistics may be partly due to patients delaying medical consultations because of worries about potentially ruinous costs for diagnosis and treatment. Since 2017, the diagnosis and treatment of cancer in Ukraine has been covered by the National Health Service of Ukraine (NHSU) via the Programme of Medical Guarantees (PMG) [4]. Chemotherapy for colorectal cancer is funded by the NHSU as part of a separate package entitled "Chemotherapy Treatment and Support for Patients with Cancer in Inpatient and Outpatient Settings", which is provided to patients free of charge. According to the World Health Organization and the World Bank, introducing the healthcare financing reform in Ukraine has improved access to healthcare services and provided greater protection against excessive out-of-pocket payments (OOPPs) [5].

It is well known that patients diagnosed with cancer often have to rely on informal and out-of-pocket payments to gain access to treatment. There are also documented cases of patients declining treatment because it is unaffordable [6-8]. Furthermore, O. Levenets *et al*. [9] have found that such practices are not only widespread in Ukraine, but are also generally characteristic of post-communist countries. More broadly, the financial toxicity associated with cancer treatment is a global problem. For instance, R. Lentz *et al*. [10] have highlighted the link between financial toxicity and patients' demographic and socioeconomic status, the type of treatment selected, and other factors in the United States. The authors identified female sex, younger age, and unemployment as particular contributing factors. L. Doshmangir *et al*. [11] observed that out-of-pocket payments (OOPPs) can lead to catastrophic expenditure for households. According to a systematic review of 19 studies, an average of 43.3% of cancer patients experienced catastrophic healthcare expenditure. An inverse relationship with the Human Development Index was identified, with a prevalence of 23.4% in countries with higher levels of human development, compared to 67.9% in countries with lower levels. The factors associated with financial hardship during CRC treatment have been investigated in retrospective, cross-sectional and prospective studies. G. Sadigh *et al*. [12] discovered that, among patients with early-stage CRC, the severity of financial hardship was linked to age, sex, educational attainment, employment status, receipt of chemotherapy, and other factors. S. Kircher *et al*. [13] also highlighted the link between the financial burden of CRC treatment and patients' household income and the socio-economic status of their area of residence. A. Rashidi *et al*. [14] examined interventions intended to reduce financial hardship among patients with cancer in a systematic review and meta-analysis. However, the findings indicated that these strategies had only a limited effect.

Therefore, it is important to identify the factors that cause patients to make out-of-pocket payments (OOPPs) despite the availability of guaranteed NHS funding. This study aimed to compare the social and demographic characteristics, as well as the subjective assessments, of two groups of patients with colorectal cancer who received chemotherapy. The groups were distinguished by their out-of-pocket payment habits.

MATERIALS AND METHODS

This study employed a cross-sectional design. A total of 459 patients who had received treatment for colorectal cancer under the "Chemotherapy Treatment and Support for Patients with Cancer in Inpatient and Outpatient Settings" medical guarantees package between 1 July 2023 and 30 June 2024 were surveyed. Both patients and relatives who had been directly involved in the treatment process were permitted to participate in the study. The questionnaire consisted of four sections. The first section was general information. The second section was about perceptions of informal payments. The third section was a review of the patient and medical history relating to colorectal cancer. The fourth section was about patient satisfaction. It was designed to take approximately 45 minutes to complete. The survey was conducted in person. It was done by independent interviewers. They did it in a private location. This was outside the healthcare facility. There were no third parties present. Respondents' answers were entered into an online questionnaire on a tablet. The respondents were told that they could choose whether or not to take part and that their answers would not be shared publicly and would keep their identity secret. No personal data were collected. All responses were used for analysis in an aggregated and anonymised form only. Patients were selected randomly. This was to ensure adequate regional representation within the sample. Almost all patients received treatment at 25 municipal healthcare facilities, 22 of which were oncology centres. These facilities were located in 21 Ukrainian regions and the city of Kyiv. Due to the ongoing war, the Donetsk, Luhansk and Kherson regions, as well as the Autonomous Republic of Crimea, were excluded from the sample.

The main thing we were comparing was whether patients had to make any out-of-pocket payments for their chemotherapy. The following payments were included: payments for diagnostic procedures; money or monetary equivalents given to a doctor or other healthcare professional; remuneration for a doctor, compensation for their time, expressions of gratitude, donations, or charitable contributions; the purchase of medicines or medical devices from a list provided by the healthcare facility; gifts in the form of goods, such as confectionery, alcohol, or coffee, or services, such as discounts or services provided free of charge; informal payments; and other similar forms of payment. The first group of respondents (n = 338) reported that they had not made any out-of-pocket payments (OOPPs), whereas the second group (n = 121) reported that they had. The groups were compared based on the following sociodemographic characteristics: age group, sex, educational attainment, employment status, average monthly income per household member, and type of settlement in which the patient resided. In addition, the study assessed respondents' perceptions of the accessibility of cancer care. It also looked at their awareness of services provided free of charge under the PMG. Finally, it examined patient satisfaction as an indirect indicator of the quality of healthcare delivery. To account for regional differences, patients were also classified into subregions based on the NHSU structure [15].

Statistical analysis was performed using the R programming language (version 4.3.1) with the EZR graphical user interface (version 1.64). The results are presented as absolute values (n) and relative frequencies (%). For certain variables, the number of responses was lower than the total sample size because some respondents either omitted answers or did not provide the relevant information. In such cases, the analysis for each variable was based on the available data. No computer programs were used to replace missing answers. The chi-squared test was used for comparisons between groups. Fisher's exact test was applied when expected frequencies were low. The Cochran–Armitage trend test was used to assess the presence of a linear trend. Statistical significance was set at $p < 0.05$ for all tests.

The study was done following the rules of the Declaration of Helsinki [16]. The study protocol was approved by the Bioethical Review and Research Ethics Commission of Bogomolets National Medical University (Protocol No. 206, 2026).

RESULTS AND DISCUSSION

The findings suggest that family members were more willing than patients to report out-of-pocket payments (OOPPs). Among those who did not report such payments, patients predominated, accounting for 190 out of 338 respondents (56.2%), compared to 148 family members (43.8%) (p = 0.001) (Table 1).

Table 1. Sociodemographic characteristics of respondents receiving chemotherapy for CRC, categorised by whether they made out-of-pocket payment

Factor	Category	OOPPs		p-value
		no	yes	
		n = 338	n = 121	
Questionnaire respondent	Patient	190 (56.2%)	46 (38.0%)	**0.001**
	Family member	148 (43.8%)	75 (62.0%)	
Age	under 40	17 (5.0%)	3 (2.5%)	0.103
	40-49	51 (15.1%)	10 (8.3%)	
	50-59	83 (24.6%)	26 (21.5%)	
	60-69	130 (38.5%)	61 (50.4%)	
	70+	57 (16.9%)	21 (17.4%)	
Sex	Female	103 (30.5%)	41 (33.9%)	0.495
	Male	235 (69.5%)	80 (66.1%)	
Education	Higher	105 (31.1%)	35 (28.9%)	0.904
	Secondary	51 (15.1%)	18 (14.9%)	
	Vocational education	182 (53.8%)	68 (56.2%)	
Employment status	Employed	123 (36.8%)	30 (25.4%)	0.055
	Retired	163 (48.8%)	72 (61.0%)	
	Unemployed persons of working age	48 (14.4%)	16 (13.6%)	
Average monthly income per member of the patient's household	below UAH 4,000	79 (26.1%)	24 (21.6%)	0.480
	UAH 4,001-7,000	83 (27.4%)	36 (32.4%)	
	UAH 7,001-10,000	57 (18.8%)	18 (16.2%)	
	UAH 10,001-19,000	72 (23.8%)	25 (22.5%)	
	More than UAH 19,000	12 (4.0%)	8 (7.2%)	
Type of settlement of residence	Regional capital	148 (46.2%)	62 (54.9%)	0.155
	Large city (population over 100,000)	48 (15.0%)	20 (17.7%)	
	Town or city with a population of up to 100,000	62 (19.4%)	18 (15.9%)	
	Village or urban-type settlement	62 (19.4%)	13 (11.5%)	

Table 1. *Continued*

Factor	Category	OOPPs		p-value
		no	yes	
		n = 338	n = 121	
Subregion	West	125 (37.0%)	27 (22.3%)	**< 0.001**
	South	17 (5.0%)	0 (0.0%)	
	North	27 (8.0%)	39 (32.2%)	
	East	57 (16.9%)	12 (9.9%)	
	Centre	112 (33.1%)	43 (35.5%)	

Source: compiled by the authors

No statistically significant difference in age was found between the groups (p = 0.103). As the age groups were ordered categories, Cochran-Armitage test for linear trend was performed. This yielded a chi-squared value of 4.9 and a p-value of 0.026. Therefore, the likelihood of patients reporting payments increased with age. This was particularly apparent in the 40-49 age group, where 15.1% of those who did not make payments and 8.3% of those who did were represented. By contrast, the distribution shifted towards a higher frequency of payments in the 60-69 age group, at 38.5% and 50.4% respectively.

The groups did not differ significantly in terms of sex distribution (p = 0.495) or educational attainment (p = 0.904). While the distribution of patients by employment status did not reach statistical significance (p = 0.055), there was a tendency for retired people to make payments more frequently (no OOPPs: 48.2%; OOPPs: 61.0%), whereas employed people were more likely not to make payments (no OOPPs: 36.6%; OOPPs: 25.4%). At the same time, no significant differences were found between the groups in terms of average monthly income per member of the patient's household (p = 0.48). Additional analysis revealed no linear trend (χ^2 = 0.449, p = 0.5). Therefore, there was no evidence that the frequency of OOPPs increased with income.

The groups did not differ according to patients' place of residence (p = 0.155). However, linear trend analysis indicated a significant difference (χ^2 = 4.745, p = 0.029). In other words, the frequency of OOPPs increased with the size of the settlement in which the patient lived. The most frequent OOPPs were made by residents of regional capitals, who accounted for 54.9% of all payments made, while the least frequent were made by residents of villages and urban-type settlements, who accounted for 11.5%. The distribution of patients by subregion revealed a statistically significant difference between the two groups of respondents (p < 0.001). Payments were less common in the West (no OOPPs: 37.0%; OOPPs: 22.3%) and the East (no OOPPs: 16.9%; OOPPs: 9.9%). Conversely, patients in the North were more likely to pay out of pocket (no OOPPs: 8.0%; OOPPs: 32.2%), whereas in the Centre, the proportions were almost identical (no OOPPs: 33.1%; OOPPs: 35.5%). The next section analysed patients' subjective assessments of treatment accessibility, awareness and satisfaction as indirect measures of healthcare service quality (Table 2).

Table 2. Perceived accessibility, awareness and satisfaction with chemotherapy, according to whether respondents made OOPPs

Factor/question	Category	OOPPs		p-value
		no	yes	
		n = 338	n = 121	
Did you postpone cancer diagnosis or treatment because you anticipated catastrophic expenditure?	No	304 (91.6%)	93 (78.2%)	**<0.001**
	Yes	28 (8.4%)	26 (21.8%)	
How aware are you of the services provided free of charge and guaranteed by the state for CRC chemotherapy in municipally and state-owned facilities?	Low	91 (27.2%)	56 (46.7%)	**<0.001**
	Moderate	87 (26.0%)	36 (30.0%)	
	High	157 (46.9%)	28 (23.3%)	
How satisfied are you with the quality of the CRC chemotherapy services you received?	Satisfied	279 (85.3%)	76 (70.4%)	**0.001**
	Neutral assessment	41 (12.5%)	25 (23.1%)	
	Dissatisfied	7 (2.1%)	7 (6.5%)	

Source: compiled by the authors

The study methodology was followed. The actual number of responses presented in Table 2, as in Table 1, could be lower than the total number of respondents. This is because of missing or unspecified responses.

The analysis was conducted using the available data for each variable. Patients who denied making out-of-pocket payments (OOPPs) had a significantly different assessment of healthcare accessibility to those who reported making them ($p < 0.001$). Patients in the latter group were more likely to acknowledge that they had postponed a cancer diagnosis or treatment (21.8% versus 8.4%). There was also a statistically significant difference ($p < 0.001$) and a strong linear trend ($\chi^2 = 22.641$, $p < 0.001$) in patient awareness of chemotherapy services provided free of charge. Thus, patients who were better informed about the PMG were less likely to make payments. Moreover, respondents who did not make OOPPs were more likely to be satisfied with the quality of healthcare than those in the other group ($p = 0.001$). A linear trend was also present ($\chi^2 = 12.925$, $p < 0.001$).

The study findings showed that the group of patients who made out-of-pocket payments (OOPPs) had certain differences and characteristics in common with the group that denied making such payments. Firstly, family members reported OOPPs more frequently than patients themselves ($p = 0.001$). This was probably because patients felt dependent on healthcare professionals and were therefore less inclined to report payments, particularly informal ones. According to K. Kroenke *et al*. [17], patients' assessments often correspond with family members' views and can be used to evaluate patients' conditions. It is important to note that around 73% of family members are directly involved in decisions concerning inpatient cancer treatment, while 25% report experiencing a financial burden because of the disease [18].

The work of O. Levenets *et al*. [6] established that older patients and women were more likely to make informal payments to access cancer care. The present study found no association between OOPPs and sex ($p > 0.05$). However, the Cochran-Armitage test revealed a statistically significant trend of increased payment frequency with age ($\chi^2 = 4.9$, $p = 0.026$). Older patients made payments more frequently than younger patients. T. Heisser *et al*. [19] demonstrated that the risk of colorectal cancer increases with age, with more complex cases requiring more expensive treatment. Nevertheless, the literature also suggests that the impact of age may have a threshold, with very elderly patients incurring lower costs due to receiving less aggressive treatment owing to their clinical condition and general age-related health deterioration. Nevertheless, the observed association may also be explained by payment practices inherited from the Soviet healthcare system that persist among older age groups. Furthermore, older age groups may be less aware that healthcare and PMG services are provided free of charge. A systematic review by Y. Zhang *et al*. [20] highlighted inadequate e-health literacy among cancer patients and identified age, sex, education, place of residence and other characteristics as influential factors.

The study found no statistically significant differences between the groups in terms of educational attainment ($p = 0.904$). This may be because patients tend to make irrational decisions when making decisions about cancer treatment, which override the effect of educational attainment. These decisions are instead based on the experiences of other patients, prevailing practices within their social environment, and other factors, as described by S. Whyte *et al*. [21] and M.S. Karuturi *et al*. [22]. However, O. Levenets *et al*. [6] found that higher education influenced patients' behavioural strategies regarding treatment. In the present study, the relationship between patients' employment status and the use of out-of-pocket payments (OOPPs) did not reach statistical significance ($p = 0.055$). Nevertheless, the findings suggest a tendency for retired people to be more likely to use OOPPs than the employed population. The risk of catastrophic treatment expenditure in these groups may be increased by this [11], as well as the risk of delays, incomplete receipt of healthcare services, or complete refusal of such services [22-24]. Consistent with this, patients who incurred OOPPs were significantly more likely to delay cancer diagnosis or treatment than those who did not ($p < 0.001$). The WHO reports that even before the full-scale invasion in 2022, 17% of Ukrainian households (2.5 million people) experienced catastrophic healthcare expenditure. This proportion was higher than the corresponding European levels, with the greatest impact on older individuals, retired individuals, and lower-income households. Overall, OOPPs were estimated to account for 48% of total healthcare expenditure [25]. This problem is further highlighted by the absence of any difference in payment frequency according to the average monthly income of the patient's household members ($p = 0.48$), and by the absence of a linear trend ($\chi^2 = 0.449$, $p = 0.5$). In other words, wealthier patients were no more likely to incur out-of-pocket patient payments (OOPPs). Therefore, it can be assumed that OOPPs pose a greater risk to the financial stability of less affluent households. However, a 2022 US study by G. Sadigh *et al*. [26] found that older age and higher patient income were associated with lower levels of financial toxicity.

The final sociodemographic indicators looked at were the links between OOPPs and the type of settlement and subregion where the patient lived. While no statistically significant difference was identified between groups according to settlement type ($p = 0.155$), a linear trend was observed ($p = 0.029$): payment frequency increased with settlement size. Residents of regional capitals made payments most frequently and this group was also the largest. As stated in the study methodology, 22 of the 25 healthcare facilities included in the study were oncology centres, which tend to be located in large cities or regional capitals. The issue of access to cancer care for residents of smaller settlements

and villages should also be considered. For instance, in 2024, while 80% of electronic prescriptions were issued in villages, only 22% were dispensed there [5]. A 2025 study also found that urban residence was an important factor influencing the strategies patients with cancer used to overcome barriers to accessing healthcare [6].

The distribution by subregion demonstrated a statistically significant difference ($p < 0.001$). Payments were less frequent in the East and West, and more frequent in the North. The eastern regions have been severely affected by the burden of war – this is because of the full-scale invasion. This may explain why OOPPs are less common there. Additionally, many internally displaced persons, including CRC patients, relocated to western Ukraine, which may have influenced the statistics in that region. Alternatively, OOPPs may have been less common in the West prior to the invasion. The northern subregion was also affected during the initial phase of the invasion, experiencing partial occupation before being subsequently liberated. The reasons for the high levels of OOPPs in this region therefore warrant further investigation.

The final section of the report included an analysis of subjective assessments. Patients who rated their knowledge of the PMG more highly were less likely to incur out-of-pocket expenses (OOPPs) ($p < 0.001$), and a strong linear trend was also observed ($p < 0.001$). It is also important to note that payments were associated with lower satisfaction with chemotherapy treatment ($p = 0.001$), and again, a strong linear trend was present ($p < 0.001$). Therefore, OOPPs may represent a factor that places additional psychological pressure on patients and reduces their satisfaction with the quality of healthcare services. However, S.Y. Zafar *et al.*'s [27] study of colorectal and lung cancer, which used data from 2003-2006, found no association between patients' perceptions of the quality of their treatment and financial toxicity. However, the current results align with other studies, which suggest that patients who are dissatisfied with the quality of their treatment are more likely to utilise a variety of strategies, including OOPPs [6].

The study therefore analysed the sociodemographic characteristics and subjective assessments of patients with CRC who received chemotherapy according to whether they made OOPPs. The findings were then compared with current literature evidence. Overall, in line with previous studies, the present study demonstrated the statistical significance of age and settlement size. At the same time, while sex, educational attainment and income have been identified as significant factors in some previous studies, they were not statistically significant in this study. It should be emphasised that respondent identity – whether patient or family member – was a statistically significant factor. This suggests the need to engage not only with patients themselves, but also with members of their immediate social and family environment.

CONCLUSIONS

1. The study identified several factors that could potentially be used to prevent OOPPs. A statistically significant linear trend was observed. This trend was towards an increased frequency of OOPPs. This increased frequency was with increasing age ($p = 0.026$). It was also with increasing settlement size ($p = 0.029$). However, there were no differences between the groups in terms of sex, educational attainment or income ($p > 0.05$). Family members were more likely than patients themselves to acknowledge that payments had been made ($p = 0.001$). Patients who made OOPPs were significantly more likely to postpone diagnosis or treatment (21.8% versus 8.4%, $p < 0.001$). A strong linear trend was identified: patients who were better informed about free services were less likely to make payments ($p < 0.001$). Patients who did not make OOPPs also reported a significantly higher level of satisfaction with the quality of care ($p = 0.001$).

2. Respondents who received chemotherapy and incurred out-of-pocket medical expenses (OOPPs) were more likely to be aged 60 years or older, retired, and living in a regional capital. Meanwhile, patients who made OOPPs were significantly more likely to postpone cancer diagnosis or treatment. This is because they anticipated substantial financial expenditure. This indicates limited accessibility of healthcare services for this group. They were also more likely to be unaware that chemotherapy was provided free of charge, and consequently were less satisfied with this service. No differences were identified in terms of sex, educational attainment or average monthly household income.

3. One possible approach to preventing OOPPs for chemotherapy services would be to improve patients' awareness of their right to free services and establish an accessible clinical care pathway. Future research should investigate OOPPs among CRC patients receiving chemotherapy in relation to the clinical manifestations of the disease, with the aim of developing a system to prevent OOPPs in healthcare facilities.

Study limitations. The statistical methods that were used in the present study included the χ^2 test, Fisher's exact test, and the Cochran-Armitage trend test, but multivariable analysis was not included. Future research will examine the association between patients' clinical characteristics during chemotherapy for CRC and OOPPs. This approach enables sociodemographic and clinical characteristics to be analysed separately and in detail without overloading the present paper. At the next stage, a multivariable analysis of selected sociodemographic and clinical patient characteristics will be conducted and the results presented in subsequent publications.

Practical significance. These findings could be used to raise patients' awareness of their rights and entitlements under the Programme of Medical

Guarantees, increase transparency within the healthcare system and reduce, and ultimately eliminate, out-of-pocket payments for services that have already been funded by the healthcare purchaser.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the United States Agency for International Development (USAID), the USAID Health Reform Support Project, and the Kyiv School of Economics.

FUNDING

The study was conducted as part of the authors' postgraduate research. It was also part of the preparation of an original doctoral dissertation. Data collection for this study was carried out by Deloitte Consulting LLC with the support of USAID under Contract No. 72012118C00001.

CONFLICT OF INTEREST

None.

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Андрій Маранов

Аспірант
Національний медичний університет імені О. О. Богомольця
01601, просп. Берестейський, 34, м. Київ, Україна
https://orcid.org/0009-0001-3938-6305

Тетяна Вежновець

Доктор медичних наук, професор
Національний медичний університет імені О. О. Богомольця
01601, просп. Берестейський, 34, м. Київ, Україна
https://orcid.org/0000-0003-1156-8614

Зв'язок соціально-демографічних характеристик пацієнтів з платежами з власної кишені під час хіміотерапії колоректального раку

Анотація

Актуальність. Колоректальний рак (КРР) входить до трійки найпоширеніших онкологічних патологій за захворюваністю та смертністю в Україні та світі. Попри реформу фінансування охорони здоров'я в Україні, проблема платежів з власної кишені (ПзВК) пацієнтів залишається актуальною.

Мета. Порівняти соціально-демографічні характеристики та суб'єктивні оцінки пацієнтів із КРР, які отримували хіміотерапію КРР, залежно від здійснення ПзВК.

Матеріали та методи. У поперечному дослідженні опитано 459 респондентів. Проаналізовано соціально-демографічні показники, суб'єктивну оцінку доступності послуг, поінформованість та задоволеність. Порівняння двох груп (з ПзВК та без) проведено із використанням критерію χ^2 та тесту Кохрейна-Армітажа у середовищі R з графічною оболонкою EZR.

Результати. Спостерігався статистично значущий лінійний тренд до зростання частоти ПзВК зі збільшенням віку ($p = 0,026$) та розміру населеного пункту ($p = 0,029$), проте групи не відрізнялися за статтю, освітою чи доходом ($p > 0,05$). Члени родини частіше за пацієнтів визнавали факти оплати ($p = 0,001$). Пацієнти з ПзВК статистично значимо частіше відкладали діагностику чи лікування (21,8 % проти 8,4 %, $p < 0,001$). Виявлено сильний лінійний тренд: краще поінформовані про безоплатні послуги пацієнти платили рідше ($p < 0,001$). Також пацієнти без ПзВК демонстрували статистично значимо вищий рівень задоволеності якістю допомоги ($p = 0,001$).

Висновки. Дослідження виявило низку асоційованих факторів, які потенційно можуть бути використані для попередження ПзВК. Респонденти, які отримували хіміотерапію та здійснювали ПзВК, частіше належали до вікової групи 60+, були пенсіонерами і проживали в обласному центрі. Вони достовірно частіше відкладали діагностику або лікування раку через очікувані фінансові витрати, що свідчить про низьку доступність медичної послуги. Такі пацієнти також були менш поінформовані про безоплатне хіміотерапевтичне лікування та менш задоволені його якістю. Відмінностей за статтю, освітою і рівнем доходу не виявлено.

Ключові слова: фінансування охорони здоров'я; онкологія; рак ободової та прямої кишки; поінформованість пацієнтів; задоволеність пацієнтів; якість медичних послуг; доступність медичних послуг.

PAEDIATRICS

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.756.21-018.6-007.26-089.844-092.18-097:576.31 Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
DOI: https://doi.org/10.32345/2664-4738.2.2026.14 Received: 22.12.2025 Revised: 30.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Yurii Marushko

Doctor of Medical Sciences, Professor
O.O. Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-8066-9369

Iryna Kondratenko

Acting Head of the Hearing and Speech Pathology Department "SUVAG"
MNPE "St. Michael's Clinical Hospital of Kyiv"
01601, 39/1 Shovkovychna Str., Kyiv, Ukraine
https://orcid.org/0009-0003-6261-7567

Olha Khomych*

PhD in Medical Sciences, Associate Professor
O.O. Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-9272-7159

Svitlana Khodakivska

PhD in Medical Sciences, Associate Professor
O.O. Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-0082-6561

Implementation of assistive technologies for rehabilitation of children with hearing impairments

Abstract

Relevance. Hearing impairments in children negatively affect speech development, cognitive functions, learning and social adaptation, whereas the use of assistive technologies helps compensate for sensory deficits, improve speech perception and promote the child's more effective integration into educational and social environments.

Aim: To analysed recent scientific publications on assistive technologies for the rehabilitation of children with hearing impairments, with a focus on the effectiveness of their use in children with cochlear implants.

Materials and methods. A systematic literature review was conducted in accordance with the PRISMA 2020 guidelines, with the research question formulated using the PICO framework. Clearly defined inclusion criteria and a standardised search strategy were applied across PubMed, Scopus, and Web of Science databases covering the period from 2010 to 2025.

Results. The analysis of 21 selected studies demonstrated that the use of assistive technologies is associated with improved speech perception, reduced negative effects of background noise, and increased academic engagement among children. The most pronounced effect was observed with the combined use of hearing aids or cochlear implant systems together with signal enhancement technologies (FM systems, induction loop systems), which improve the signal-to-noise ratio in challenging acoustic environments. The integration of multiple technological solutions contributes to individualised rehabilitation and enhances its functional effectiveness.

Conclusions. Technological rehabilitation is a relevant and effective method for supporting patients with sensorineural hearing loss, ensuring restoration or improvement of sound and speech perception through hearing aids, cochlear implants, and sound amplification systems. The integration of assistive communication

Suggested Citation:
Marushko Yu, Kondratenko I, Khomych O, Khodakivska S. Implementation of assistive technologies for rehabilitation of children with hearing impairments. Med Sci Ukr. 2026;22(2):133–143. DOI: https://doi.org/10.32345/2664-4738.2.2026.14

*Corresponding author (*khomychov@gmail.com*)

technologies enables children with hearing impairments to participate more actively in the educational process, social interactions, and daily life, thereby improving their quality of life and psychosocial well-being. The practical significance of the results lies in substantiating the early individualised use of assistive technologies in the rehabilitation of children with hearing impairments.
Keywords: assistive technologies; FM systems; hearing aids; cochlear implant; hearing impairment; rehabilitation intervention; paediatric patients; speech recognition.

INTRODUCTION

Hearing impairment in childhood remains a major medical and social concern, with a substantial impact on child development, including speech and language acquisition, cognitive function, communication skills, and social adaptation. The timely identification of hearing disorders and the implementation of contemporary rehabilitation approaches are essential for ensuring the optimal development of paediatric patients and improving their quality of life. Advances in early diagnostic methods, together with the use of assistive technologies, hearing aids, cochlear implants, and comprehensive rehabilitation interventions, have expanded the opportunities to support children with hearing impairment. At the same time, these developments highlight the need for further investigation into the effectiveness of modern rehabilitation strategies.

Between 1990 and 2021, the global prevalence of hearing impairment among children across different age groups increased steadily. According to the Global Burden of Disease Study 2021, approximately 97.83 million children and adolescents under the age of 20 were living with hearing impairment of varying severity in 2021, with significant long-term consequences for their physical, cognitive, and psychosocial development. Between 1990 and 2021, the number of children affected by hearing impairment increased from approximately 79.9 million to 97.8 million, while the prevalence rate per 100,000 population rose from 3,537 to 3,711. These findings indicate a substantial increase in the scale of the problem and emphasise the need for greater attention to the prevention, early diagnosis, and rehabilitation of hearing impairment among children and adolescents worldwide [1].

According to estimates by the World Health Organisation (WHO), more than 1.5 billion people worldwide experience some degree of hearing impairment. Approximately 430 million of these individuals have disabling hearing loss, a condition that significantly limits everyday communication and requires specialised treatment and rehabilitation. This number is expected to continue increasing by 2050 [2]. According to the project report of The BEARR Trust, approximately 30,600 people in Ukraine were living with hearing impairment as of 2025 [3]. The same report indicates that the global prevalence of clinically significant hearing impairment among newborns is approximately 1-3 cases per 1,000 live births, making it one of the most common congenital conditions detected through universal newborn hearing screening in the first days of life. In Ukraine, analyses of regional audiological screening programmes indicate a prevalence of approximately one case per 2,000 newborns. However, around 40% of cases remain undiagnosed until after the child reaches six months of age, substantially delaying timely intervention and rehabilitation. These findings were obtained during the 2023 assessment of newborn hearing screening programmes conducted across 16 regions of Ukraine [4]. Consequently, in 2025, the Ministry of Health of Ukraine approved a new regulation, "On Approval of the Procedure for the Provision of Medical Care for the Organisation of Hearing Screening and Diagnosis of Hearing Impairment in Children", which establishes the organisational and methodological framework for hearing screening, including screening stages, risk assessment criteria for hearing loss, and standards for audiological assessment in children up to six years of age [5].

Furthermore, according to O. Kuzenko *et al.* [6] and J. Wang *et al.* [7], approximately 15-17% of school-aged children exhibit some degree of hearing impairment, ranging from mild to moderate forms that may adversely affect academic achievement and social adaptation. Hearing impairment during the school years is often gradual or subclinical, making timely detection through routine medical examinations more challenging. At the same time, this period is critical for the development of cognitive, linguistic, and socio-communicative skills; therefore, even mild hearing loss may have cumulative adverse effects on learning, behaviour, and the child's emotional and psychological development. These findings highlight the need for continuous audiological monitoring not only during the neonatal period but throughout childhood and adolescence, with particular attention to school-aged children. In particular, the systematic review by J. Wang *et al.* [7] demonstrated the increasing prevalence of hearing impairment among children and emphasised the importance of early detection and comprehensive rehabilitation. Similarly, the systematic review by R.S. Melo *et al*. [8] reported positive effects of rehabilitation programmes on balance and functional performance in children with sensorineural hearing loss.

According to the Ministry of Health of Ukraine and the WHO, approximately 40,000 people in Ukraine live with a disability related to hearing impairment. Among pupils attending different types of general secondary

schools, around one-fifth are children with hearing loss or deafness, highlighting the need to provide specialised conditions for education, communication, and rehabilitation [2, 6]. Hearing impairment is one of the most common developmental disorders identified in newborns. In approximately 85% of cases, hearing loss is congenital or develops during the first one to two years of life, that is, during the pre-linguistic period and the earliest stages of speech and language development, which are critical for subsequent cognitive, linguistic, and social development. According to published evidence, up to 80% of hearing impairment cases are sensorineural in origin, for which modern hearing rehabilitation approaches, including cochlear implantation systems, may be used [4]. Given the high prevalence of hearing impairment among children, the increasing global number of individuals with hearing loss, and the fundamental importance of hearing for speech and language acquisition, cognitive development, and social integration, cochlear implantation has become widely established as one of the most effective interventions for preventing and reducing the consequences of profound hearing loss. However, the effectiveness of cochlear implantation is not limited to the surgical procedure itself; it depends to a large extent on subsequent rehabilitation incorporating modern assistive technologies aimed at improving auditory perception, developing communication skills, increasing the child's independence, and enabling full participation in education and social life.

Thus, there remains a need to synthesise current scientific evidence regarding the role of assistive technologies in the comprehensive rehabilitation of children with hearing impairment and to identify promising directions for their application in improving auditory perception, communication, and social integration. The aim of this study was to systematise and analyse current scientific evidence concerning the use of assistive technologies in the rehabilitation of children with hearing impairment, with particular emphasis on children with cochlear implants.

MATERIALS AND METHODS

A systematic review of contemporary scientific literature was conducted to evaluate assistive technologies used in the rehabilitation of children with hearing impairment, including children with cochlear implants. The literature analysis encompassed studies investigating the effectiveness of vibration and visual alert systems, FM systems, induction loop systems, as well as text- and video-based communication devices, with particular emphasis on their impact on independence, social integration, and participation in education. The systematic review was conducted in accordance with the PRISMA 2020 Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), following the updated recommendations for transparent and comprehensive reporting [9].

The research question was formulated using the PICO framework, where Population (P) comprised children aged 0-18 years with hearing impairment, including those following cochlear implantation; Intervention (I) included assistive technologies (hearing aids, cochlear implant systems, FM systems, induction loop systems, vibration and visual alert devices, and text- and video-based communication technologies); Comparison (C) consisted of standard rehabilitation approaches or the absence of specialised assistive technologies; and Outcomes (O) included measures of speech recognition, participation in education, social integration, and quality of life [9].

The literature search was conducted in the PubMed, Scopus and Web of Science databases for the period from 1 January 2010 to 31 December 2025. Combinations of keywords and MeSH terms were used: "hearing impairment", "children", "assistive technology", "cochlear implant", "FM system", "assistive listening devices", "speech perception", using the logical operators AND/OR. In addition, references in relevant articles were analysed to identify further sources. The inclusion criteria comprised: (1) studies involving children under the age of 18 with various forms of hearing impairment; (2) a description of the use of at least one type of assistive technology in the context of rehabilitation; (3) the presentation of quantitative or qualitative results relating to clinical, functional or psychosocial outcomes; (4) publication in peer-reviewed journals in English or Ukrainian. The analysis excluded review articles without a clear search methodology, expert opinions, individual case reports without a systematic assessment of effectiveness, and studies relating exclusively to adult patients.

Results of the systematic search. During the identification phase, 312 records were identified in the databases. After removing duplicates (n = 44), 268 publications were retained for further analysis. During the initial screening of titles and abstracts, 194 studies that did not meet the predefined inclusion criteria were excluded. A full-text assessment was carried out for 74 articles, of which 21 studies met all selection criteria and were included in the qualitative synthesis. A schematic representation of the study selection process in accordance with the PRISMA 2020 guidelines is presented in Figure 1, which shows the number of records and the reasons for their exclusion at each stage.

The risk of bias in the included studies was assessed using appropriate tools: the Newcastle-Ottawa Scale for cohort and observational studies, and the AMSTAR-2 tool for published systematic reviews. The analysis was carried out by two independent researchers; any discrepancies in the assessments were resolved through discussion until a consensus was reached.

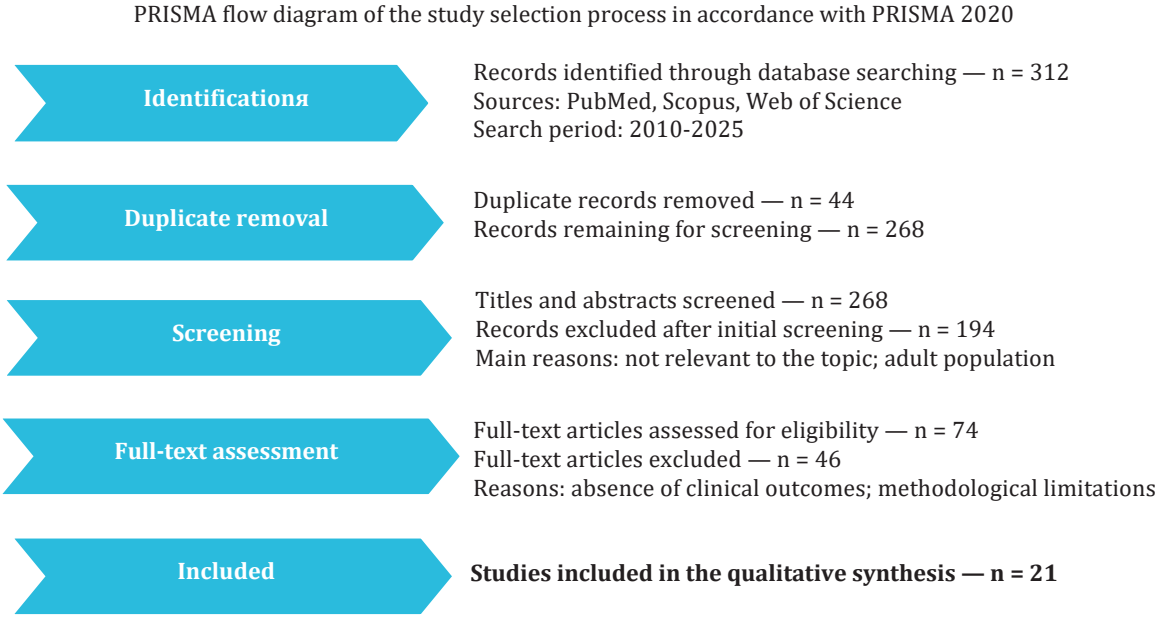

Figure 1. PRISMA flow diagram of the study selection process in accordance with PRISMA 2020

Source: developed by the authors in accordance with the PRISMA 2020 recommendations, based on the results of the systematic search and study selection

Characteristics of the included studies. The qualitative synthesis included 21 studies published between 2010 and 2025. These were predominantly prospective cohort studies, clinical observations and comparative studies of the effectiveness of hearing aids and assistive technologies in children with hearing impairments. In particular, the studies by Z. Guo *et al.* [1], J. Wang *et al.* [7] and R.S. Melo *et al.* [8] were analysed. Studies were selected in accordance with the PRISMA 2020 guidelines. The main outcomes assessed were speech recognition scores, signal-to-noise ratio (SNR), level of learning engagement, social integration and quality of life indicators [10].

RESULTS AND DISCUSSION

The analysed studies examined a broad range of assistive technologies used to support children with hearing impairment. These included hearing aids, cochlear implant systems, FM systems, induction loop systems, visual and vibration alert devices, and digital communication technologies, including text- and video-based communication platforms. Most studies focused on evaluating the effectiveness of hearing aids, cochlear implants, and FM systems, whereas visual and vibration alert devices were generally considered supplementary tools for supporting daily activities and enhancing the safety of children with hearing impairment.

A national policy priority is the development and optimisation of support systems for children with special educational needs, including those with hearing impairment. In Ukraine, international standards of care for children with hearing impairment are being implemented, including universal neonatal hearing screening, expanded access to advanced hearing rehabilitation technologies such as cochlear implants, strengthened early intervention programmes targeting hearing and speech disorders in newborns and young children, and the further development of inclusive education and social integration initiatives. These developments highlight the need to improve existing approaches to auditory-verbal development in children with hearing impairment, as well as to modernise the organisational and technological aspects of corrective and developmental support. According to S.T. Mohamed *et al.* [10], the period from 2020 to 2025 witnessed substantial advances in understanding the special educational needs of children with hearing impairment, reflected in the adoption of more inclusive approaches, wider implementation of assistive technologies, and greater emphasis on the individualisation of educational and rehabilitation support.

The findings are consistent with contemporary international evidence [1-2], confirming the effectiveness of the comprehensive use of assistive technologies in children with hearing impairment. The combined use of hearing rehabilitation devices and signal enhancement systems creates favourable conditions for the development of auditory-verbal skills, improved academic achievement, and enhanced social adaptation. Given the clinical heterogeneity of hearing impairment, Table 1 presents a classification according to aetiology, severity (hearing threshold), time of onset, symmetry of impairment, and audiogram configuration to facilitate a systematic approach to assessment.

Table 1. Classification of hearing impairment according to the main clinical criteria

By aetiology	By severity (hearing threshold)	By time of onset	By symmetry	By audiogram configuration
Conductive hearing loss Sensorineural hearing loss Mixed hearing loss Central hearing loss	Mild: 20-40 dB Moderate: 41-55 dB Moderately severe: 56-70 dB Severe: 71-90 dB Profound: over 90 dB	Congenital Acquired	One-way Two-way	Flat High-frequency Low-frequency Dome-shaped / U-shaped

Source: compiled by the authors based on [1-2, 7]

According to Y.C. Hung *et al.* [11], hearing impairment may be classified into several principal forms according to its aetiology, each characterised by distinct pathogenic mechanisms, clinical manifestations, and approaches to treatment and rehabilitation. Sensorineural hearing loss results from damage to the sensory structures of the inner ear (the cochlear hair cells), the auditory nerve, or the central auditory pathways. This is the most common form of hearing impairment and is generally permanent or progressive in nature. Its causes include genetic factors, intrauterine infections, perinatal injury, ototoxic medications, noise-induced trauma, viral infections, and vascular disorders. A distinct clinical entity is sudden hearing loss, characterised by a rapid decline in hearing function occurring within a period of up to 72 hours. According to O. Kuzenko *et al*. [6] and J. Wang *et al*. [7], when the pathological process involves the inner ear or the auditory nerve, the condition is referred to as sudden sensorineural hearing loss (SSNHL). When no underlying cause can be identified despite comprehensive clinical investigation, the condition is diagnosed as idiopathic sudden sensorineural hearing loss, which represents the most common form of SSNHL encountered in clinical practice.

According to C. Pflug *et al*. [12] and R.S. Melo *et al.* [8], conductive hearing loss is caused by impaired transmission of sound through the structures of the outer or middle ear. The most common causes include inflammatory disorders of the middle ear (acute and chronic otitis media), otitis media with effusion, tympanic membrane perforation, congenital abnormalities of the auditory ossicles, and other mechanical obstructions that interfere with sound conduction. In this form of hearing loss, the inner ear remains functionally intact, and hearing function can often be fully or partially restored following treatment of the underlying cause.

Mixed hearing loss combines features of both conductive and sensorineural hearing loss, indicating the simultaneous involvement of the middle and inner ear structures. According to E. Nightengale *et al.* [13], central hearing loss results from impaired processing of auditory information within the central nervous system, involving the subcortical auditory pathways or the cerebral cortex. In such cases, the peripheral components of the auditory system may remain anatomically and functionally intact. According to N. Tye-Murray *et al.* [14], this type of hearing impairment is frequently associated with prolonged chronic inflammatory diseases of the middle ear complicated by secondary damage to the sensory apparatus and therefore requires a comprehensive multidisciplinary approach to treatment and rehabilitation.

A detailed classification of hearing impairment according to its type, severity, time of onset, symmetry, and audiogram configuration not only enables the systematic organisation of clinical information but also provides the basis for accurate diagnosis and assessment of a child's medical and rehabilitation needs. Hearing assessment is critically important throughout all stages of child development, as the timely identification of hearing disorders allows appropriate intervention strategies to be selected and helps prevent secondary impairments in speech and language, cognitive development, and social functioning. However, according to PravoChuty [4], even after a diagnosis has been established, comprehensive rehabilitation remains essential. This includes the use of modern assistive technologies, hearing aids or cochlear implantation, auditory-verbal training, and support for the child's adaptation to educational and social environments.

Rehabilitation is essential for patients with incomplete recovery of hearing and aims to restore functional abilities and improve quality of life. Counselling regarding the potential benefits of hearing rehabilitation technologies and other supportive interventions is recommended, as systematic reviews have demonstrated their positive effects on functional performance and social participation. According to E.M. Fitzpatrick *et al*. [15], the successful implementation of these technologies requires appropriate counselling and adequate resource provision. The regular use of hearing devices and complementary rehabilitation measures should therefore be regarded as an integral component of comprehensive rehabilitation, promoting optimal functional integration and social participation for the child.

Rehabilitation of patients with residual sensorineural hearing loss following an acute episode is necessary to restore functional abilities and improve quality of life. According to the Clinical Guideline "Management of Patients with Sudden and Acute Sensorineural Hearing Loss" [16], approved by the Ministry of Health of Ukraine in 2022, patients should receive counselling regarding the potential benefits of hearing rehabilitation technologies and other assistive interventions. The use

of hearing devices contributes to improved auditory function, enhanced quality of life, and better emotional well-being, while also increasing opportunities for participation in everyday activities.

Device-based rehabilitation for children with hearing impairment is based on the use of technological solutions designed to compensate for hearing deficits and improve communication abilities. These include hearing aids, cochlear implant systems, sound amplification devices, and vibration and visual alert systems. Additional support is provided by modern digital communication technologies, including text-based services and specialised mobile applications. Hearing aids remain one of the principal interventions for auditory rehabilitation in children with hearing impairment. Unlike hearing rehabilitation in adults, paediatric hearing aid fitting is intended not only to compensate for hearing loss but also to facilitate the development of auditory perception, speech and language, and communication skills. Consequently, specialised paediatric hearing aids and age-appropriate fitting algorithms are used, taking into account the developmental characteristics of the auditory system, the degree of hearing loss, and the child's speech and language needs [17]. Specific requirements apply to paediatric hearing aids, as summarised in Table 2.

Table 2. Functional and safety criteria for paediatric hearing aids

Criterion	Description of characteristics
Flexibility of features	Configured according to the paediatric DSL fitting algorithm with minimal distortion
Mechanical safety	Use of hypoallergenic materials, robust construction, and the absence of small detachable parts
Acoustic safety	Control of the maximum output sound pressure level, compression (preferably speech compression), and the option to disable the volume control
Predictability of use	Availability of visual indicators showing device operation, systems for monitoring the correct placement of the earmould, and remote control functionality
Operational reliability	Reliable operation under a range of operating conditions
Ability to activate/deactivate "adult" features	Availability of options to activate or deactivate specific features, including the directional microphone and programme switching, according to the user's needs

Note: DSL – desired sensation level
Source: compiled by the authors based on [2, 7, 17]

According to J.N. Li *et al.* [17], contemporary hearing aids are available in a range of designs, the most common being behind-the-ear and in-the-ear models. Behind-the-ear devices are worn behind the pinna and offer extensive opportunities for individual adjustment according to the degree of hearing loss. In-the-ear models are custom manufactured to fit the anatomical characteristics of the user's external auditory canal and are positioned directly within the ear.

In paediatric practice, behind-the-ear hearing aids are generally preferred because the anatomical characteristics of the external auditory canal in young children limit the suitability of in-the-ear devices. Furthermore, the child's continuous growth necessitates the regular replacement of custom earmoulds and periodic adjustment of hearing aid settings to ensure optimal sound quality. The effectiveness of hearing rehabilitation depends not only on the appropriate selection of the hearing device but also on subsequent auditory rehabilitation. Following hearing aid fitting, it is essential to develop the child's ability to perceive and interpret auditory information. The rehabilitation process includes gradual exposure to different acoustic stimuli, training in sound source localisation, discrimination between speech and non-speech sounds, and the enhancement of auditory attention and communication skills. Such a comprehensive approach facilitates successful adaptation to hearing aid use and improves auditory-verbal outcomes [15, 17].

Cochlear implantation is a modern, high-technology method of auditory rehabilitation indicated for patients with severe or profound sensorineural hearing loss when conventional hearing aids do not provide sufficient speech perception or auditory development [17]. Unlike hearing aids, which amplify acoustic signals and rely on the remaining function of the auditory system, cochlear implant systems provide direct electrical stimulation of the auditory nerve fibres, thereby compensating for the impaired function of damaged sensory cells within the inner ear [18].

According to F. Nassrallah *et al*. [18], a cochlear implant system consists of two components: an internal and an external unit. The internal component comprises the receiver-stimulator and an electrode array implanted into the cochlea. The external component includes the speech processor, transmitting coil, and connecting elements responsible for transmitting information between the external and internal parts of the system. Signal transmission is achieved through magnetic coupling between the transmitting coil and the implanted receiver. Studies by J.N. Li *et al*. [17] and F. Nassrallah *et al.* [18] have shown that cochlear implants improve the perception of environmental sounds, enhance speech intelligibility, and increase communication effectiveness across a variety of acoustic environments. Cochlear implantation is particularly important in childhood because it provides the foundation for the development of auditory-verbal skills,

educational attainment, and social adaptation. However, the effectiveness of cochlear implantation depends not only on the surgical procedure but also on comprehensive post-implantation rehabilitation. Following device activation, key components of rehabilitation include individual programming of the speech processor, ongoing technical support, auditory training, speech and language development, and the enhancement of communication skills. It is this combination of technological hearing restoration and long-term auditory-verbal rehabilitation that enables the full potential of cochlear implantation to be realised.

According to J.S. Kim & C.H. Kim [19], Assistive Listening Systems (ALSs), also referred to as Assistive Listening Devices (ALDs), comprise a group of technologies designed to improve speech understanding and sound quality in challenging acoustic environments, particularly in public settings where background noise, distance from the sound source, or reverberation reduce speech intelligibility for individuals with hearing impairment. ALSs operate by improving the signal-to-noise ratio, which is essential for effective speech recognition by people with hearing loss in everyday listening situations, particularly when conventional hearing aids or cochlear implants alone do not provide sufficient benefit. An FM system is a wireless type of ALS that uses frequency modulation to transmit sound directly from a source, such as a lecturer's microphone or a public address system, to the user's receiver. The receiver may either be integrated into the hearing aid or cochlear implant or provided as a separate device connected to a hearing aid or headphones. Figure 2 illustrates the principal capabilities of FM systems in improving speech perception.

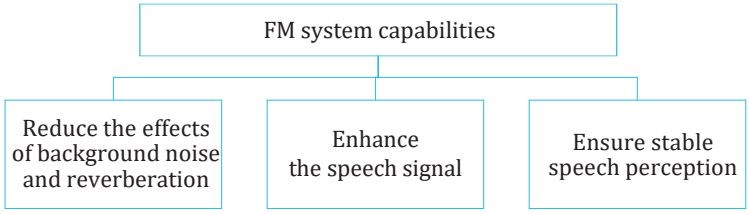

Figure 2. Key capabilities of FM systems
Source: compiled by the authors based on [2, 7, 19]

The system presented in Figure 2 amplifies the speech signal without being affected by background noise or the distance between the sound source and the listener. It reduces the effects of reverberation by transmitting the signal on a dedicated radio frequency independent of the room's overall sound field, thereby ensuring stable speech perception even in large halls or open spaces. Scientific studies have demonstrated that the use of FM systems significantly improves speech recognition in noisy environments, which is particularly important in educational settings. An induction loop is a type of ALS that generates an electromagnetic field within a defined area, which can be received wirelessly by hearing aids or cochlear implant processors equipped with a telecoil (T-coil). This technology overcomes problems associated with background noise and distance by transmitting the signal directly to the hearing device without intermediate acoustic transmission [20]. Both FM systems and induction loop systems are widely used; their comparative characteristics are presented in Table 3.

Table 3. Main characteristics of FM systems and induction loop systems

Characteristic	FM systems	Induction loop systems
Principle of transmission	Radio-based signal modulation (radio frequency) to the receiver	Magnetic field generated within a room and received by the hearing aid/telecoil
Connection to the hearing aid	Requires a separate receiver or integration	Directly via the T-coil (telecoil) in the hearing aid or cochlear implant
Signal transmission	Via a dedicated receiver	Direct transmission
Sound quality / SNR	Excellent SNR over distance	Very high SNR over distance
Power consumption	Receivers may increase the hearing aid's battery consumption	No impact on the user's hearing aid battery; power is supplied by the loop system
Applications	Open spaces, large halls, and classrooms	Public venues, theatres, conference halls, cinemas, and lecture theatres
Advantages	Flexible transmission range; supports a large number of users	Easy to use; no separate receivers required

Note: SNR – signal-to-noise ratio
Source: compiled by the authors based on [2, 20]

The findings reported by A. Flores Ramones & M.S. Del-Rio-Guerra [21] demonstrate that vibration and visual alert systems are important components of assistive technologies, providing alternative notification

channels for individuals who are deaf or have severe hearing loss. Conventional auditory alerts are often inaccessible to people with hearing impairment, creating safety risks and limiting participation in everyday activities. By using vibration (tactile) and visual (light-based) alerts, information about important events can be conveyed through alternative sensory systems, consistent with the principles of sensory substitution and multisensory support in assistive technologies.

Vibration alert systems use tactile stimulation to notify users of important auditory events, such as telephone calls, alarm clocks, or emergency warnings. These systems may take the form of wearable devices, wristbands, vibrating mats, or bed shakers that activate when the surrounding system detects a relevant sound event. Practical studies have shown that wearable vibration devices can effectively detect important sounds and communicate them to the user through tactile feedback, thereby improving awareness of environmental events and enhancing safety in everyday life [22]. According to "Healthy Hearing" [23], tactile alerts are particularly effective when auditory signals are unavailable or insufficient, such as during sleep or in noisy environments.

Visual alert systems employ flashing strobe lights, LED indicators, or visual notification devices that flash or vary their light intensity when an auditory event is detected, for example a doorbell, telephone call, or smoke alarm. These visual notifications enable users to recognise important events immediately without relying on auditory cues, which is particularly valuable in domestic and public environments where conventional sound-based alerts are inaccessible to individuals with severe hearing loss. Combining visual and vibration alerts further improves the reliability of notification systems and enhances environmental accessibility by engaging multiple sensory modalities simultaneously [24].

These technologies are increasingly integrated into modern smart home systems incorporating intelligent sensors, mobile notifications, IoT devices, and wearable technologies, enabling users to receive real-time alerts with adjustable vibration intensity and visual indicators according to individual preferences. The development of such solutions reflects the broader trend towards implementing assistive technologies that enhance accessibility, independence, and everyday functioning for people with hearing impairment. According to E. Bahçekapılı & A. Ayaz [25], the use of visual and vibration alerts in assistive systems is consistent with the concept of sensory substitution, whereby information about auditory events is transmitted through alternative sensory modalities, such as tactile or visual input, thereby compensating for the loss of auditory information. This approach is based on the principle of neuroplasticity, which enables the brain to adapt to signals received through alternative sensory pathways.

Text telephones and devices supporting text- or video-based communication are important components of contemporary assistive technologies, providing accessible and barrier-free communication for people with hearing impairment. These technologies enable users to exchange information through alternative communication methods, including text messaging, chat interfaces, and video calls incorporating sign language or real-time captions. According to P.A. Rodríguez-Correa *et al*. [26], modern smartphones equipped with text-based communication functions support SMS, instant messaging (IM), chat applications, and adaptive keyboards, substantially improving access to telephone communication compared with conventional voice calls. Studies have shown that text-based communication enhances independence and social participation among individuals with hearing loss by eliminating reliance on auditory speech perception, which may be difficult or impossible for these users.

In addition, contemporary smartphones and computer-based platforms support video communication using sign language, enabling people who use sign language to participate in video calls and video conferencing in which information is exchanged visually. This mode of communication is particularly valuable for users whose primary language is sign language rather than written text, providing a highly accurate and natural means of interaction. According to the review by M. Rivas Velarde *et al*. [27], video platforms supporting ASL significantly improve communication accessibility in professional, educational, and social settings.

The effectiveness of these technologies is supported by research on digital accessibility and inclusive communication, demonstrating that the integration of text and video-based communication tools reduces communication barriers, improves psychosocial well-being, and enhances social participation among individuals with sensory impairments. For example, studies by M.J. Myers *et al.* [28] and S. Sabbagh *et al*. [29] have shown that the use of video communication incorporating sign language or automatic captioning in customer service settings improves the quality of interactions across healthcare, education, and employment.

Overall, the findings indicate that the integration of assistive technologies into the rehabilitation of children with hearing impairment is consistent with contemporary evidence-based practice, as reflected in the clinical and experimental studies included in this review. These technologies enhance the effectiveness of auditory-verbal rehabilitation, expand opportunities for children's communication development, and support their successful adaptation to educational and social environments. Consequently, assistive technologies should be regarded as an integral component of comprehensive auditory-verbal and psychosocial support for children with hearing impairment.

CONCLUSIONS

1. The results of an analysis of 21 scientific publications released between 2010 and 2025 highlight the

important role of assistive technologies in the comprehensive rehabilitation of children with hearing impairments. The most common forms of assistive technology remain hearing aids, cochlear implants and remote sound transmission systems (FM systems), the effectiveness of which has been confirmed by numerous clinical and review studies.

2. The analysis of the literature showed that the use of modern hearing rehabilitation technologies improves auditory perception, speech intelligibility, speech perception in the presence of background noise, and overall communication effectiveness. The integration of assistive communication technologies enables children with hearing impairment to participate more actively in educational activities, social interactions, and everyday life, thereby improving their quality of life and psychosocial well-being.

3. It was established that, alongside conventional hearing aids and cochlear implants, additional assistive technologies play an important role, including FM systems, induction loop systems, vibration and visual alert devices, text communication tools, video communication platforms, and automatic captioning technologies. Their use expands access to information, enhances safety, and promotes greater independence for children in their daily lives.

4. The findings of the analysed studies indicate that the integration of assistive technologies into educational environments has a positive impact on academic achievement, social adaptation, and the quality of life of children with hearing impairment. The use of modern communication support technologies encourages more active participation in the learning process, improves interaction with peers, and facilitates inclusion in society.

5. The practical significance of these findings lies in confirming the value of the early implementation of assistive technologies as an integral component of the multidisciplinary rehabilitation of children with hearing impairment. The selection of specific technological solutions should be individualised according to the child's age, degree of hearing loss, educational needs, and everyday functional requirements. Future research should focus on evaluating the long-term effectiveness of emerging digital assistive technologies, automatic speech recognition and captioning systems, and their impact on educational outcomes, social integration, and the quality of life of children with cochlear implants.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Юрій Марушко

Доктор медичних наук, професор
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-8066-9369

Ірина Кондратенко

Виконуючий обов'язки завідувача відділення патології слуху і мовлення «СУВАГ»
КНП «Свято-Михайлівська клінічна лікарня м. Києва»
01601, вул. Шовковична, 39/1, м. Київ, Україна
https://orcid.org/0009-0003-6261-7567

Ольга Хомич

Доктор філософії, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-9272-7159

Світлана Ходаківська

Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-0082-6561

Впровадження асистивних технологій для реабілітації дітей з порушенням слуху

Анотація

Актуальність. Порушення слуху у дітей негативно впливають на розвиток мовлення, когнітивні функції, навчання та соціальну адаптацію, тоді як використання асистивних технологій допомагає компенсувати сенсорні дефіцити, покращити сприйняття мовлення й сприяти ефективнішій інтеграції дитини в освітнє та соціальне середовище.

Мета. Аналіз сучасних наукових публікацій, присвячених асистивним технологіям у реабілітації дітей із порушеннями слуху, з акцентом на ефективність їх використання у дітей із кохлеарними імплантами.

Матеріали та методи. Проведено систематичний огляд літератури відповідно до вимог PRISMA 2020 із визначенням дослідницького питання за моделлю PICO, чіткими критеріями включення та стандартизованою стратегією пошуку в базах PubMed, Scopus та Web of Science за 2010-2025 роки.

Результати. Аналіз 21 відібраного дослідження засвідчив, що застосування асистивних технологій асоціюється з покращенням розпізнавання мовлення, зменшенням негативного впливу фонового шуму та підвищенням академічної активності дітей. Найбільш виражений ефект спостерігався при комбінованому використанні слухових апаратів або систем кохлеарної імплантації з технологіями підсилення сигналу (FM-системи, індукційні петлі), що забезпечують покращення співвідношення сигнал/шум у складних акустичних умовах. Інтеграція декількох технологічних рішень сприяє індивідуалізації реабілітації та підвищенню її функціональної результативності.

Висновки. Апаратна реабілітація є актуальним і ефективним засобом підтримки пацієнтів із сенсоневральними порушеннями слуху, забезпечуючи відновлення або покращення сприйняття звуків і мовлення за допомогою слухових апаратів, кохлеарних імплантів та систем підсилення звуку. Інтеграція допоміжних технологій для комунікації дозволяє дітям із порушеннями слуху активніше брати участь у навчальному процесі, соціальних взаємодіях та повсякденному житті, покращуючи їхню якість життя та психосоціальне благополуччя. Практичне значення результатів полягає в обґрунтуванні раннього індивідуалізованого застосування допоміжних технологій у реабілітації дітей із порушеннями слуху.

Ключові слова: допоміжні технології; FM-система; слухові апарати; кохлеарний імплант; слухові порушення; реабілітаційне втручання; пацієнти дитячого віку; розпізнавання мовлення.

MEDICAL DIAGNOSTICS AND
TREATMENT TECHNOLOGIES

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 615.33:616-089:614.2
DOI: https://doi.org/10.32345/2664-4738.2.2026.15

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 30.12.2025 Revised: 26.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Mykola Khaitovych*

Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-6412-3243

Olena Vityuk

Head of the Department
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0009-0004-5915-4001

Dynamics of antimicrobial consumption in an inpatient surgical department following the implementation of an antimicrobial stewardship programme

Abstract

Relevance. Antimicrobial stewardship (AMS) programmes have become an important strategy for optimising antibiotic use and combating antimicrobial resistance in surgical practice.

Aim. To evaluate the impact of implementing an AMS on antibiotic consumption in an inpatient surgical department.

Materials and methods. A retrospective analysis of antimicrobial consumption was conducted in the surgical department of a university hospital between 2023 and 2025. Consumption was assessed using the defined daily dose (DDD) and DDD per 100 bed-days, with analysis of the prescribing structure according to the WHO AWaRe classification.

Results. Despite an almost fivefold increase in the total volume of antibiotics used, from 558.1 to 2,387.0 DDD, due to a substantial expansion of surgical services, including the treatment of patients with combat-related injuries, the intensity of antibiotic consumption decreased from 33.5 to 6.8 DDD per 100 bed-days. The proportion of Access group antibiotics increased from 5.8% to 57.3%, whereas the proportion of Reserve group antibiotics declined from 82.6% to 4.7%, indicating a more appropriate pattern of use. A marked reduction was observed in the prescribing of third-generation cephalosporins (particularly ceftriaxone, which is classified as a Reserve antibiotic according to the national healthcare standard), as well as other Reserve antibiotics, including colistin and tigecycline. The use of carbapenems and fluoroquinolones also decreased, while the use of aminoglycosides, metronidazole, and clindamycin, all of which belong to the Access group, increased.

Practical significance. The implementation of a comprehensive AMS resulted in more rational antibiotic use, optimisation of prescribing patterns in accordance with the AWaRe classification, and a reduction in the intensity of antibiotic consumption, confirming the effectiveness of a multidisciplinary approach involving a clinical pharmacist in the inpatient surgical setting.

Keywords: antimicrobial resistance; clinical pharmacist; antibiotics; surgery; medicine consumption; defined daily dose; AWaRe classification.

INTRODUCTION

The rational use of antibiotics in surgery is not only a matter of clinical protocol but also a strategic objective for ensuring global safety. Surgical wards are high-risk areas where the consumption of antimicrobial medicines is traditionally high, both for prophylaxis and for the treatment of complex infections; therefore, for a

Suggested Citation:
Khaitovych M, Vityuk O. Dynamics of antimicrobial consumption in an inpatient surgical department following the implementation of an antimicrobial stewardship programme. Med Sci Ukr. 2026;22(2):144–151. DOI: https://doi.org/10.32345/2664-4738.2.2026.15

*Corresponding author (*nik3061@gmail.com*)

surgeon, an antibiotic is not merely a medicine but a critical tool for the success of a surgical procedure. This is primarily because antimicrobial resistance (AMR) is recognised as one of the most serious threats to global public health and economic stability.

The principal driver of this problem is the excessive and inappropriate use of antibiotics. According to Y. Wang *et al*. [1], between 20% and 50% of antimicrobial prescriptions in hospitals are inappropriate or unnecessary. Thus, taking into account these findings, as well as those reported by I. Kourbeti *et al*. [2], the rational use of antibiotics is recognised as a key strategy for limiting the spread of AMR. M. Bashar *et al*. [3] reported that surgical site infections (SSIs) remain a leading cause of postoperative morbidity and mortality, prompting surgeons to prescribe broad-spectrum antibiotics for prolonged periods. However, it has been demonstrated that extending surgical antibiotic prophylaxis beyond 24 hours does not reduce the risk of infection but significantly increases the likelihood of adverse events, including acute kidney injury and *Clostridioides difficile* infection. A. Marino *et al*. [4] demonstrated that surgical antimicrobial prophylaxis is essential for preventing SSIs, although inappropriate antibiotic use remains a major challenge. M. Piscaglia *et al*. [5] found that patients with SSIs were significantly more likely to develop additional healthcare-associated infections. Similarly, H. Habteweld *et al*. [6] reported that inappropriate antibiotic selection or unnecessarily prolonged treatment significantly increases the risk of adverse surgical outcomes.

To address these challenges, antimicrobial stewardship (AMS) programmes have been implemented worldwide. The primary objective of these programmes is to optimise clinical outcomes while minimising the risks associated with antibiotic use, including toxicity and the selection of resistant bacterial strains. According to Y. Wang *et al.* [1], in the surgical setting this involves the adoption of de-escalation strategies, whereby empirical broad-spectrum antibiotic therapy is replaced with targeted narrow-spectrum treatment guided by microbiological findings. The effectiveness of such programmes largely depends on a multidisciplinary approach. Evidence indicates that the involvement of clinical pharmacists in daily ward rounds and prescription audits significantly reduces antibiotic consumption and hospitalisation costs in surgical departments [1]. Likewise, the implementation of the "handshake stewardship" model, based on direct communication between the AMS team and treating physicians, has demonstrated high effectiveness in general surgical units. As reported by A. Kosharek *et al.* [7], this approach not only reduces antibiotic consumption but also improves prescribing quality.

The assessment of antimicrobial consumption is generally based on the calculation of defined daily doses (DDD). A study conducted by M. Bashar *et al*. [3] in South Africa demonstrated that the systematic implementation of AMS in surgical departments resulted in a sustained reduction in DDD per 1,000 bed-days, accompanied by an increased proportion of targeted antimicrobial therapy. A. Jover-Sáenz *et al*. [8] emphasised that a considerable proportion of inappropriate antibiotic prescribing occurs during the transition from inpatient to outpatient care, and that interventions aimed at optimising antimicrobial therapy during this stage can reduce treatment duration by 40% or more.

The implementation of AMS is particularly important in surgical intensive care units. J. Yu *et al.* [9] demonstrated in a neurosurgical intensive care unit that active intervention by a multidisciplinary stewardship team substantially reduced the use of last-resort antibiotics, including polymyxins and tigecycline, while improving the susceptibility of Gram-negative bacteria to antipseudomonal β-lactam antibiotics. C. Pallares *et al.* [10] likewise reported that the implementation of AMS in tertiary-care hospitals reversed unfavourable resistance trends in *Pseudomonas aeruginosa* and *Escherichia coli*. Despite these successful examples, the implementation of AMS remains challenging in many countries because of shortages of trained personnel, the absence of national guidelines, and cultural barriers within the medical community.

The aim of this study was to analyse changes in antibiotic consumption following the implementation of an antimicrobial stewardship programme in the inpatient surgical department of a university hospital.

MATERIALS AND METHODS

A retrospective analysis of antibiotic consumption was conducted in the inpatient surgical department of the University Hospital of the O.O. Bogomolets National Medical University between 2023 and 2025. From 2024 onwards, the surgical department experienced a substantial increase in clinical activity owing to the provision of surgical care for patients with combat-related injuries. This was accompanied by an expansion in the range of surgical procedures performed. In 2025, the spectrum of surgical interventions continued to expand, while the number of patients requiring treatment for severe infections also increased. During the study period, several AMS interventions were implemented, including pre-authorisation of Reserve antibiotics, the introduction of a new local protocol for perioperative antibiotic prophylaxis, a series of educational workshops on the rational use of antimicrobial agents for perioperative prophylaxis and antibiotic therapy, and prospective audit with feedback, during which a clinical pharmacist provided consultations aimed at optimising the duration of antimicrobial therapy and perioperative antibiotic prophylaxis. The pre-authorisation process required selected antimicrobial agents (including carbapenems, polymyxins, ceftazidime/avibactam, cefiderocol, linezolid, daptomycin, ceftriaxone, and

levofloxacin) to be prescribed only after approval by a clinical pharmacist from the Infection Prevention and Control Department. Each request was assessed with regard to the appropriateness of the prescription for the clinical diagnosis, compliance with current clinical guidelines, microbiological findings or the presence of risk factors for infections caused by multidrug-resistant microorganisms, previous antibacterial therapy, the appropriateness of the prescribed dose, route of administration and treatment duration, renal and hepatic function, and potential drug interactions. Following expert review, either approval for the requested antimicrobial agent was granted or an alternative treatment regimen was recommended.

The overall consumption of antimicrobial agents, the consumption of individual antimicrobial medicinal products and specific groups of antibiotics, including analyses according to the WHO AWaRe classification, was assessed in DDDs per 100 bed-days. For each antibiotic, the total amount of active substance used annually in 2023, 2024 and 2025 was determined. Current DDD values were assessed based on the use of the ATC/DDD index. To determine the number of DDDs, the total quantity of the antimicrobial medicinal product consumed was divided by its ATC/DDD index value. To determine the relative consumption of antibiotics, the quantity of antimicrobial medicine consumed in DDDs was calculated per 100 bed-days using the formula: DDD/100 bed-days = Total number of DDDs × 100/Number of bed-days. The study did not require ethical approval. Artificial intelligence was used exclusively for technical editing of the manuscript, in particular to standardise and format the reference list in accordance with the journal's requirements, as well as to make linguistic, stylistic and editorial amendments. The generation, analysis and interpretation of scientific data, the formulation of conclusions and the final approval of the manuscript's content were carried out by the authors themselves.

RESULTS AND DISCUSSION

According to the data presented in Table 1, total antibiotic consumption over the two-year period increased significantly by almost fivefold (from 558.1 DDD in 2023 to 2,387.0 DDD in 2025), but the total number of bed-days increased by more than twentyfold (from 1,667 bed-days to 34,916 bed-days); as a result, total antibiotic consumption per 100 bed-days fell by almost a factor of 5 (from 33.5 to 6.8 DDD/100 bed-days).

Table 1. Overall consumption of antimicrobial agents at the National Medical University Hospital, 2023-2025

Antimicrobial agent consumption	Years		
	2023	2024	2025
Total consumption, DDD	558.1	1,387.7	2,387.0
Number of bed-days	1,667	28,169	34,916
Total consumption, DDD/100 bed-days	33.5	4.9	6.8

Source: data from the clinic's statistical report

In 2023, Access antibiotics accounted for 5.8% of total antimicrobial consumption, while Watch and Reserve antibiotics represented 11.6% and 82.6%, respectively. Following the implementation of the AMS in 2024, the proportion of Access antibiotics increased to 78.0%, whereas the proportions of Watch and Reserve antibiotics declined to 4.6% and 17.4%, respectively. In 2025, the predominance of Access antibiotics was maintained (57.3%), accompanied by an increase in the proportion of Watch antibiotics to 38.0% and a further reduction in the consumption of Reserve antibiotics to 4.7% (Table 2).

Table 2. Structure of antimicrobial consumption at the National Medical University Hospital according to the WHO AWaRe classification, 2023-2025

AWaRe antimicrobial group	Years		
	2023	2024	2025
Access, %	5.8	78.0	57.3
Watch, %	11.6	4.6	38.0
Reserve, %	82.6	17.4	4.7

Source: data from the clinic's statistical report

According to the data presented in Table 3, the implementation of the AMS in the surgical department was associated with a substantial reduction in the consumption of cephalosporins and carbapenems among β-lactam antibiotics. In contrast, the use of broad-spectrum penicillins, including β-lactam/β-lactamase inhibitor combinations, was introduced. A marked decrease was also observed in the use of fluoroquinolones and Reserve antibiotics used to treat resistant Gram-negative infections, particularly tigecycline and colistin. Conversely, aminoglycosides, which belong to the Access group, were introduced into routine practice. In addition, antibiotics targeting Gram-positive infections, including the Access antibiotics clindamycin and metronidazole, as well as the Watch antibiotics vancomycin and lincomycin, began to be prescribed more frequently.

Table 3. Consumption of individual groups of antimicrobial agents in the surgical department, expressed as DDD per 100 bed-days, 2023-2025

Antimicrobial group/agent	Antimicrobial consumption, DDD per 100 bed-days		
	2023	2024	2025
β-Lactam antibiotics (with and without β-lactamase inhibitors)			
Amoxicillin			0.027
Piperacillin			0.017
Cefazolin	1.955189	3.757	2.748
Cefuroxime	2.285063	0.000	0.029
Ceftriaxone	12.04799	0.110	0.006
Cefotaxime	0		0.011
Ceftazidime	0		0.004
Meropenem	0.113977	0.146	0.023
Amoxicillin/clavulanic acid	0		0.045
Piperacillin/tazobactam	0		0.012
Ceftazidime/avibactam	0	0.030	
Meropenem/vaborbactam	0	0.039	
Fluoroquinolones	0		
Ciprofloxacin	0.988722	0.029	0.090
Levofloxacin	2.887403	0.454	0.077
Moxifloxacin	0.25189		
Macrolides	0		
Azithromycin	0		0.029
Clarithromycin	0		0.115
Tetracyclines	0		
Doxycycline	0		0.057
Tigecycline	0.233893	0.036	0.189
Aminoglycosides	0		
Gentamicin	0		9.547
Tobramycin	0		1.031
Amikacin	0		0.034
Glycopeptides	0		
Vancomycin	0		0.013
Lincosamides	0		
Clindamycin	0		0.033
Lincomycin	0		0.010
Nitroimidazoles	0		
Metronidazole	0		0.254
Polymyxins	0		
Colistin	0.19832	0.063	

Source: ata from the clinic's statistical report

the findings of the study, the implementation of the AMS programme at the clinic was aimed at reducing and optimising the pattern of antibiotic use, in particular using the WHO AWaRe classification. In their systematic reviews, L. Naseralallah *et al.* [11] and J. Martinez-Sobalvarro *et al*. [12] concluded that AMSs improve antibiotic prescribing practices, reduce the incidence of surgical infections, and optimise the duration of perioperative antibiotic therapy. Similarly, the systematic review by I. Sefah *et al*. [13] demonstrated that AMS interventions improve adherence to clinical guidelines while reducing expenditure on antibiotics. M. Bashar *et al*. [3], A. Kosharek *et al*. [7], and A. Jover-Sáenz *et al.* [8] reported reductions in antibiotic consumption of 24-53% following the implementation of AMSs in surgical departments. Furthermore, A. Jover-Sáenz *et al*. [8] demonstrated that pharmaceutical care facilitated a successful transition from intravenous to oral antibiotic therapy for urological infections, thereby improving continuity of care between inpatient and outpatient settings. This approach enabled appropriate completion of treatment at home without unnecessary days of parenteral therapy, minimised errors in treatment duration, and reduced post-discharge antibiotic prescribing in surgical patients by approximately 60%. M. Batlle *et al*. [14] also demonstrated that a surgery-specific AMS focused on prolonged antimicrobial therapy significantly reduced the number of antibiotic courses lasting seven days or longer in surgical patients with infections.

In the present study, interventions aimed at optimising treatment duration resulted in an almost fivefold reduction in antibiotic consumption expressed as DDD

per 100 bed-days. The AMS included the involvement of a clinical pharmacist in both the pre-authorisation of Reserve and Watch antibiotics (particularly during 2024) and prospective audit with feedback for prolonged antibiotic therapy and the use of Reserve antibiotics, including ceftriaxone. Y. Liu *et al*. [15] and B. Okposio *et al.* [16] highlighted the importance of multidisciplinary collaboration in improving antimicrobial prescribing protocols and combating antimicrobial resistance in surgical practice. Likewise, A. Kosharek *et al.* [7] emphasised the value of collaboration between infectious diseases specialists and clinical pharmacologists or clinical pharmacists, who jointly conducted prescribing audits and discussed recommendations directly with the surgical team. Such an approach promotes greater clinician engagement, enhances trust, and facilitates individualised antimicrobial therapy. Evidence consistently supports the superiority of multidisciplinary, interactive stewardship models over purely restrictive interventions. A. Kosharek *et al*. [7] further reported that AMS implementation reduced the Antibiotic Spectrum Index from 2,839 to 2,519, reflecting successful antimicrobial de-escalation and optimisation of therapy. The effectiveness of prospective audit with feedback in surgical practice is attributable to its ability to tailor general recommendations to the individual patient's clinical condition and the complexity of the surgical procedure. Moreover, following implementation of the AMS, the incidence of *Clostridioides difficile* infection declined from 2.1% to 0%, providing further evidence of the safety of strategies based on treatment shortening and antimicrobial de-escalation. In addition, a substantial reduction in the average cost of treatment was observed.

According to G. Surat *et al.* [17], O. Pechak *et al*. [18], and G. Betito *et al.* [19], inappropriate or unnecessary postoperative antibiotic prophylaxis can be substantially reduced or eliminated, primarily through the revision of institutional protocols and the reinforcement of evidence-based recommendations. In the present study, significant improvements in perioperative antibiotic prescribing were achieved following the implementation of a new local protocol for perioperative antibiotic prophylaxis. This was accompanied by a marked reduction in the use of Reserve and Watch antibiotics with activity against Gram-negative pathogens, including colistin, tigecycline, ceftazidime, ceftriaxone, meropenem, ciprofloxacin, levofloxacin, and moxifloxacin. Similar findings have been reported by J. Díaz-Madriz *et al.* [20], G. Wu *et al.* [21], and O. Pechak *et al*. [18], who demonstrated a shift from broad-spectrum to narrow-spectrum cephalosporins for both prophylaxis and treatment, particularly an increased use of cefazolin accompanied by reduced prescribing of ceftriaxone and fourth-generation cephalosporins. M. Bashar *et al*. [3] further confirmed that AMS implementation not only reduces overall antibiotic consumption but also improves the appropriateness of antimicrobial therapy through prescribing guided by microbiological culture results. In their study, increased use of piperacillin/tazobactam reflected the rising prevalence of *Pseudomonas aeruginosa* infections. In addition, they reported the discontinuation of unnecessary postoperative use of amoxicillin/clavulanic acid, which is frequently continued without indication after surgery, in favour of cefazolin with prophylaxis limited to a maximum of 24 hours. They also observed a reduction in the use of fluoroquinolones and third-generation cephalosporins because of their association with the selection of resistant *Enterobacteriaceae*.

The present study also demonstrated an increased use of aminoglycosides, which are classified as Access antibiotics according to the WHO AWaRe classification, reflecting the preserved susceptibility of multidrug-resistant Gram-negative pathogens to this class of antibiotics. M. Thy *et al.* [22] likewise emphasised that aminoglycosides remain important bactericidal agents against resistant Gram-negative bacteria, including multidrug-resistant and carbapenem-resistant strains. S. Story *et al.* [23] reported that combination therapy incorporating aminoglycosides with other antibacterial agents provides synergistic activity that may help overcome resistance in extensively drug-resistant Gram-negative organisms. Furthermore, S. Goutelle *et al.* [24] proposed optimised aminoglycoside dosing regimens to improve both efficacy and safety, including the use of a fixed initial dose of 2,500 mg of amikacin to simplify dosing in emergency surgical patients.

Nevertheless, several important barriers continue to hinder the implementation of AMS in surgical practice. Resource limitations remain a major challenge, as prospective audit with feedback requires the continuous involvement of infectious diseases specialists and clinical pharmacists, which may not be feasible in many non-academic hospitals. Although overall adherence to stewardship recommendations has been reported to range between 71% and 72%, successful implementation is often constrained within surgical teams. Recommendations communicated to junior doctors or nursing staff may be overridden by senior consultants who were not directly involved in the AMS. As reported by S. Cabral *et al.* [25], adherence to antimicrobial stewardship recommendations remains suboptimal even in high-income countries.

The authors developed and implemented a series of training sessions for doctors, particularly junior doctors, on current issues relating to surgical antibiotic prophylaxis and antibiotic therapy. M. Bashar *et al*. [3] emphasise the importance of involving surgical residents in weekly discussions on approaches to antimicrobial therapy, as this is critical for changing the culture of prescribing. Training directly at the patient's bedside transforms the younger generation of doctors' approach to antibiotic therapy. J. Díaz-Madriz *et al.* [20] point out that even in the absence of

strict administrative restrictions, a strategy of training and feedback can alter patterns of consumption; for example, by replacing the excessive use of ceftriaxone with the more rational use of cefazolin in surgical prophylaxis.

Among the common problems is the inappropriate use of vancomycin, which can increase the incidence of adverse effects, such as acute kidney injury. According to the study's findings, vancomycin consumption remains negligible (0.013 DDD/100 bed-days), as it is restricted solely to cases where a patient is at risk of infection caused by methicillin-resistant Staphylococcus aureus (MRSA). Consequently, a strategic approach to the use of antimicrobials in surgery must be based on the principle of reducing the duration of therapy to the minimum necessary; this is key to the environmental safety of the hospital and the clinical effectiveness of treatment. It is important to ensure direct collaboration between the clinical pharmacist and the surgeon through the use of prospective audits with feedback; to move away from fixed-dose regimens towards individualised dose calculations, ensuring that patients receive the exact amount of medication.

CONCLUSIONS

1. The implementation of an AMS in the inpatient surgical department demonstrated high effectiveness in optimising antibiotic therapy and the pattern of antimicrobial consumption. Despite a substantial increase in the number of hospital admissions and bed-days, the intensity of antibiotic use decreased almost fivefold, indicating a marked improvement in the appropriateness of antibiotic prescribing. The implementation of a comprehensive stewardship strategy, including pre-authorisation of Reserve antibiotics, the introduction of a local protocol for perioperative antibiotic prophylaxis, clinician education, and prospective audit with feedback involving a clinical pharmacist, contributed to more appropriate use of antibacterial agents.

2. Following the implementation of the AMS, the proportion of Access antibiotics increased substantially, while the use of Reserve antibiotics declined markedly, in accordance with current WHO recommendations for combating antimicrobial resistance. At the same time, the use of broad-spectrum cephalosporins, carbapenems, fluoroquinolones, colistin, and tigecycline decreased, and antibiotic therapy became more targeted and individualised. These findings support the wider implementation of AMS's in inpatient surgical departments. Key factors contributing to the programme's success include multidisciplinary collaboration between surgeons, clinical pharmacists, and infection prevention and control specialists, regular monitoring of antibiotic consumption using DDD per 100 bed-days, and continuous education of healthcare professionals. Together, these measures contribute to improved quality of care and a reduced risk of antimicrobial resistance.

This study has several limitations. It was conducted in a single university hospital surgical department, which may limit the generalisability of the findings to other healthcare settings, particularly hospitals with different patient populations, resource availability, and antimicrobial stewardship models. The retrospective study design, based on the analysis of antibiotic consumption indicators (DDD and DDD per 100 bed-days), does not allow causal relationships to be established between individual AMS interventions and the observed outcomes. Furthermore, the implementation of the AMS coincided with major changes in the hospital's clinical activity, including an increased number of patients with combat-related injuries, expansion of the range of surgical procedures performed, and treatment of more severe infectious complications, all of which may have influenced antibiotic prescribing patterns. In addition, the study did not evaluate clinical outcomes, including the incidence of surgical site infections, in-hospital mortality, length of hospital stay, hospital readmissions, the incidence of *Clostridioides difficile* infection, or changes in antimicrobial resistance patterns among hospital pathogens.

Future research should evaluate the contribution of individual AMS components, including antibiotic pre-authorisation, prospective audit with feedback, local perioperative antibiotic prophylaxis protocols, and educational interventions, to clinical outcomes. Further studies are also warranted to investigate the relationship between changes in antibiotic consumption according to the AWaRe classification and trends in antimicrobial resistance among hospital pathogens, as well as the incidence of surgical site infections, *Clostridioides difficile* infection, length of hospital stay, in-hospital mortality, and pharmacoeconomic outcomes.

ACKNOWLEDGEMENTS

None.

FUNDING

The study was conducted without external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Микола Хайтович

Доктор медичних наук, професор
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-6412-3243

Олена Вітюк

Керівник відділу
Національний медичний університет імені О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0009-0004-5915-4001

Динаміка споживання антимікробних препаратів в стаціонарному хірургічному відділенні при впровадженні програми адміністрування антимікробних препаратів

Анотація

Актуальність. Програми адміністрування антимікробних препаратів (ААП) стали важливою стратегією для оптимізації використання антибіотиків та боротьби з резистентністю до антимікробних лікарських засобів у хірургічній практиці.

Мета. Оцінити вплив впровадження програми ААП на споживання антибіотиків у стаціонарному хірургічному відділенні.

Методи аналізу. Проведено ретроспективний аналіз споживання антимікробних препаратів у 2023-2025 рр. у хірургічному відділенні університетської клініки. Оцінку здійснювали за показниками DDD та DDD/100 ліжко-днів із аналізом структури відповідно до класифікації ВООЗ AWaRe.

Результати. Незважаючи на майже п'ятикратне зростання загального обсягу використаних антибіотиків з 558,1 до 2387,0 DDD через значне збільшення хірургічної допомоги зокрема і постраждалим від бойових поранень, інтенсивність споживання антибіотиків зменшилася з 33,5 до 6,8 DDD/100 ліжко-днів. Частка препаратів групи доступу збільшилась з 5,8 % до 57,3 %, тоді як частка препаратів групи резерву зменшилась з 82,6 % до 4,7 %, що вказує на оптимізацію їх використання. Відмічено суттєве зменшення призначення цефалоспоринів 3 покоління (зокрема цефтриаксону, який згідно галузевому стандарту медичної допомоги віднесено до препаратів групи резерву), і інших препаратів резерву, зокрема – колістину та тайгецикліну. Також зменшилось використання карбапенемів і фторхінолонів, а натомість зросло застосування аміноглікозидів, метронідазолу та кліндаміцину, які відносяться до групи доступу.

Практична цінність. Впровадження комплексної програми ААП забезпечило більш раціональне використання антибіотиків, оптимізацію їх структури відповідно до класифікації AWaRe та зменшення інтенсивності їх споживання, що підтверджує ефективність мультидисциплінарного підходу із залученням клінічного фармацевта у хірургічному стаціонарі.

Ключові слова: антимікробна резистентність; клінічний фармацевт; антибіотики; хірургія; споживання лікарських засобів; визначена добова доза; класифікація AWaRe.

CASE STUDIES
FROM PRACTICE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.98:578.834
DOI: https://doi.org/10.32345/2664-4738.2.2026.16

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 13.12.2025 Revised: 17.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Ivetta Shestakova*

PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-7700-1931

Oksana Gudzenko

PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0009-0004-6762-4077

Adverse course of COVID-19 despite the use of molnupiravir: A clinical case

Abstract

Relevance. Patients with type 2 diabetes mellitus are at high risk of severe COVID-19, multiple organ failure, and death. Despite the introduction of direct-acting antiviral agents, including molnupiravir, some patients may still experience an unfavourable outcome despite early initiation of treatment, highlighting the need for further investigation.

Aim. To evaluate the course of COVID-19 in a patient with type 2 diabetes mellitus using a clinical case and to analyse the possible reasons for the unfavourable outcome despite the timely administration of molnupiravir.

Materials and methods. A retrospective descriptive case study was conducted. The course of COVID-19 was analysed in a 56-year-old woman with type 2 diabetes mellitus who received antiviral therapy with molnupiravir from the fourth day of illness. Clinical manifestations, laboratory and instrumental findings, treatment characteristics, and the possible causes of the unfavourable outcome were assessed.

Results. The illness began with moderately severe respiratory symptoms and a low-grade fever. On hospital admission, signs of decompensated diabetes mellitus were identified, including hyperglycaemia (14.7 mmol/L), ketonuria (3+). Also elevated C-reactive protein (CRP) level of 91.5 mg/L and lymphopenia were revealed. Although there were no clinical and radiological signs of pneumonia on admission, the patient's condition deteriorated rapidly, with the development of metabolic acidosis, diabetic ketoacidotic coma, bilateral polysegmental pneumonia, acute respiratory distress syndrome, and multiple organ failure. Early administration of molnupiravir did not prevent a fatal outcome.

Conclusions. This clinical case demonstrates that, in patients with decompensated diabetes mellitus, COVID-19 may progress rapidly to a critical condition even in the absence of signs of pulmonary involvement at the early period of the disease. One of the key factors contributing to the poor prognosis was likely metabolic decompensation associated with ketoacidosis and a systemic inflammatory response. COVID-19 vaccination did not prevent the fatal outcome in this patient. The effectiveness of antiviral therapy for COVID-19 depends not only on the timely initiation of treatment but also on the degree of control of underlying comorbidities and the early correction of metabolic disordes. The clinical effectiveness of molnupiravir may depend on the SARS-CoV-2 variant, the baseline viral load, and individual patient peculiarities. Specialised molecular genetic studies are required to assess the potential role of antiviral resistance.

Keywords: coronavirus disease; SARS-CoV-2; type 2 diabetes mellitus; diabetic ketoacidosis; antiviral therapy; multiple organ failure.

Suggested Citation:
Shestakova I, Gudzenko O. Adverse course of COVID-19 despite the use of molnupiravir: A clinical case. Med Sci Ukr. 2026;22(2):152–159. DOI: https://doi.org/10.32345/2664-4738.2.2026.16

*Corresponding author (*sivetta11@gmail.com*)

INTRODUCTION

Despite the end of the pandemic phase of COVID-19, the disease continues to be a significant medical and social problem due to the risk of severe forms and fatal outcomes in patients with underlying conditions. Particular attention is drawn to patients with diabetes mellitus, in whom SARS-CoV-2 infection is significantly more frequently associated with hospitalisation, the development of acute respiratory distress syndrome, multiple organ failure and death. In this context, the search for effective approaches to early antiviral treatment of COVID-19 in high-risk patients remains one of the priority areas in modern medicine. Molnupiravir became the first oral antiviral drug to demonstrate the ability to reduce the risk of hospitalisation and death in patients with COVID-19. In the randomised, placebo-controlled MOVe-OUT trial conducted by A.J. Bernal *et al.* [1], the use of molnupiravir within the first five days of symptom onset in unvaccinated high-risk patients was associated with a reduction in the rate of hospitalisation or death compared with placebo. The authors concluded that early suppression of viral replication may have a positive effect on the clinical course of the infection. A separate analysis of the results of the study by A.J. Bernal *et al*. in patients with immunodeficiency conditions, carried out by D. Focosi *et al.* [2], confirmed the drug's favourable safety profile and its ability to reduce viral load. At the same time, the authors noted that even with timely initiation of antiviral treatment, the risk of adverse outcomes is largely determined by the severity of comorbidities and the patient's baseline condition. Subsequent studies, conducted whilst Omicron variants were circulating and population immunity was high, demonstrated less conclusive results. For instance, in the large-scale randomised PANORAMIC trial by C.C. Butler *et al.* [3], which involved over 25,000 at-risk patients, the addition of molnupiravir to standard therapy did not result in a statistically significant reduction in the rate of hospitalisation or death compared with standard care. However, the authors noted a reduction in the duration of symptoms and rapid clinical recovery in patients receiving antiviral therapy. Commenting on the PANORAMIC results, M.R. Kidd & P.M. Kelly [4] pointed out that the efficacy of molnupiravir may depend on the epidemiological context, the level of population immunity, vaccination coverage and the composition of at-risk groups. According to the authors, the results of early studies cannot always be extrapolated to current conditions where new variants of SARS-CoV-2 are circulating.

The results of studies of real-world clinical practice also remain inconclusive. In a study by R. Flisiak *et al*. [5], conducted whilst the Omicron variant was dominant, the use of molnupiravir was associated with a reduction in mortality among hospitalised patients, particularly when treatment was initiated within the first five days of illness. At the same time, the authors emphasised that the drug demonstrated the greatest benefit in patients without decompensated comorbidities. Similar conclusions were reached by W. Abu Ahmad *et al*. [6], who, in a large cohort study, demonstrated that the efficacy of molnupiravir is most significant in older patients and those with risk factors for the progression of COVID-19. However, even in these patient groups, antiviral therapy does not guarantee complete protection against the development of severe disease. Diabetes mellitus plays an important role in determining an unfavourable prognosis. According to studies by S. Lim *et al.* [7], K. Khunti *et al.* [8] and J.E. Nyland *et al*. [9], hyperglycaemia is associated with impaired function of neutrophils, macrophages and T-lymphocytes, increased production of pro-inflammatory cytokines, and the development of endothelial dysfunction and coagulopathy. This is precisely why people with diabetes are considered to be one of the most vulnerable groups of patients with COVID-19. Furthermore, there is a growing body of evidence regarding the mutual exacerbation of COVID-19 and carbohydrate metabolism disorders, whereby the infection may contribute to diabetic decompensation and the development of ketoacidosis even in patients whose diabetes was relatively stable prior to infection [10-11]. There are also reports of a reduction in the clinical efficacy of certain antiviral drugs as SARS-CoV-2 evolves and accumulates mutations, including studies by C.K.H. Wong *et al*. [12], G.S. Tatz *et al.* [13] and Y. Xie *et al*. [14]. Although no conclusive evidence of clinically significant SARS-CoV-2 resistance to molnupiravir has yet been obtained, a number of authors point to the possibility of variations in response to therapy depending on the viral variant, the initial viral load and the characteristics of the patient's immune response [3-4].

Thus, despite the availability of effective antiviral agents, the challenge of predicting treatment outcomes for COVID-19 in high-risk patients remains a pressing issue. Cases of severe or fatal disease progression despite early initiation of etiological therapy are of particular scientific interest, as their analysis allows for a better understanding of the role of comorbidities and other factors that may influence treatment efficacy. It is for this reason that the clinical case presented here warrants detailed analysis and discussion. The aim of this study was to evaluate the course of COVID-19 in a high-risk patient and to analyse the possible reasons for the unfavourable disease outcome despite the timely administration of molnupiravir.

MATERIALS AND METHODS

Study type: retrospective descriptive study as a clinical case. Study design: retrospective analysis of a clinical case of fatal COVID-19. Object: the course of COVID-19 in high-risk patients receiving early antiviral therapy. Subject: factors that may have contributed to the un-

favourable course of the disease despite the early administration of molnupiravir. The study was conducted in accordance with the principles of the World Medical Association's Declaration of Helsinki on the ethical principles of medical research involving human subjects [15] and Order No. 690 of the Ministry of Health of Ukraine [16]. During the preparation of this clinical case report, the confidentiality of the patient's personal data and her anonymity were ensured. Consent to conduct the study and publish its results was obtained from the patient's daughter. A clinical case of an unfavourable course of COVID-19 is presented in a 56-year-old female patient with concomitant type 2 diabetes mellitus who received inpatient treatment at St Michael's Clinical Hospital of Kyiv from 11 September 2025 to 17 September 2025 (medical record No. 9101738). According to her medical history, the patient had received two doses of the COVID-19 vaccine in 2023; no further information regarding the vaccines is available. She had previously contracted COVID-19 in 2021. No antiviral therapy was prescribed before admission. In the hospital, due to possible renal impairment, associated with diabetes mellitus, molnupiravir was preferred for antiviral therapy (administered from the 4th day of illness at a dose of 800 mg twice daily for 5 days). Supportive care involved management of the intoxication syndrome, blood glucose levels and homeostatic parameters. Oxygen support was provided via inhalation of humidified oxygen through a face mask; the patient was subsequently transferred to mechanical ventilation. With the onset and progression of respiratory failure, dexamethasone 8 mg per day intravenously was added to the treatment. To prevent thromboembolic complications, flenox was administered subcutaneously at a dose of 0.4 ml once daily. The diagnosis of COVID-19 was confirmed by SARS-CoV-2 rapid test during the pre-hospital stage and polymerase chain reaction (PCR) in the hospital. Pulmonary ultrasound and chest radiography were used to confirm the presence of pneumonia. The severity of the patient's condition was assessed on the basis of clinical findings, oxygen saturation, and laboratory markers, including blood glucose levels, urinary ketones, arterial blood gas analysis, acid-base balance, C-reactive protein level, and lymphocyte count.

RESULTS AND DISCUSSION

Despite the clinical efficacy of molnupiravir, as demonstrated in numerous studies at the start of the pandemic, even its early administration does not always prevent severe disease progression in patients with underlying chronic conditions. The following case is presented as an example. On day 1 of the illness, the patient complained of a sore throat, a runny nose and mild weakness, with no fever. The following day, her condition worsened: she experienced nausea, repeated vomiting, a headache, increased weakness and a low grade temperature. On the third day of the illness, the patient complained of significant general weakness, a headache, a dry mouth, nausea and vomiting, and sought advice from a general practitioner at a private clinic, who suspected a stroke. This diagnosis was ruled out by a neurosurgeon on the basis of the results of a computed tomography (CT) scan of the brain. The presence of respiratory symptoms and a raised body temperature, as well as the epidemiological situation, formed the basis for conducting a rapid SARS-CoV-2 antigen test. Following a positive result, the patient was admitted to the hospital. At the time of admission (on day 3 of illness) condition of the patient was moderate severe moderately severe due to systemic toxicity: she was lethargic and adynamic. Body temperature 36.50°C, pulse 116 beats per minute, blood pressure 140/90 mm Hg, respiratory rate 22-24 per minute, oxygen saturation 98% whilst breathing room air. There were no clinical and radiological signs of pneumonia. Laboratory test results: complete blood count on 11 September 25 – white blood cells 12.17×10^9/L, metamyelocytes – 1, band cells – 10, segmented neutrophils – 62, eosinophils – 1, monocytes – 11, lymphocytes – 15%, red blood cells – 4.76×10^{12}/L, haemoglobin – 135 g/L, platelets 268×10^9/L, erythrocyte sedimentation rate 37 mm/h. Biochemical blood analysis on 11 September 25 – glucose 14.7 mmol/L, urea – 6.9 mmol/L, creatinine – 97.3 μmol/L, total bilirubin – 3.3 μmol/L, alanine aminotransferase 17.3 U/L, aspartate aminotransferase 15.8 U/L, alpha-amylase 47.5 U/L, C-reactive protein 91.5 mg/L, sodium 141 mmol/L, potassium 5.32 mmol/L, and chloride 103.0 mmol/L. Coagulation studies showed fibrin 240 mg, fibrinogen 6.0 g/L, and prothrombin activity 88%. Urinalysis revealed ketonuria (3+).

COVID-19 was diagnosed in the patient with decompensated type 2 diabetes mellitus. The diagnosis was confirmed by PCR. The patient was switched to insulin therapy; she was also prescribed Flenox 0.4 ml × once daily subcutaneously, Sterofundin 1,000 ml and sodium bicarbonate solution (Soda-Buffer®) 100 ml intravenously. The following day (day 4 of the illness), her condition deteriorated: weakness increased, dysarthria and a sense of depersonalisation developed, tachycardia increased to 124 beats per minute, and she experienced impaired consciousness resembling stupor; as a result, she was transferred to the infectious diseases intensive care unit. Examination of acid base balance revealed acidosis (pH 7.167). Lagevrio (trade name for molnupiravir) – 800 mg twice daily – was added to her treatment, whilst detoxification therapy and correction of metabolic disturbances were continued. However, the patient's condition progressively deteriorated. On 13 September 25 (on day 5 of illness), vasopressors were added to her treatment to correct haemodynamic disorders. From 14 September 25 (on day 6 of illness), the patient was unconscious; metabolic disturbances (acidosis, acetonuria, hypokalaemia, hypoalbuminaemia)

progressed; blood urea and creatinine levels rose; radiographic signs of bilateral pneumonia appeared, and respiratory failure progressed rapidly. From 16 September 25 (on day 8 of illness), the patient was transferred to invasive artificial ventilation. Despite intensive care, the patient's condition progressively deteriorated, and signs of multiple organ failure increased. On 17 September 25 (on day 9 of illness), the patient died. Post-mortem diagnosis was: COVID-19, bilateral polysegmental pneumonia, acute respiratory distress syndrome. Type 2 diabetes mellitus, diabetic angiopathy, nephropathy. Cerebral oedema with dislocation of the brain. COVID-19 triggered the decompensation of underlying type 2 diabetes mellitus, leading to the development of ketoacidotic coma, electrolyte imbalances and multiple organ failure, which resulted in the rapid progression of the infectious process with a fatal outcome. Antiviral therapy with molnupiravir, initiated at an early stage (on day 4 of illness), failed to prevent an unfavourable outcome of the disease. A timeline of the patient's disease progression and treatment, highlighting key events, is shown in Figure 1.

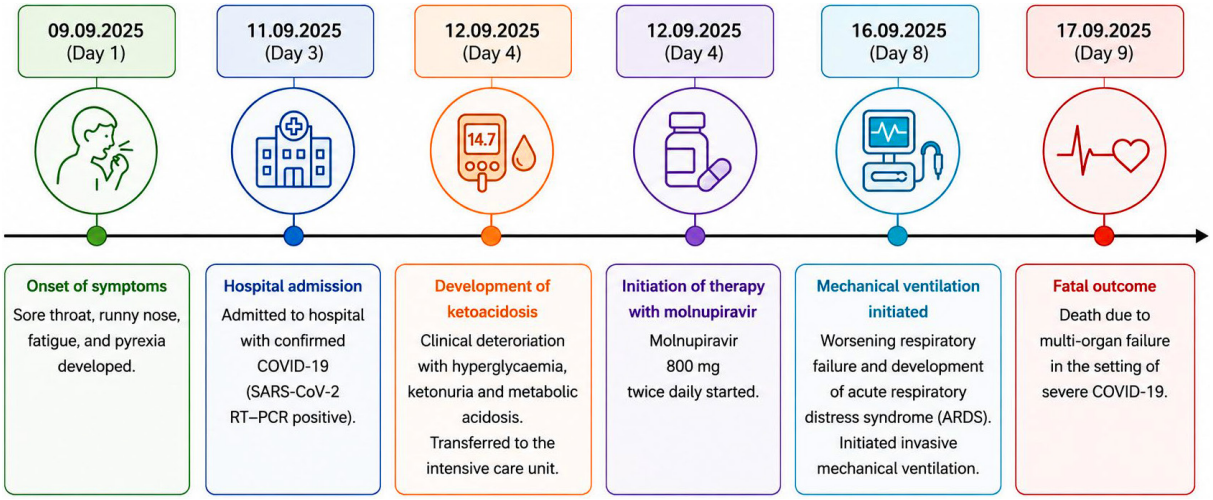

Figure 1. Timeline of clinical course and treatment of a 56-year-old female patient with COVID-19
Note: RT-PCR – reserve transcription polymerase chain reactions; ARDS – acute respiratory distress syndrome
Source: compiled by the authors

This clinical case demonstrates the rapid progression of COVID-19 in a female patient with decompensated type 2 diabetes mellitus, despite the absence of signs of pneumonia and respiratory failure at the time of admission and the early initiation of antiviral therapy with molnupiravir. Most likely, the unfavourable outcome followed several reasons. First and foremost, the presence of decompensated diabetes mellitus with hyperglycaemia and acetonuria at the time of admission is noteworthy, indicating significant metabolic disorders even before the development of severe lung involvement. Hyperglycaemia is associated with impaired innate and adaptive immune responses, increased systemic inflammation and endothelial dysfunction [17-18]. It also increases the risk of thrombotic complications, which may contribute to the rapid progression of COVID-19 [19-20]. The patient presented with signs of severe systemic disorders, including progressive intoxication, impaired consciousness and metabolic acidosis, despite the early (on day 4 from the onset of the illness) administration of molnupiravir. This suggests that critical pathophysiological processes associated with the decompensation of diabetes mellitus and a systemic inflammatory response had already been triggered before the start of aetiological treatment. Under these circumstances, the suppression of viral replication may have proved insufficient to prevent the subsequent development of multiple organ failure.

Other factors capable of influencing the efficacy of antiviral therapy cannot be ruled out, in particular a high initial viral load, individual variations in the drug's pharmacokinetics against a background of severe metabolic disorders, or infection with a SARS-CoV-2 variant exhibiting reduced sensitivity to the drug due to the possible development of resistance to molnupiravir. At the same time, it is not possible to conclude, on the basis of a single clinical case, that molnupiravir is ineffective as a drug in general. The choice of antiviral therapy for high-risk patients remains an important clinical issue. Given the high likelihood of diabetes decompensation against the background of an infectious process, it might be more effective to initiate antiviral therapy before the development of severe metabolic disordes – on days 1-2 of COVID-19. The possibility of using alternative antiviral drugs or combined approaches in patients with severe comorbidities also requires further investigation. The case presented here highlights the need for particular vigilance regarding patients with diabetes mellitus, even in the absence of severe lung

involvement, and the importance of early detection of metabolic decompensation as one of the key predictors of an unfavourable course of COVID-19.

Molnupiravir remains one of the recommended oral antiviral drugs for the treatment of patients with COVID-19 who are at high risk of disease progression. The results of early randomised trials have demonstrated its ability to reduce the risk of hospitalisation and death when administered within the first five days of symptom onset. At the same time, data from C.C. Butler *et al*. [3] and W. Abu Ahmad *et al.* [6], collected during the circulation of later SARS-CoV-2 variants, indicated a more moderate clinical effect of the drug and a significant dependence of treatment outcomes on patients' age, comorbidities, vaccination status and the timing of treatment initiation. The clinical case presented here demonstrates an unfavourable course of COVID-19 in a high-risk patient. Early administration of molnupiravir was unable to prevent the development of severe metabolic disorders associated with decompensated diabetes mellitus, which may have contributed to subsequent clinical deterioration and the development of multiple organ failure. The findings are partly consistent with current literature data on the efficacy of molnupiravir. In a study by A.J. Bernal *et al.* [1], early administration of the drug to patients with risk factors for COVID-19 progression was associated with a reduced risk of hospitalisation or death compared with placebo. At the same time, further studies of real-world clinical practice and the results of the large-scale randomised PANORAMIC trial have demonstrated that, in the context of circulating new variants of SARS-CoV-2 and against a background of prior vaccination of the population, the effect of molnupiravir on the rate of hospitalisations and mortality is less pronounced, although the drug promotes faster clinical recovery and viral clearance [3]. Data from the meta-analyses by Y.M. Mesfin *et al*. [21] and S.H. Lin *et al*. [22] also demonstrated that the clinical effect of molnupiravir varies depending on patients' age, the presence of comorbidities and the timing of treatment initiation.

Particular attention is drawn to the role of diabetes mellitus as one of the leading predictors of an unfavourable prognosis in COVID-19. According to cohort studies, the risk of hospitalisation, the development of acute respiratory distress syndrome and death in patients with uncontrolled diabetes mellitus is significantly higher than the corresponding figures in individuals without carbohydrate metabolism disorders. S. Lim *et al.* [7] and R. Pal *et al*. [10] have shown that the presence of diabetic ketoacidosis or severe hyperglycaemia at the time of hospitalisation is an independent predictor of a poor prognosis, regardless of the severity of lung involvement. In the present case, hyperglycaemia, acetonuria and laboratory signs of systemic inflammation were already present on admission, supporting the assumption that metabolic decompensation may have contributed to the subsequent severe course of COVID-19. It is evident that antiviral drugs are most effective early in the disease course, when active viral replication plays a leading role. Once a systemic inflammatory response, metabolic disorders and organ dysfunction have developed, the course of the disease is largely determined by immunopathological mechanisms. Thus, the lack of clinical response to molnupiravir in this patient does not necessarily indicate the drug's ineffectiveness, but may reflect the severity of the underlying condition and the already established cascade of pathophysiological changes at the time treatment began. A distinctive feature of this case was the absence of signs of pneumonia and respiratory failure on admission, despite the concurrent presence of marked metabolic disturbances. Hyperglycaemia, acetonuria and elevated C-reactive protein levels were observed as early as the first few days of the illness, indicating the development of a systemic inflammatory response and decompensation of diabetes mellitus. Type 2 diabetes remains one of the most significant risk factors for severe COVID-19. Hyperglycaemia contributes to impaired functional activity of neutrophils and lymphocytes, increased production of pro-inflammatory cytokines, and the development of endothelial dysfunction and coagulopathy. Furthermore, SARS-CoV-2 infection can impair glycaemic control and trigger the development of diabetic ketoacidosis, even in patients whose diabetes had previously been relatively stable. In the present case, it was the decompensation of diabetes mellitus that likely constituted one of the key mechanisms underlying the progression of the disease and the development of multiple organ failure.

Despite the initiation of antiviral therapy within the recommended timeframe (on day 4 of illness), by the time molnupiravir was prescribed, the patient was already exhibiting signs of severe systemic complications, including metabolic acidosis, progressive intoxication and impaired consciousness. This suggests that the pathological cascade associated with diabetic decompensation and systemic inflammation had already been triggered before the start of aetiological treatment. Since molnupiravir's mechanism of action involves inhibiting viral replication, its clinical efficacy is predictably reduced in situations where metabolic and immuno-inflammatory disorders already play a leading role in the pathogenesis. It is also worth noting that recent studies demonstrate heterogeneity in the clinical efficacy of molnupiravir. In some high-risk patients, particularly those with severe comorbidities, the drug does not fully prevent hospitalisation, the development of respiratory failure or fatal outcomes. The influence of factors such as a high initial viral load, characteristics of the immune response, the drug's pharmacokinetics in the context of severe metabolic disorders, or individual variability in the virus's sensitivity to therapy cannot be ruled out.

From a clinical perspective, this case highlights the need for the earliest possible identification of patients with decompensated diabetes mellitus and the timely initiation of antiviral therapy before the development of severe metabolic disorders. Equally important are aggressive correction of hyperglycaemia, careful monitoring of acid-base balance, and early diagnosis of diabetic ketoacidosis. Further research is needed to evaluate the efficacy of alternative antiviral drugs and personalised approaches to the treatment of patients with COVID-19 and severe comorbid conditions. Thus, the presented case demonstrates that even early administration of molnupiravir does not always prevent an unfavourable course of COVID-19 in patients with severe metabolic disorders. It should be noted that vaccination against COVID-19 did not prevent a fatal outcome. Not only early antiviral therapy, but also the degree of control of the underlying condition, the timeliness of correction of metabolic disorders, and individual characteristics of the course of the infectious process may be of decisive importance for the prognosis.

CONCLUSIONS

1. In patients with type 2 diabetes mellitus, COVID-19 can rapidly progress to a critical condition even in the absence of signs of pneumonia in the early stage of the disease.

2. Decompensation of diabetes mellitus with the development of metabolic acidosis may be one of the key factors contributing to an unfavourable prognosis of COVID-19.

3. In the presented clinical case, early administration of molnupiravir (on day 4 of illness) didn't prevent disease progression and a fatal outcome. This may have been associated with severe metabolic disorders in the context of decompensated diabetes mellitus.

4. The clinical efficacy of molnupiravir may depend on the SARS-CoV-2 variant, the baseline viral load and the patient's individual peculiarities. Specialised molecular genetic studies are required to assess the role of possible antiviral resistance.

5. Further studies are warranted to determine how concomitant metabolic disorders influence the response to antiviral therapy and to optimise treatment strategies for patients with COVID-19 and diabetes mellitus.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Іветта Шестакова

Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-7700-1931

Оксана Гудзенко

Кандидат медичних наук, доцент
Національний медичний університет імені О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0009-0004-6762-4077

Несприятливий перебіг COVID-19 із застосуванням молнупіравіру: клінічний випадок

Анотація

Актуальність. Пацієнти з цукровим діабетом належать до групи високого ризику тяжкого перебігу COVID-19, розвитку поліорганної недостатності та летального наслідку. Незважаючи на впровадження противірусних препаратів прямої дії, зокрема молнупіравіру, окремі хворі навіть за умов раннього початку лікування можуть мати несприятливий наслідок хвороби, що потребує подальшого вивчення.

Ціль. На прикладі клінічного випадку оцінити перебіг COVID-19 у пацієнтки з цукровим діабетом II типу та проаналізувати можливі причини несприятливого наслідку захворювання попри своєчасне призначення молнупіравіру.

Матеріали та методи. Проведено ретроспективне описове дослідження у форматі клінічного випадку. Проаналізовано перебіг COVID-19 у пацієнтки 56 років із цукровим діабетом II типу, яка отримувала противірусну терапію молнупіравіром з 4-го дня захворювання. Оцінювали клінічні прояви, результати лабораторних та інструментальних досліджень, особливості лікування та причини несприятливого наслідку.

Результати. Захворювання розпочалося з помірно виражених респіраторних симптомів та субфебрильної температури тіла. На момент госпіталізації виявлено ознаки декомпенсації цукрового діабету: гіперглікемію (14,7 ммоль/л), ацетонурію (3+), а також підвищення рівня С-реактивного білка до 91,5 мг/л та лімфопенію. За відсутності клініко-рентгенологічних ознак пневмонії при поступленні у стаціонар, стан пацієнтки швидко погіршувався з розвитком метаболічного ацидозу, кетоацидотичної коми, двобічної полісегментарної пневмонії, гострого респіраторного дистрес-синдрому та поліорганної недостатності. Раннє призначення молнупіравіру не запобігло летальному наслідку.

Висновки. Представлений клінічний випадок демонструє, що у пацієнтів із декомпенсованим цукровим діабетом COVID-19 може швидко прогресувати до критичного стану навіть за відсутності ознак ураження легень на початку захворювання. Одним із ключових чинників несприятливого прогнозу, ймовірно, була метаболічна декомпенсація з розвитком кетоацидозу та системної запальної відповіді. Щеплення від COVID-19 не попередило летальний наслідок хвороби у пацієнтки. Ефективність противірусної терапії при COVID-19 залежить не лише від своєчасності її призначення, а й від ступеня контролю супутньої патології та ранньої корекції метаболічних порушень. Клінічна ефективність молнупіравіру може залежати від варіанта SARS-CoV-2, вихідного вірусного навантаження та індивідуальних особливостей пацієнта. Для оцінки ролі можливої противірусної резистентності необхідні спеціальні молекулярно-генетичні дослідження.

Ключові слова: коронавірусна хвороба; SARS-CoV-2; цукровий діабет II типу; діабетичний кетоацидоз; противірусна терапія; поліорганна недостатність.

CASE STUDIES
FROM PRACTICE

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.711-007.5-071-08-053.2:614.253.1/.2
DOI: https://doi.org/10.32345/2664-4738.2.2026.17

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 11.01.2026 Revised: 23.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Anastasiia Horobets
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-7610-9278

Nataliia Horobets*
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0001-7674-3140

Tetyana Pochynok
Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0003-0802-2071

Nataliia Horobets
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-8296-879X

Lyudmyla Levadna
PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-0768-2652

Routine screening for scoliosis in children at primary care level and its significance in the prevention and timely diagnosis of complications

Abstract

Relevance. Scoliosis in children is a common orthopaedic condition that may be accompanied by progressive spinal deformity, impaired function of internal organs and a reduced quality of life. Early detection of postural abnormalities at the primary care level is crucial for timely treatment and the prevention of complications.

Aim. To analyse current approaches to the early detection of scoliosis in children and to assess the importance of routine screening at the primary care level based on a clinical case.

Materials and methods. An analysis of current scientific literature was conducted, along with a clinical analysis of a case of idiopathic scoliosis in an adolescent. The following were assessed: medical history, clinical manifestations, results of laboratory and instrumental diagnostic tests, the progression of the condition, and the effectiveness of treatment and rehabilitation measures.

Results. The presented clinical case demonstrates the progression of spinal deformity in the child, despite the systematic implementation of conservative treatment, which necessitated surgical correction. It has been established that scoliosis in children may be accompanied by multisystem manifestations, which emphasises the need for a multidisciplinary approach involving a paediatrician, orthopaedic surgeon, neurologist, cardiologist and other specialists to ensure comprehensive diagnosis, treatment and rehabilitation. The critical importance

Suggested Citation:
Horobets A, Horobets N. Pochynok T, Horobets N, Levadna L. Routine screening for scoliosis in children at primary care level and its significance in the prevention and timely diagnosis of complications. Med Sci Ukr. 2026;22(2): 160–169. DOI: https://doi.org/10.32345/2664-4738.2.2026.17

*Corresponding author (*natko147@ukr.net*)

of the timely detection of early clinical signs of scoliosis at the primary care level has been demonstrated, as this enables the prevention of the progression of the deformity and the development of complications.
Practical significance. It is recommended that the results of this study be applied in the clinical practice of primary care specialists – paediatricians and general practitioners – for the early detection of scoliosis and the timely referral of children for specialist assessment.
Keywords: postural abnormalities; spinal deformity; orthopaedic condition; adolescents; rehabilitation; multidisciplinary approach.

INTRODUCTION

Scoliosis in children is a common orthopaedic condition that may be accompanied by progressive spinal deformity, impaired function of internal organs and a reduced quality of life. Early detection of postural abnormalities in children by primary care specialists is crucial for the timely implementation of treatment and rehabilitation measures and the prevention of complications. The authors S.C. Poon *et al*. [1] noted in their work that early diagnosis of scoliosis in children helps to reduce the risk of progressive spinal deformities and the need for surgical intervention. Researchers J.A. Janicki & B. Alman [2], whilst investigating the problem of scoliosis in children, found that the majority of cases encountered by general practitioners are idiopathic. The severity of the condition depends on the causes and the child's age, and determines the treatment strategy, methods for preventing complications, and quality of life. Therefore, a comprehensive medical history, imaging, early screening, and ultrasound and radiographic examinations are critically important for assessing the presence of abnormalities. It is very important to recognise non-idiopathic scoliosis early in order to identify the cause of the abnormalities and determine the timing and type of intervention. After all, children with congenital scoliosis may already have heart and kidney abnormalities at birth. School-based scoliosis screening is unsatisfactory and is losing popularity. The authors emphasise the importance of outpatient screening programmes, particularly at the primary care level. P. Trobisch *et al*. [3] drew attention to parents' lack of awareness regarding early clinical signs of postural abnormalities in children and the importance of early screening in school-age children at the primary care level. H. Dong *et al*. [4] noted that current research into scientific approaches to the conservative treatment of scoliosis offers somewhat varied perspectives, but the most effective approach is a combination of various evidence-based physiotherapy techniques and exercises specific to scoliosis. C.C. Rymond *et al*. [5] hypothesised that intermittent bracing prevents the progression of the curvature and often leads to a reduction in the degree of curvature in patients, thereby minimising the need for continuous bracing. Analysis of the data revealed that the progression of idiopathic scoliosis in adolescents at the time of peak growth velocity depends on the degree of curvature, the stage of skeletal maturation, and the rate of the pubertal growth spurt. Plotting curvature measurements against height measurements and the stages of ischial tuberosity maturation provides a reliable prediction of the risk of curvature progression in idiopathic scoliosis based on the Risser scale (stages of skeletal maturity based on pelvic radiographs), which assesses the ossification of the iliac crest on a scale from 0 to 5. In other words, if skeletal growth plates are not yet mature and bone growth is continuing, the risk of scoliosis progression is high because of residual skeletal growth potential. Y. Jiang *et al*. [6] recommend using the Schroth method, combined with training to stabilise the trunk muscles, as part of the treatment strategy. The authors consider the application of this method to be the optimal strategy for addressing the problems of idiopathic scoliosis. O.A. Bubenchyk & V.I. Boiko [7] analysed in their work modern innovative approaches to the physiotherapy of idiopathic scoliosis, which is the most common form in children. It is emphasised that the main treatment options are observation, scoliosis-specific physiotherapy exercises (Schroth Method, SEAS, BSPTS, Dobomed, FITS, Side Shift), immobilisation and surgical correction. All other methods are used as supplementary general strengthening measures, etc. The authors have proposed a rehabilitation programme that includes mobilisation of the curved section of the spine, correction of the deformity, and stabilisation of the spine in the corrected position. For each child, a rehabilitation programme is developed based on an individualised approach, regularity and consistency, the integration of general and specific exercises, and a gradual increase in workload, which has a positive effect on preventing the progression of scoliosis in adolescents. V.I. Bondarchuk *et al*. [8] point out that scoliosis is a significant scientific and practical problem in paediatric traumatology and orthopaedics, whilst postural abnormalities in children constitute a multidisciplinary problem, particularly in cases where complications arise involving other organs and systems. Approaches to the early diagnosis of postural abnormalities in children at the primary care level play a key role in prevention, appropriate treatment and rehabilitation. For mass screening of postural abnormalities in schoolchildren, physical examination methods (the Adams forward bend test) and computer-based technologies (scoliometry, topography) can be used. However, existing methods do not fully address the challenges of scoliosis diagnosis; therefore, a thorough search and development of specialised programmes for mass screening of children to

detect postural abnormalities continue, which would meet the requirements of evidence-based medicine: non-invasiveness; safety; standardisation of approaches; ease of implementation; cost-effectiveness; and diagnostic efficacy. The aim of this study was, based on a review of the literature and a clinical case study of a child, to examine current perspectives on scoliosis and to determine the clinical significance of its early diagnosis in children by primary care specialists.

MATERIALS AND METHODS

The study was conducted as a clinical case report incorporating elements of an analytical review of the current scientific literature on the problem of scoliosis in children, its early diagnosis and the importance of routine screening in primary care. The research methodology included an analysis of scientific publications, a clinical and medical history-based approach, a physical examination of the patient, an analysis of the results of laboratory and instrumental diagnostic tests, and an assessment of the condition progression. A search and analysis were conducted of scientific sources indexed in PubMed and Google Scholar, focusing on the aetiology, pathogenesis, clinical manifestations, screening and treatment of scoliosis in children and adolescents. Publications primarily from the last 3-5 years were used for the analysis. The search for sources was carried out using keywords.

The clinical part of the study was based on a case analysis of patient D., aged 15, who had been diagnosed with progressive idiopathic scoliosis. As part of the study, an assessment was carried out of the patient's medical history and personal history, physical examination findings, laboratory findings, and the results of electrocardiography, echocardiography, and ultrasound examinations of the abdominal organs and kidneys, as well as the consultative opinions of relevant specialists. During the assessment of the clinical case, general clinical examination methods were applied: taking a history of complaints and medical history, examination, palpation, percussion, auscultation, and laboratory and instrumental diagnostic tests in accordance with current clinical approaches to the management of children with musculoskeletal disorders. The analysis of the clinical case was conducted taking into account the specific features of the clinical course of scoliosis, the presence of complications, and a multidisciplinary approach to the patient's management and treatment.

The study was conducted in accordance with the principles of bioethics and deontology. Written informed consent was obtained from the patient's parents and the patient herself for participation in the study and for the use of clinical data and photographic material for scientific purposes. During the study, international ethical standards for conducting medical research involving human subjects, as set out in the World Medical Association's Declaration of Helsinki [9] and Ethics and data protection [10], were adhered to in order to ensure the confidentiality of personal data and the ethical conduct of the research.

RESULTS

Understanding of the prevalence and early prognostic factors of scoliosis in children and adolescents is limited, which poses challenges for the development of preventive strategies. These are essentially healthy children who do not complain of any symptoms. The prevalence of scoliosis among children and adolescents is high (mostly concentrated in the 10°-19° range), with an upward trend, and occurs in 2-4% of children, most commonly between the ages of 10 and 16. The incidence is roughly the same among boys and girls; however, in girls, scoliosis is significantly more likely to be progressive and to be accompanied by the development of complications [11-12].

Scoliosis is a lateral curvature of one or more segments of the spine combined with rotation of the vertebrae, leading to a deviation of the spine. Severe spinal curvatures lead to alterations in the position of the organs within the thoracic and abdominal cavities, a reduction in their functional capacity, chronic pain and psychological distress [13-14]. The development of scoliosis may be associated with various factors, including genetic and environmental ones; the most common of these are: hereditary factors, connective tissue dysfunction, congenital developmental anomalies, trauma, metabolic disorders, excess body weight, and so on [15-16]. At the same time, in a significant proportion of patients, the cause remains unknown, allowing the condition to be classified as idiopathic scoliosis. Consequently, the predictors of scoliosis development include: gender, age, body mass index, ethnicity, environmental factors and lifestyle [17].

The pathogenesis of scoliosis is characterised by the development of a three-dimensional deformity of the spine: a frontal deviation of the spinal axis, which gave rise to the term "scoliosis"; horizontal rotation of the vertebrae about the vertical axis, usually towards the convex side of the curve – a pathological rotation that is most pronounced at the apex of the spinal deformity; in the sagittal plane – flattening of the physiological curves, primarily thoracic kyphosis, leading to the formation of a so-called "flat back" [18-19]. The classification of scoliosis is based on a number of criteria: by aetiology: congenital – associated with developmental abnormalities of the vertebrae, ribs and connective tissue dysplasia; acquired – resulting from diseases, injuries and other causes [20-21]. Depending on the location of the pathological process, the following are distinguished: cervical, thoracic, lumbar and mixed (thoracolumbar, lumbosacral, etc.). Taking into account static function, a distinction is made between compensated and uncompensated scoliosis. Based on the shape of the spinal deformity, the following types

are distinguished: with a single curve (C-shaped); with two curves – S-shaped; with three curves – Z-shaped. Radiographic classification is based on the angle of lateral curvature and is expressed in four degrees of severity. Based on the age of onset, the following types are distinguished: infantile: occurring in children under 3 years of age; juvenile: occurring in children aged 4 to 10 years; adolescent: occurring in children aged 11 to 18 years. Idiopathic scoliosis in adults: diagnosed at any time after the age of 18, once skeletal growth is complete.

Congenital scoliosis – arises as a result of vertebral abnormalities present at birth. This is a consequence of improper vertebral formation during embryonic development [22]. Neuromuscular scoliosis – is caused by specific mechanisms associated with insufficient muscular support and nervous control. It can be caused by various conditions or diseases affecting the functioning of the muscles and the nervous system, such as trauma, cerebral palsy, spina bifida, myodystrophies and other neuromuscular disorders. Neuromuscular scoliosis often progresses and causes serious problems, such as respiratory and cardiac dysfunction, back pain, restricted movement and physical deformities [23].

Degenerative scoliosis in adults (usually after the age of 40-60) is also recognised, associated with age-related changes in the spine. It can often develop as a consequence of mild scoliosis in childhood, but is usually linked to age-related changes in the spine, such as degenerative changes in the intervertebral discs (disc degeneration), osteoporosis, osteoarthritis (arthritis) or osteochondrosis (degeneration of cartilage and bone). These changes lead to a deterioration in the structure of the spine, resulting in the development of scoliosis. Symptoms and their severity may appear as the body ages and vary depending on the degree of scoliosis and the patient's individual characteristics [24-25].

The most commonly diagnosed form is idiopathic scoliosis. In most children, it is asymptomatic in the early stages; however, as the deformity progresses, symptoms such as back pain, muscle weakness, rapid fatigue, pain in the limbs or paraesthesia may develop. Phenotypic features include asymmetry of the shoulder girdle and shoulder blades (winged), abnormal positioning of the head relative to the pelvis, an uneven waistline, pelvic tilt, limb length discrepancy, a constant lean to one side, and sometimes skin markers along the spine, such as dimples, patches of hair, or changes in skin colour. These changes become more pronounced as scoliosis progresses [26].

Mild forms of scoliosis often go unnoticed. Initial symptoms may include mild back pain or stiffness following prolonged sitting or standing. It is therefore vital that parents and teachers are aware of the early clinical signs of the condition to ensure timely screening and referral of the child for specialist assessment. To determine the subsequent management strategy for the patient – in particular, to confirm the diagnosis, assess the degree of deformity, and select treatment and rehabilitation measures – a consultation with an orthopaedic surgeon is essential. This is due to a number of factors that increase the risk of scoliosis progression: the greater the angle of curvature, the higher the likelihood of further deformity, particularly during periods of rapid growth and puberty [27].

In most children, spinal curvature does not tend to progress significantly and remains consistently mild; however, even in such cases, regular monitoring by a specialist is necessary. Severe forms of scoliosis can lead to secondary changes in internal organs, in particular displacement of mediastinal organs, lung deformation, and impaired heart and kidney function. Consequently, early treatment significantly increases the chances of preventing the development of serious complications and reducing the negative impact of the condition on the child's body [28]. Thus, a review of current scientific literature on the problem of scoliosis in children demonstrates that idiopathic scoliosis does not always have a clear cause, genetic determinant or triggering factor. Early detection of scoliosis at the primary care level helps to reduce the incidence of severe deformities and the need for surgical treatment.

CLINICAL CASE

A 15-year-old girl, D., was admitted to the paediatric ward for treatment of obstructive bronchitis against a background of acute respiratory infection. On admission, she complained of a headache, a rise in body temperature to 39.7°C, a cough and shortness of breath, which had developed the night before her admission. The illness began one day prior to admission with hyperthermia, headache and a cough. The medical history indicates that the child had developed in line with age-appropriate norms, had suffered from upper respiratory tract infections from time to time and had received outpatient treatment. She was vaccinated in accordance with the immunisation schedule and has no history of allergies. Previous infections include chickenpox and rubella at the ages of 3.5 and 6 years, respectively.

At the age of 8-9 years, the first signs of scoliosis appeared: slight asymmetry of the shoulder girdle; the right shoulder was slightly higher than the left, but this did not bother the child. Subsequently, the spine began to curve to the right, and later to the left as well. During puberty (aged 10-12), progression of the spinal deformity was noted, with a pronounced abnormal curvature and protrusion of the right shoulder blade. At the same time, the child began to suffer more frequently from acute respiratory infections and periodically complained of headaches and stabbing pains in the heart region.

The patient was seen several times by an orthopaedic surgeon and systematically followed the recommended treatment measures, including courses of manual therapy, massage, physiotherapy exercises

and physiotherapy. Despite a slight positive effect, the spinal deformity gradually progressed, necessitating surgical correction, which was carried out in several stages from the age of 12. The photographs show the child's condition before (Fig. 1) and after (Fig. 2) surgical correction.

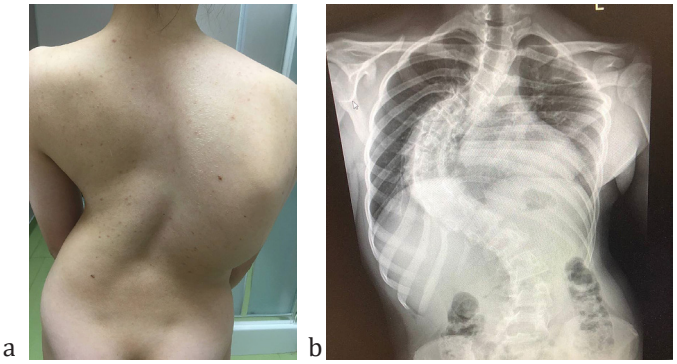

Figure 1. The child before surgical correction
Note: a) – photograph of the patient; b) – radiograph
Source: provided by the authors

Figure 2. The child after surgical correctionn
Note: photograph of the patient following surgical treatment
Source: provided by the authors

The child was screened for genetic predisposition, but the result was negative. The child's general condition was assessed as moderate. Blood pressure was 105-110/70 mm Hg. The skin was pale, breathing was laboured, and wheezing was auscultated. On physical examination of the respiratory system, auscultation revealed weakened, laboured breathing with numerous dry wheezing sounds. On percussion, the cardiac borders were unaltered; heart sounds were rhythmic and resonant; heart rate was 78 beats per minute. The abdomen was soft, painless and accessible to palpation; the liver and spleen did not protrude beyond the costal margin, and the bowel showed no pathological changes. Pasternatsky's sign was negative on both sides. Urination was unimpeded and painless, with adequate diuresis, and bowel movements were regular.

According to the results of laboratory tests, the full blood count revealed no significant abnormalities: haemoglobin level – 125 g/L, red blood cells – 4.8×10^{12}/L, white blood cells – 4.5×10^{9}/L: e – 2%; p – 4%; s – 63%; l – 22%; m – 9%, erythrocyte sedimentation rate (ESR) – 13 mm/h. Blood biochemical parameters were within the age-appropriate range: total protein 67 g/L; albumin 54%; globulins 46% (α1 – 4%; α2 – 10%; β – 12%; γ – 20%); creatinine – 0.46 mmol/L; urea – 6.7 mmol/L; ALT – 18 mmol/L; AST – 21 mmol/L; cholesterol – 4.7 mmol/L; glucose – 4.15 mmol/L; potassium – 4.2 mmol/L; sodium – 128 mmol/L; total bilirubin – 14.7 μmol/L; inflammatory markers (CRP, ASL-O) were negative. Urinalysis showed no abnormalities. The ECG showed sinus arrhythmia with a normal electrical axis of the heart. Echocardiography: satisfactory myocardial contractility (ejection fraction – 66%), abnormal chordae in the left ventricle.

Ultrasound of the abdominal organs and kidneys revealed no abnormalities: the liver was not enlarged, with a homogeneous structure; the gallbladder showed an anatomical bend, with a wall thickness of 0.2 cm

and homogeneous contents. The pancreas had clear contours and a homogeneous structure. The spleen was unaltered. Right kidney: 11.7 × 6.2 cm; left kidney: 12.4 × 6.4 cm. The renal pelvis is not dilated; echogenicity is unremarkable. Consultations with an otolaryngologist and an ophthalmologist revealed no abnormalities. Thus, this clinical case demonstrates that, despite the absence of a genetic determinant, significant causes, constant dynamic monitoring by an orthopaedic surgeon, and the systematic implementation of recommendations – in particular, manual therapy, massage, physiotherapy exercises and physiotherapy – the girl's spinal deformity gradually progressed, necessitating surgical correction.

A review of recent scientific literature on the problem of scoliosis in children and the clinical case of an adolescent patient with idiopathic scoliosis demonstrates that early detection of the problem at the primary care level and timely treatment prevent the progression of idiopathic scoliosis and the development of its complications. In particular, J. Li *et al*. [29] highlight the increasing prevalence of scoliosis among children and adolescents today, which necessitates more thorough research into the causes, as well as the development and refinement of screening methods for this condition by primary care specialists. Paediatric and adolescent idiopathic scoliosis occupies a special place in research, representing a pressing medical and social problem due to the rising incidence of cases, the increasing severity of the condition, and the progression of complications.

The aetiopathogenesis of paediatric scoliosis remains a topical area of research that requires thorough scientific investigation. The authors T.N. Aulia *et al*. [30] regarded scoliosis as a multifactorial condition in which genetic, hormonal, neuromuscular and biomechanical factors play an important role. It has been established that the progression of the deformity depends on the complex interaction of hereditary and environmental factors. Particular attention is paid to the early detection of the condition and the refinement of diagnostic methods. According to A.H. Jinnah *et al*. [31], early diagnosis allows conservative treatment to be initiated in a timely manner and prevents the development of severe forms of the condition. The progression of idiopathic scoliosis is most commonly observed during periods of rapid growth in children, particularly in adolescent girls. The clinical case presented here confirms that idiopathic scoliosis does not always have a clear genetic link, a significant cause or trigger. It is evident from the clinical case presented that the first clinical signs were detected in the child as early as the age of 8-9 years; however, the gradual progression of the deformity persisted even despite conservative treatment, and the most pronounced progression of the deformity was observed at the age of 10-12 years. Furthermore, C. Shere & E.M. Clark [32] found a correlation between joint hypermobility and the development of adolescent idiopathic scoliosis, which implies a higher risk of developing scoliosis in children with undifferentiated dysplasia of the body's connective tissue framework, i.e. an additional risk factor for the onset of scoliosis. Y. Fan and Q. Zhan [33], as well as J.A. Morcuende *et al*. [34], highlight the importance of an individualised approach to each child and emphasise the importance of the general practitioner's involvement in screening for postural abnormalities in school-age children. The clinical case presented here also confirms the need for general practitioners to be more vigilant regarding the early signs of scoliosis.

Scientific research suggests that the effectiveness of conservative treatment methods for patients with adolescent idiopathic scoliosis remains a matter of debate and requires an in-depth study of the interaction between the factors influencing the course of pathological changes. At the same time, modern technologies for monitoring spinal deformities are designed to reduce radiation exposure. A literature review by T.P.C. Schlösser & R.M. Castelein [35] highlights the potential of using three-dimensional surface topography, digital photogrammetry and other non-invasive methods for assessing posture. An important area of current research is the evaluation of the effectiveness of various methods of treatment and rehabilitation measures for children with scoliosis. A meta-analysis by M. Mangone & M. Vanadia [36] confirms that scoliosis-specific physiotherapy exercises help to reduce the angle of curvature and improve patients' functional status. Similar results were obtained by Y. Chen & X. Yuan [37], who demonstrated the positive impact of individualised, specialised rehabilitation programmes on the progression of scoliosis. Of particular interest is the correlation between the level of physical activity and the risk of developing scoliosis, as reported by X. Qi *et al*. [38]. It has been demonstrated that regular physical activity can have a positive effect on patients' functional status and contribute to an improved quality of life, as shown by E. Hannink *et al*. [39]. Further data on the effectiveness of various types of specialised exercises are presented in the study by J. Miao *et al*. [40], where Schroth exercises and active self-correction techniques demonstrate the best results in controlling the progression of the deformity. Equally important are the consequences of scoliosis for the quality of life of children and adolescents. Patients also frequently complain of pain, restricted physical activity and psychological distress, which necessitates a multidisciplinary professional approach to treating the condition.

Thus, the findings of recent international studies and the clinical case presented here confirm that scoliosis in children is a complex, multifactorial condition that requires routine screening at the primary care level. It is the paediatrician or general practitioner (GP) who may be the first to detect early clinical signs of postural

abnormalities and refer the child to an orthopaedic surgeon in a timely manner. Early detection of the condition will allow treatment to begin promptly and reduce the risk of severe deformities and complications. Scoliosis is a condition that requires early diagnosis, the widespread implementation of modern non-invasive monitoring methods, and the use of evidence-based physiotherapy and rehabilitation programmes to prevent the progression of spinal deformity and complications affecting other organs and systems.

CONCLUSIONS

1. A review of the literature has revealed that scoliosis in children is a complex, multifactorial condition, and the clinical case presented here demonstrates that even with regular monitoring and the implementation of conservative treatment and rehabilitation measures, spinal deformity may progress and require surgical correction. Raising awareness of the issue of scoliosis among primary care specialists – paediatricians and general practitioners (GPs) – will facilitate the early detection of signs of scoliosis and the timely referral of children to specialists such as orthopaedic surgeons, vertebrologists and others.

2. This clinical case confirms the multidisciplinary nature of the problem of scoliosis, as the child's treatment involved a paediatrician, an orthopaedic surgeon, a neurologist, a cardiologist, a cardiac surgeon and other specialists. This highlights the need for a comprehensive approach to the diagnosis, treatment and rehabilitation of children with scoliosis. The insidious nature of scoliosis lies in the fact that even with early detection, timely rehabilitation measures and appropriate conservative treatment, it is not always possible to fully prevent severe deformities and complications, as demonstrated by this clinical case.

3. Postural abnormalities primarily result in a cosmetic defect and non-physiological dysmorphism, which in turn leads to a reduction in physical activity and functional capacity, as well as the suppression of the child's individual physical abilities. Over time, pain develops. As the biomechanics of the spine change, children as young as those in primary school may be diagnosed with degenerative-dystrophic changes, osteochondrosis and even intervertebral disc herniation. Furthermore, the progression of scoliosis leads to changes in the topography and functional capacity of the internal organs of the thoracic and abdominal cavities, as well as the central nervous system.

4. The principles of an individualised approach to a child's rehabilitation programme are based on regularity and consistency, a combination of general and specific exercises, and a gradual increase in physical activity, which has a positive effect on preventing the progression of scoliosis and its complications. A lack of awareness among parents, nursery staff and teachers regarding the early signs of postural abnormalities can lead to delays in seeking medical help for the child. The use of simple visual criteria for assessing a child's posture allows even a non-specialist to suspect spinal deformity at an early stage. The high risk of early disability and impaired quality of life highlights the urgency of the problem of scoliosis and calls for an intensive search for new methods of diagnosis, correction and prevention of complications.

5. Prospects for further research lie in studying the effectiveness of early screening programmes, personalised rehabilitation approaches and multidisciplinary models for monitoring children with scoliosis, with a view to preventing the progression of the deformity, the development of complications and a reduced quality of life in a timely manner.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the child and her parents, who, recognising the challenges associated with spinal disorders in children, treated the research team with empathy and provided comprehensive information on the course of the child's scoliosis, which made this study possible.

FUNDING

None.

CONFLICT OF INTEREST

None.

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Анастасія Горобець

Кандидат медичних наук, доцент
Національний медичний університет імені О.О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-7610-9278

Наталія Горобець

Кандидат медичних наук, доцент
Національний медичний університет імені О.О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0001-7674-3140

Тетяна Починок

Доктор медичних наук, професор
Національний медичний університет імені О.О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0003-0802-2071

Наталія Горобець

Кандидат медичних наук, доцент
Національний медичний університет імені О.О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-8296-879X

Людмила Левадна

Кандидат медичних наук, доцент
Національний медичний університет імені О.О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-0768-2652

Рутинний скринінг сколіозу у дітей на первинній ланці та його значення в профілактиці та своєчасній діагностиці ускладнень

Анотація

Актуальність. Сколіоз у дітей є поширеною ортопедичною патологією, що може супроводжуватися прогресуючою деформацією хребта, порушенням функції внутрішніх органів та зниженням якості життя. Раннє виявлення порушень постави на первинній ланці медичної допомоги має важливе значення для своєчасного лікування та профілактики ускладнень.

Мета. Проаналізувати сучасні підходи до раннього виявлення сколіозу у дітей та оцінити значення рутинного скринінгу на первинній ланці на основі клінічного випадку.

Матеріали та методи. Проведено аналіз сучасних наукових джерел та клінічний аналіз випадку ідіопатичного сколіозу у дитини підліткового віку. Оцінювалися анамнестичні дані, клінічні прояви, результати лабораторних та інструментальних досліджень, динаміка перебігу захворювання та ефективність лікувально-реабілітаційних заходів.

Результати. У представленому клінічному випадку продемонстровано прогресування деформації хребта у дитини, попри систематичне виконання консервативного лікування, що зумовило необхідність хірургічної корекції. Встановлено, що сколіоз у дітей може супроводжуватися мультисистемними проявами, що підкреслює необхідність мультидисциплінарного підходу із залученням педіатра, ортопеда-травматолога, невролога, кардіолога та інших спеціалістів для забезпечення комплексної діагностики, лікування та реабілітації. Показано критичну важливість своєчасного виявлення ранніх клінічних ознак
сколіозу на первинній ланці медичної допомоги, що дозволяє попереджати прогресування деформації та розвитку ускладнень.

Практичне значення. Результати дослідження рекомендується застосовувати в практичній діяльності фахівців первинної медичної допомоги – педіатрів та сімейних лікарів для раннього виявлення сколіозу та своєчасного направлення дітей на спеціалізоване обстеження.

Ключові слова: порушення постави; деформація хребта; ортопедична патологія; підлітки; реабілітація; мультидисциплінарний підхід.

LITERATURE REVIEWS

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.89:615.214
DOI: https://doi.org/10.32345/2664-4738.2.2026.18

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 13.01.2026 Revised: 28.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Vyacheslav Zaika*

Postgraduate Student, Psychiatrist
M. Yarmachenko Institute of Special Education and Psychology of the National Academy of Pedagogical Sciences of Ukraine
04060, 9 Maksym Berlynskyi Str., Kyiv, Ukraine
https://orcid.org/0009-0000-4908-8769

Yan Tytarenko

Student
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0009-0001-5900-0860

A review of the therapeutic and neuroprotective properties of ketamine

Abstract

Relevance. Depression is one of the leading causes of disability worldwide, and a significant proportion of patients suffer from treatment-resistant forms of the disorder. An innovative approach involves the use of ketamine and esketamine, which are capable of inducing a "window of neuroplasticity" – a period of enhanced synaptogenesis and the formation of new neural connections. Theoretically, this increased neuroplasticity may contribute to the improvement of not only mental but also motor and sensorimotor functions, which is critically important for neurological rehabilitation following brain injuries, strokes, and other CNS lesions.

Aim. To conduct a systematic review of the available scientific literature on the effects of ketamine and esketamine on neuroplasticity and neurological functions, with a particular focus on assessing their potential for use in neurological rehabilitation following various CNS injuries.

Materials and methods. A systematic search of the scientific literature was conducted in leading databases (PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate), focusing on studies from the past 20 years. The review included clinical trials, experimental animal studies (modelling acute CNS injuries), as well as systematic reviews and meta-analyses. The collected data were synthesised using a descriptive method.

Results. The systematic review did not identify any clinical studies that directly evaluated the use of ketamine or esketamine to enhance the effectiveness of human neurological rehabilitation programmes specifically due to their neuroplastic effects. On the other hand, preclinical data in animal models (traumatic brain injury and ischemic stroke) convincingly demonstrate that these drugs reduce neuroinflammation, excitotoxicity, and oxidative stress. Furthermore, they support structural neuroplasticity and positively correlate with improvements in sensorimotor and behavioural outcomes.

Conclusions. Ketamine and esketamine are promising candidates for use as adjunctive agents in neurological rehabilitation programmes. However, there is currently insufficient clinical evidence to formulate official recommendations. Well-designed randomised controlled trials with long-term follow-up and standardised assessment of functional outcomes are needed to confirm their efficacy and safety.

Keywords: neurorehabilitation; depression; neuroinflammation; neuroprotection; ketamine-assisted therapy.

INTRODUCTION

According to the most comprehensive study to date, the Global Burden of Disease (GBD) 2021, there were approximately 332 million cases of depressive disorders worldwide in 2021 [1]. Childhood depression is also a problem: between August 2021 and August 2023, the prevalence of depression among adolescents and

Suggested Citation:
Zaika V, Tytarenko Ya. A review of the therapeutic and neuroprotective properties of ketamine. Med Sci Ukr. 2026;22(2):170–177. DOI: https://doi.org/10.32345/2664-4738.2.2026.18

*Corresponding author (*libaurum@gmail.com*)

adults (aged 12 and older) was 13.1%. A clear correlation has been observed: the prevalence is higher among adolescents (ages 12-19) and individuals with lower household incomes [2]. An estimated 4% of the population experience depression, including 5.7% of adults (4.6% among men and 6.9% among women), and 5.9% of adults aged 70 years and older. Depression is about 1.5 times more common among women than among men. Worldwide, more than 10% of pregnant women and women who have just given birth experience depression. In 2021, an estimated 727 000 people lost their lives to suicide. Suicide is the third leading cause of death in 15-29-year-olds [3]. Despite the availability of a wide range of antidepressants, a significant proportion of patients have treatment-resistant depressive disorders, creating a need to search for new, more effective therapeutic strategies. One such innovative approach is the use of ketamine. Esketamine (the S-enantiomer of ketamine), known under the brand name Spravato, was officially approved by the FDA in March 2019 for the treatment of treatment-resistant depression as an adjunct to antidepressants [4], and subsequently as monotherapy [5]. At the same time, racemic ketamine is actively used off-label by specialised clinics as part of ketamine-assisted therapy (KAT) for the treatment of treatment-resistant depression, post-traumatic stress disorder (PTSD), anxiety, and other mental disorders. A number of studies have demonstrated the rapid antidepressant effect of ketamine, particularly in patients with suicidal thoughts, making it an important tool in modern psychopharmacotherapy [6-7].

A key neurophysiological effect of ketamine, considered one of the possible mechanisms of its antidepressant action, is the induction of the so-called "window of neuroplasticity" – a temporary period following drug administration, during which there is an enhancement of gene expression, neurotrophy, synaptogenesis, and the formation of new neural connections [8-10]. In a psychotherapeutic context, this "window" is viewed as an opportunity to enhance the effectiveness of psychotherapeutic treatment and foster deeper and more lasting changes. At the same time, increased neuroplasticity is theoretically a prerequisite for improving not only mental but also motor and sensorimotor functions, which is critically important for neurological rehabilitation processes following traumatic brain injuries, strokes, concussions, brain contusions, and other lesions of the central nervous system (CNS). Theoretically, it can be assumed that the ketamine-induced "window of neuroplasticity" can be used not only to improve the quality of psychotherapy but also to enhance the effectiveness of physical and cognitive rehabilitation by intensifying the neurophysiological component of recovery processes. However, the degree of empirical support for this hypothesis remains unclear. The aim of this study was to conduct a systematic narrative review of the available scientific literature on the effects of ketamine and esketamine on neuroplasticity and neurological functions, summarising current preclinical and clinical data on their neuroprotective and neuroplastic effects.

MATERIALS AND METHODS

To achieve the aim of the study, a systematic narrative review of the scientific literature was conducted to identify studies evaluating the effects of ketamine and esketamine on neuroplasticity, neuroprotection, and the restoration of neurological functions. The search was conducted in leading medical and scientific databases: PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate, as well as in open catalogues of clinical guidelines and clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register). There was no time limit, but the focus was on studies published in the last 20 years, given the active development of ketamine research in psychiatry and neurology. The search utilised combinations of the following keywords and their synonyms in English: "ketamine", "esketamine", "NMDA antagonist", "neuroplasticity", "synaptogenesis", "BDNF", "mTOR", "AMPAR", "neuroprotection", "traumatic brain injury", "TBI", "stroke", "ischemic stroke", "spinal cord injury", "neurorehabilitation", "motor recovery", "cognitive recovery".

The review included:

- original clinical studies (randomised controlled trials, open-label, and pilot studies) that evaluated: the effect of ketamine/esketamine on neurological functions in humans (motor, cognitive, sensory) or changes in neuroplasticity biomarkers (BDNF, measures of synaptic function, neuroimaging markers of structural/functional plasticity);
- experimental studies in animal models (rats, mice, and others) in which: acute CNS injuries were modelled (traumatic brain injury, ischemic stroke, etc.); the effects of ketamine/esketamine on behavioural, neuro-morphological, and molecular indicators related to neuroplasticity and neuroprotection were studied;
- systematic reviews and meta-analyses that synthesised data on the neuroplastic and neuroprotective effects of ketamine.

The following were excluded from the review:

- narrative reviews without a clearly described methodology;
- case reports and case series without an objective assessment of neurological or neuroplastic outcomes;
- studies focusing exclusively on psychiatric symptoms (depression, anxiety, PTSD) without analysis of neurological or neuroplastic indicators;
- publications in which ketamine was used exclusively as an anesthetic without assessment of long-term neurofunctional outcomes.

The data obtained were synthesised descriptively, with a focus on identifying common trends, mechanisms, and gaps in current knowledge. Detailed a search strategy based on PRISMA 2020 protocol is shown in Figure 1.

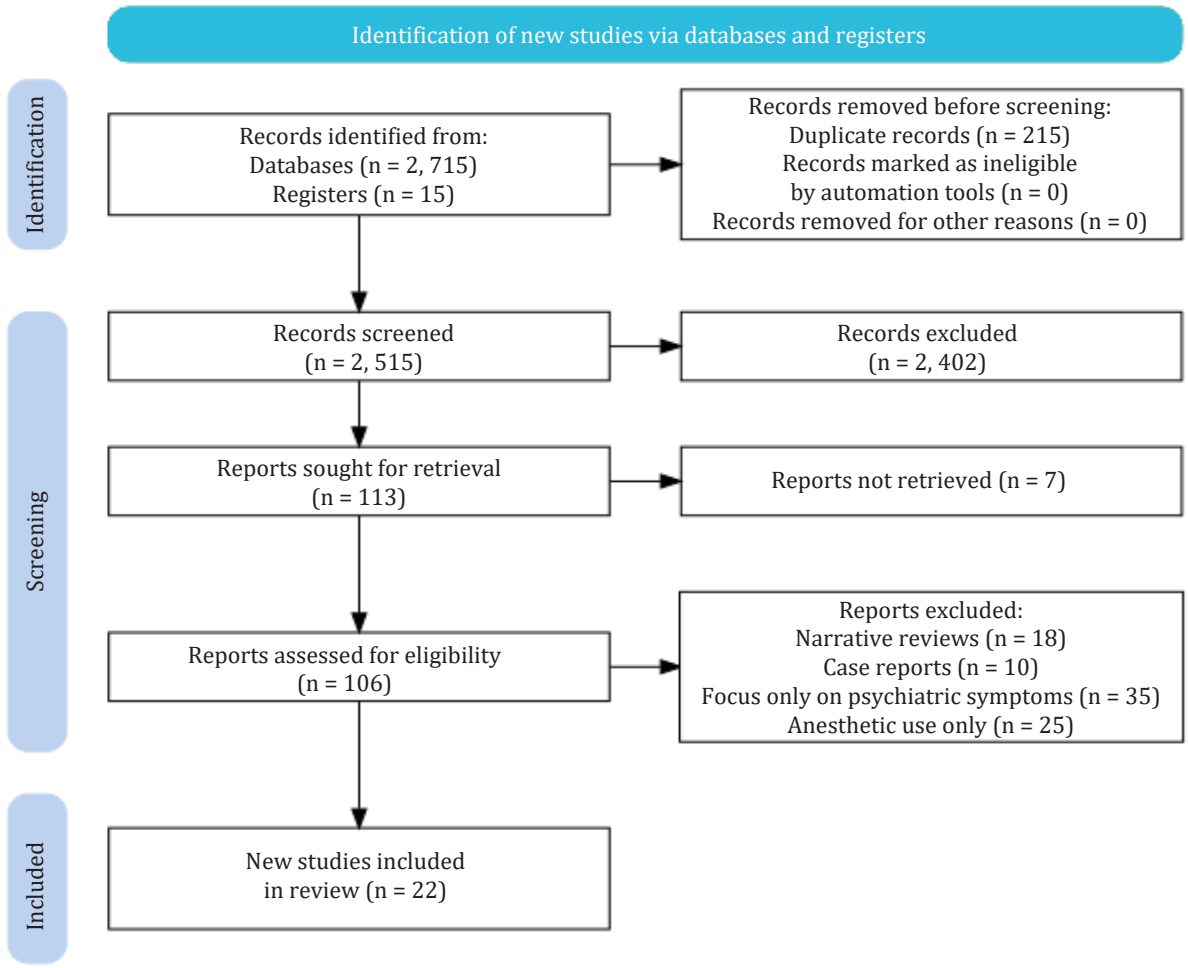

Figure 1. Detailed search strategy and workflow by PRISMA 2020 protocol
Source: compiled by the authors based on [11]

RESULTS

A systematic review did not identify any clinical studies whose primary objective was to evaluate the effect of ketamine on the restoration of human neurological functions specifically through its neuroplastic effects in the context of rehabilitation following CNS injuries. Instead, a large number of studies on depression and PTSD were found, which describe in detail the effects of ketamine on neuroplasticity, synaptic function, and related clinical changes. These studies demonstrate that ketamine, through activation of the BDNF-mTOR pathway, enhancement of AMPA receptor transmission, and stimulation of synaptogenesis, is capable of remodelling pathological neural networks and improving patients' functional status [12-14]. In contrast to the clinical setting, several experimental studies in animal models have been identified that directly demonstrate the positive effect of ketamine on neurological processes associated with functional recovery. In a mouse model of traumatic brain injury (TBI), repeated administration of sub-anaesthetic doses of ketamine (10 mg/kg for 7 days) led to a reduction in neuroinflammation, preservation of dendritic branches and synaptic spines, as well as improvements in memory and behavioural performance [15]. This indicates a neuroprotective effect associated with ketamine-induced neuroplasticity.

For esketamine, in a mouse model of TBI, a reduction in brain edema, neuronal death, and oxidative stress was demonstrated via activation of the AMPK/mTOR–TFEB pathway, accompanied by improvements in neurological parameters [16]. In a model of mild closed-head TBI in rats, intravenous ketamine increased synaptic density in the medial prefrontal cortex, although it did not restore synaptic loss in the hippocampal CA1; the functional (behavioural) consequences of these changes were not yet analysed in detail in this study [17]. This example indicates the regional specificity of ketamine's neuroplastic effects. Similarly, in a model of ischemic stroke (middle cerebral artery occlusion in rats), ketamine promoted improved sensorimotor function, reduced infarct volume, and increased BDNF levels and AMPA/GRIA1 expression, alongside enhanced dendritic branching [18].

Thus, available preclinical data convincingly demonstrate that ketamine and esketamine:

- reduce neuroinflammation, excitotoxicity, and oxidative stress;
- support structural neuroplasticity (dendrites, synaptic spines, synaptic density);
- modulate key molecular pathways (BDNF-mTOR, AMPAR, AMPK/mTOR-TFEB) associated with the restoration of neural networks (shown schematically in Figure 2);
- correlate with improvements in behavioural and sensorimotor parameters in animal models of TBI and ischemic stroke.

Ketamine indirectly leads to the activation of AMPA receptors, which in turn triggers two cascades with downstream effects: the AMPA-BDNF cascade (left) and the AMPA-AMPK cascade (right). The AMPAR-BDNF cascade (left) ultimately activates the mTORC1 complex, which stimulates protein synthesis, thereby enhancing synaptogenesis and synaptic plasticity. The AMPAR-AMPK cascade (right) inhibits the mTORC1 complex, leading to increased autophagy and the degradation of damaged cellular components, which in turn reduces neuroinflammation and apoptosis.

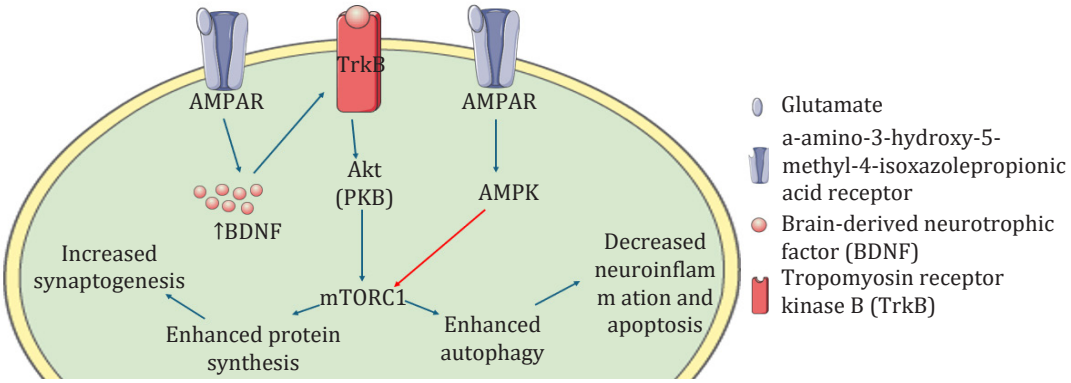

Figure 2. The main mechanisms of action of ketamine that underlie its neuroprotective and therapeutic effects
Source: compiled by the authors

The findings from psychiatric models are consistent with the theoretical concept regarding the central role of BDNF-AMPA-dependent pathways in the formation of the ketamine-induced "window of neuroplasticity". A number of review articles have also described the anti-inflammatory and neuroprotective properties of ketamine: reduction of excitotoxicity, levels of pro-inflammatory cytokines, suppression of excessive microglial activation, and reduction of oxidative stress [19]. Theoretically, these mechanisms may contribute to better neurological outcomes in acute brain injuries.

Despite strong preclinical evidence, clinical data on the use of ketamine as a neuroprotective agent in trauma or stroke, concussion, or contusion-related brain injury remain limited and insufficient for definitive conclusions. In the clinical setting, there are currently no well-designed studies that directly evaluate the use of ketamine to enhance the effectiveness of neurological rehabilitation in humans, particularly through the targeted integration of rehabilitation interventions during the "window of neuroplasticity". This creates a significant research gap and highlights the need for further clinical trials aimed at testing ketamine's potential as an adjunctive agent in recovery programmes following CNS injuries. However, it should be noted that some studies suggest the possibility of transient inhibition of neurogenesis or changes in the glial cell ratio in the hippocampus following TBI [20-21], which requires further analysis. Table 1 summarises the current state of the literature and outlines the discrepancy between preclinical successes and clinical research gaps.

Table 1. Summary of the literature on ketamine effects on neuroprotection and neurorehabilitation

Research focus	Key findings and implications	Mechanisms and characteristics	Sources
Clinical studies (neurological rehabilitation)	A systematic review did not identify any clinical studies that directly evaluated the use of ketamine/esketamine to enhance neurological rehabilitation specifically through their neuroplastic effects. Clinical data on the use of ketamine as a neuroprotective agent in cases of trauma or stroke remain limited.	Currently, there are no well-designed studies on the targeted integration of rehabilitation interventions during the "window of neuroplasticity", creating a significant gap in the research.	–

Table 1. *Continued*

Research focus	Key findings and implications	Mechanisms and characteristics	Sources
Clinical studies (psychiatry)	Studies on depression and PTSD demonstrate that ketamine is capable of remodelling pathological neural networks and improving patients' functional status.	These effects involve BDNF-mTOR activation, enhanced AMPA signalling, and synaptogenesis, along with reduced excitotoxicity, pro-inflammatory cytokines, and oxidative stress.	[12-14, 22-23]
Preclinical studies (traumatic brain injury models)	Reduced neuroinflammation, preserved dendrites and synaptic spines, and improved memory and behaviour in mice. Esketamine also reduced brain edema, neuronal death, and oxidative stress.	The action of esketamine is mediated by activation of the AMPK/mTOR-TFEB pathway. Regional specificity was observed: in rats, ketamine increased synaptic density in the prefrontal cortex but did not restore synaptic loss in the hippocampus.	[15-17, 19]
Preclinical studies (ischemic stroke)	Improvement in sensorimotor functions and reduction in infarct volume in rats.	These effects correlated with increased BDNF levels, AMPA/GRIA1 expression, and enhanced dendritic branching.	[18]
Potential risks (preclinical data)	Some studies suggest the possibility of transient suppression of neurogenesis following traumatic brain injury.	Possible changes in the glial cell ratio in the hippocampus were noted, which requires further analysis.	[20-21]

Source: compiled by the authors

As analysed in Table 1, while studies in psychiatry and preclinical models of TBI and stroke provide robust evidence of neuroplastic and neuroprotective mechanisms (such as BDNF-mTOR activation and reduced neuroinflammation), there is a complete absence of clinical trials evaluating these effects for neurological rehabilitation. This highlights the most critical promising direction for future research: bridging the gap between established preclinical models and human clinical applications.

DISCUSSION

A review of the current scientific literature reveals significant interest in the neuroprotective and neuroplastic properties of ketamine. Studies in animal models by L.R Aleksandrova & A.G. Phillips [22], Y. Gao *et al*. [24] and Y. Liu *et al*. [25], convincingly show that both racemic ketamine and its S-enantiomer (esketamine) are capable of reducing the extent of brain damage, improving sensorimotor functions, reducing inflammation and oxidative stress, and stimulate synaptogenesis and neuronal network remodelling. Furthermore, Y. Gao *et al*. [24] and Y. Liu *et al*. [25] demonstrated that the mechanisms of action include activation of BDNF/TrkB-, AMPAR-, mTOR-, and Nrf2-dependent pathways, as well as modulation of the immune response through polarisation of microglia into the M2 phenotype.

Clinical studies on the use of ketamine in TBI, ischemic stroke, or other acute and chronic neurological conditions remain extremely limited. Some studies, such as those by A.P. Carlson *et al*. [26], M.C.T. Gregers *et al*. [27], and M. Sameer & D.A. Abbas [28], demonstrate a positive effect on reducing the frequency of cortical depolarisations (SD), stabilising intracranial pressure, and improving cerebral perfusion. However, systematic reviews by M.C.T. Gregers *et al*. [27], M. Sameer & D.A. Abbas [28], and T.H. Andreasen *et al*. [29] highlight the low level of evidence for clinical effects: results regarding functional recovery are inconsistent, and the risk of bias remains high. At the same time, M.C.T. Gregers *et al*. [27], S. Himmelseher & M. Durieux [30], and C. Zanza *et al*. [31] note that no significant adverse effects of ketamine on the course of acute TBI or stroke have been identified under controlled ventilation and appropriate monitoring.

In experimental animal models of cerebral ischemia and TBI, ketamine promotes neuronal survival, reduces apoptosis, and supports plasticity through its effects on antioxidant systems (Nrf2), autophagy (AMPK/mTOR/TFEB), and regulation of the cytokine profile, as supported by N.I. Martínez-Torres *et al*. [18], G.N. Silva *et al*. [19], and Y. Liu *et al*. [25]. Esketamine additionally demonstrates the ability to modulate glial responses and metabolism via STAT3- and AKT-dependent pathways [24-25]. However, it is crucial to consider potential risks. M. Boese *et al*. [20], A. Peters *et al*. [21] and J. Liang *et al.* [32] suggest the possibility of transient inhibition of neurogenesis or changes in the glial cell ratio in the hippocampus following TBI, which requires further analysis. Overall, preclinical data support ketamine's potential as an agent for stimulating neuroplasticity and recovery from neurological injuries. However, clinical efficacy remains insufficiently proven due to the limited number of high-quality randomised trials with long-term follow-up and standardised endpoints, a limitation repeatedly emphasised by M.C.T. Gregers *et al*. [27], M. Sameer & D.A. Abbas [28] and T.H. Andreasen *et al*. [29]. It is necessary to consider the dose-dependence of effects, the difference between ketamine enantiomers, and the possible influence of concomitant therapy.

CONCLUSIONS

1. A systematic review of the existing literature has shown that, to date, there are no clinical studies that directly evaluate the use of ketamine or esketamine to enhance the effectiveness of human neurological rehabilitation

through their neuroplastic effects. Instead, there is a compelling body of data from psychiatry demonstrating ketamine's ability to induce a "window of neuroplasticity" through the activation of BDNF-mTOR and AMPAR-dependent pathways, stimulation of synaptogenesis, remodelling of neural networks, and anti-inflammatory effects.

2. Experimental animal models of traumatic brain injury and ischemic stroke indicate that ketamine and esketamine can reduce neuroinflammation, excitotoxicity, and oxidative stress, preserve dendritic architecture and synaptic density, modulate autophagy and glial responses, accompanied by improvements in sensorimotor and cognitive parameters. These data are consistent with the concept of a ketamine-induced "window of neuroplasticity" and suggest the potential for its use in supporting recovery processes following CNS injuries.

3. At the same time, existing clinical studies of ketamine in acute neurological conditions (traumatic brain injury, stroke) are largely focused on safety parameters, control of intracranial pressure, and cortical depolarisations, rather than on the targeted integration of rehabilitation interventions during the period of heightened neuroplasticity. The level of evidence for clinical effects regarding long-term functional recovery remains low, and the results are heterogeneous. Furthermore, some experimental data point to potential risks associated with dosage, administration regimen, and effects on neurogenesis and glial ratios, which requires cautious interpretation.

4. Thus, ketamine and esketamine may be considered promising candidates for use as adjunctive agents in neurological rehabilitation programmes; however, the available evidence is insufficient to formulate clinical recommendations.

5. To translate the concept of the ketamine-induced "window of neuroplasticity" from the theoretical level and preclinical models into the practical realm of evidence-based neurological rehabilitation, future research must focus on: well-designed randomised controlled trials with long-term follow-up;

standardised assessment of motor, cognitive, and functional endpoints; investigating optimal doses, administration regimens, and time windows for combination with physical and cognitive rehabilitation; analysing differences between racemic ketamine and esketamine, as well as the impact of concomitant pharmacological and rehabilitation therapy.

ACKNOWLEDGEMENTS

None.

FUNDING

The research presented in this article was funded by AmA Holding. The sponsor had no role in study design, literature selection, data interpretation, manuscript preparation or decision to publish.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Вячеслав Заіка

Аспірант, лікар-психіатр
Інститут спеціальної педагогіки і психології імені Миколи Ярмаченка НАПН України
04060, вул. Максима Берлинського, 9, м. Київ, Україна
https://orcid.org/0009-0000-4908-8769

Ян Титаренко

Студент
Національний медичний університет ім. О. О. Богомольця
01601, бульв. Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0009-0001-5900-0860

Огляд терапевтичних та нейропротективних властивостей кетаміну

Анотація

Актуальність. Депресія є однією з головних причин інвалідності у світі, і значна частина пацієнтів страждає на резистентні до лікування форми розладу. Інноваційним підходом є використання кетаміну та ескетаміну, здатних індукувати «вікно нейропластичності» – період посиленого синаптогенезу та формування нових нейронних зв'язків. Теоретично, ця підвищена нейропластичність може сприяти покращенню не лише психічних, але й моторних та сенсомоторних функцій, що є критично важливим для неврологічної реабілітації після травм головного мозку, інсультів та інших уражень ЦНС.

Матеріали. Провести систематичний огляд доступної наукової літератури щодо впливу кетаміну та ескетаміну на нейропластичність і неврологічні функції, зосередивши особливу увагу на оцінці їх потенціалу для використання в неврологічній реабілітації після різних уражень ЦНС.

Матеріали та методи. Було проведено систематичний пошук наукової літератури у провідних базах даних (PubMed, Cochrane Library, NICE, APA PsycInfo, CANMAT, UpToDate) з фокусом на дослідження за останні 20 років. До огляду включалися клінічні дослідження, експериментальні дослідження на тваринах (з моделюванням гострих травм ЦНС), а також систематичні огляди та мета-аналізи. Зібрані дані синтезувалися описовим методом.

Результати. Систематичний огляд не виявив клінічних досліджень, які б безпосередньо оцінювали використання кетаміну або ескетаміну для підвищення ефективності програм неврологічної реабілітації людини саме завдяки їх нейропластичним ефектам. З іншого боку, доклінічні дані на тваринних моделях (черепно-мозкові травми та ішемічний інсульт) переконливо демонструють, що ці препарати зменшують нейрозапалення, екситотоксичність та окислювальний стрес. Крім того, вони підтримують структурну нейропластичність та позитивно корелюють із покращенням сенсомоторних і поведінкових показників.

Висновки. Кетамін та ескетамін є перспективними кандидатами на роль допоміжних засобів у програмах неврологічної реабілітації. Проте наразі клінічних доказів недостатньо для формування офіційних рекомендацій. Для підтвердження їх ефективності та безпеки необхідні добре сплановані рандомізовані контрольовані дослідження з тривалим періодом спостереження та стандартизованою оцінкою функціональних результатів.

Ключові слова: нейрореабілітація; депресія; нейрозапалення; нейропротекція; кетамін-асистована терапія.

LITERATURE REVIEWS

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.61-089.843:616-073.756.8:616.61-089.819
DOI: https://doi.org/10.32345/2664-4738.2.2026.19

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 29.12.2025 Revised: 25.04.2026 Accepted: 28.05.2026 Published: 30.06.2026

Sergii Zemskov*

PhD, Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-5039-1324

Larysa Natrus

PhD, Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0003-1763-0618

Mykhailo Tkachenko

PhD, Doctor of Medical Sciences, Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0003-4210-1566

Iryna Krasyuk

PhD in Medical Sciences, Associate Professor
Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-3483-5247

Dynamic renal scintigraphy with 99mTc-DTPA in the differential diagnosis of acute tubular necrosis and acute renal allograft rejection in the early post-transplant period

Abstract

Relevance. Worldwide, people recognise kidney transplantation as the standard treatment for end-stage kidney failure. However, impaired graft function frequently complicates the early postoperative period. The most common causes of early dysfunction are acute tubular necrosis and acute rejection. These conditions are difficult to distinguish from one another because they have similar clinical manifestations and routine monitoring methods are limited.

Aim. To describe the evidence relating to the diagnostic accuracy and capabilities of dynamic renal scintigraphy with 99mTc-DTPA in distinguishing acute tubular necrosis from renal allograft rejection.

Materials and methods. To identify relevant publications, searches were conducted in the international databases PubMed, Scopus, Web of Science and Google Scholar, with a focus on the period from January 2020 to January 2026. The analysis included studies that looked at how 99mTc-DTPA scintigraphy is used in adult kidney transplant patients. This was confirmed by either a biopsy or by checking the patient's progress over time. This review is limited by the fact that no formal risk-of-bias assessment was performed. A total of 22 sources were included in the final analysis. The comprehensiveness of the global evidence included in this review may have been affected by the fact that it was limited to English- and Ukrainian-language publications.

Results. Analysis of the literature indicates that the key criterion for scintigraphic differentiation is assessing the relationship between graft perfusion and function. Acute tubular necrosis is characterised by a dissociation phenomenon, with preserved perfusion despite reduced excretory function. In contrast, acute rejection is accompanied by a parallel deterioration in haemodynamics and function caused by increased vascular resistance.

Suggested Citation:
Zemskov S. Natrusk L, Tkachenko M, Krasyuk I. Dynamic renal scintigraphy with 99mTc-DTPA in the differential diagnosis of acute tubular necrosis and acute renal allograft rejection in the early post-transplant period. Med Sci Ukr. 2026;22(2):178–185. DOI: https://doi.org/10.32345/2664-4738.2.2026.19

*Corresponding author (*szemskov@yahoo.com*)

Using semi-automated quantitative parameters, particularly the Hilson and Kirchner indices, has been shown to strongly correlate with biopsy findings. According to the available literature, this method has a sensitivity of 98% for diagnosing acute tubular necrosis and 87% for detecting acute rejection. Even in cases of reduced graft function, 99mTc-DTPA is the optimal radiopharmaceutical for the routine assessment of perfusion indices thanks to its cost-effectiveness.

Conclusions. Dynamic renal scintigraphy with 99mTc-DTPA is an effective non-invasive diagnostic method. It enables haemodynamic abnormalities in the allograft to be detected at the preclinical stage. Quantitative perfusion indices provide an objective basis for the diagnostic process, allow reliable differentiation between ischaemic and immunological complications, and minimise the need for invasive procedures. This facilitates the timely selection of an appropriate treatment strategy.

Keywords: glomerular filtration rate; kidney transplantation; functional imaging; post-transplant complications; graft dysfunction; graft rejection; scintigraphic monitoring.

INTRODUCTION

For patients with end-stage kidney failure, kidney transplantation is the most effective treatment available, offering significant improvements in both quality of life and life expectancy. However, despite continuous advances in surgical techniques and immunosuppressive therapy, the early postoperative period is often characterised by a high risk of graft dysfunction. The two most common causes of this condition are acute tubular necrosis and acute rejection. These conditions have almost identical clinical manifestations, but require fundamentally different therapeutic approaches. Therefore, accurately and promptly diagnosing these complications non-invasively is crucial for preserving allograft viability and avoiding unnecessary invasive procedures. This highlights the considerable scientific and practical importance of researching functional imaging techniques.

Leading researchers have actively investigated the problem of the early diagnosis of post-transplant complications in recent years. In particular, M. Strader & S. Kant [1] noted in their review that conventional biomarkers have limited sensitivity. Biomarkers such as serum creatinine represent "late" indicators of rejection. This creates an urgent need for the introduction of more sensitive imaging techniques. M. Ostermann *et al*. [2] emphasised that acute kidney injury, including tubular necrosis, is a major cause of early graft dysfunction, and that this must be immediately differentiated from immunological crises. The reliability of routine Doppler ultrasonography in distinguishing acute tubular necrosis from rejection during the early postoperative period was called into question by I. Ahmad *et al*. [3], who reported that the specificity of ultrasonographic markers is insufficient. In contrast, H. Ale Ali & P. Scherer [4] concluded that renal scintigraphy is a reliable tool for differentiating between these conditions, as it enables visualisation of the dissociation phenomenon (preserved perfusion in tubular necrosis), as opposed to the parallel deterioration in haemodynamics observed during rejection. Examining the effectiveness of radiopharmaceuticals, D. Theerakulpisut *et al*. [5] found that 99mTc-DTPA and 99mTc-MAG3 have similarly high predictive value. However, DTPA is the optimal agent for accurately assessing glomerular filtration. When evaluating alternative laboratory markers, M. Oellerich *et al*. [6] found that, while liquid biopsy based on the analysis of donor-derived cell-free DNA is specific for rejection, it is often limited in practice due to high costs and logistical constraints, making radionuclide diagnostics a more accessible option. As Y. Song *et al*. [7] showed, new non-invasive methods, including molecular imaging, are much better than standard clinical tests at detecting rejection before it becomes a clinical problem. Finally, Ukrainian researcher M. Nechaiev [8] demonstrated the considerable clinical value of renal scintigraphy in the timely detection of kidnemy allograft complications. He emphasised the importance of incorporating quantitative scintigraphic parameters into routine clinical practice to minimise the need for percutaneous biopsy.

This study aimed to summarise and systematise the current scientific evidence concerning the diagnostic capabilities of dynamic renal scintigraphy with 99mTc-DTPA as an effective tool for non-invasively diagnosing ischaemic and immunological injury to the kidney allograft in the early postoperative period.

MATERIALS AND METHODS

The search was conducted in the PubMed, Scopus, Web of Science and Google Scholar databases using the following keywords: "kidney transplantation", "radionuclide imaging", "graft rejection" and "kidney tubular necrosis". It predominantly covered publications issued between January 2020 and January 2026. The inclusion criteria were: adult patients following kidney allotransplantation from deceased or living-related donors; dynamic renal scintigraphy with 99mTc-DTPA; analysis of the resulting data; histological verification by biopsy; and reported sensitivity, specificity and accuracy in detecting rejection of the transplanted kidney and acute tubular necrosis. The following were the exclusion criteria: individual case reports, experimental animal studies, articles without full-text availability and publications in languages other than English or Ukrainian. The study was designed and conducted as a descriptive narrative literature review. Given its descriptive design,

no formal assessment of the risk of systematic bias was performed, for example using AMSTAR tools. This is a recognised limitation of the present study. The aim was to provide a conceptual synthesis of the available approaches to differential diagnosis, not to produce a statistical synthesis.

An initial search of the PubMed, Scopus, Web of Science and Google Scholar databases identified 1,452 publications in total. After removing duplicates (n = 385), 1,067 articles remained for screening of titles and abstracts. At this stage, 982 studies were excluded because they were not relevant to the research topic, were concerned with paediatric practice or animal experiments, or did not examine the use of 99mTc-DTPA. The full texts of 85 publications were assessed in detail to determine their compliance with the inclusion criteria. However, 54 articles were excluded from the analysis, primarily due to the lack of histological verification of the findings, the exclusive use of tubule-targeting radiopharmaceuticals, or their format as individual clinical case reports. The final qualitative analysis included a total of 22 sources containing valid data on the use of dynamic renal scintigraphy for the differential diagnosis of postoperative complications.

RESULTS AND DISCUSSION

For patients with end-stage kidney failure, kidney transplantation aims to prolong life and improve quality of life. This is achieved through open or laparoscopic surgery. The world's first successful kidney transplant was performed by Dr Joseph Murray in 1954. Since then, considerable time has elapsed, and substantial improvements have been made in the methods used to select and prepare recipients and donors, perform the surgical procedure, and manage patients postoperatively. Nevertheless, kidney transplantation is still associated with a number of complications that occur after surgery, and these are not always exclusively related to the surgical technique. The post-transplant period is conventionally divided into two periods. The first is the early period. This comprises the first three months. The second is the late period. The first months after a transplant are a time of particular vigilance, as this is when the risk of complications is increased. These include haemorrhage, thrombosis, infection, arterial stenosis, lymphocele, urinoma, ureteric stenosis, vesicoureteric reflux, acute or chronic rejection and acute tubular necrosis, among others [10-12].

Acute tubular necrosis is a multifactorial syndrome most commonly caused by ischaemic or nephrotoxic injury. It involves damage to renal tubular cells despite the major vessels remaining open, and is characterised by a rapid decline in the glomerular filtration rate. This results in the build-up of metabolic waste products in the body. The most common cause of graft failure is acute tubular necrosis, which occurs in 50% of cases following ciclosporin administration, particularly during the early post-transplant period [2, 13]. The immunological reaction known as acute rejection usually happens between a few days and a few weeks after a transplant. The development of circulating donor-specific alloantibodies is a possible complication, and the condition may also be accompanied by immunological features of antibody-mediated renal injury, such as glomerulitis or peritubular capillaritis. Another possible cause is a T-cell-mediated response, which is marked by the presence of lymphocytes in the tubules and interstitium. In rare cases, this response can also lead to inflammation of the arterial intima. The incidence of acute rejection during the first year is approximately 7.9%. This complication occurs less frequently following living-donor transplantation than deceased-donor transplantation, possibly due to shorter cold ischaemia time and better donor–recipient matching [11]. Both complications may present with non-specific shared symptoms. These include oliguria or anuria, peripheral oedema, elevated blood pressure and increased serum creatinine levels. Acute rejection may occasionally present with a low-grade fever, pain in the graft area, general weakness and myalgia, which are not classically observed in acute tubular necrosis. However, all these symptoms are non-specific. This means they always require differentiation from other pathological conditions. Some of these may not be directly related to kidney transplantation.

Dynamic renal scintigraphy is a nuclear medicine technique which allows renal function to be assessed quantitatively and qualitatively by administering specific radiopharmaceuticals. This involves monitoring their distribution dynamically from the moment of intravenous administration until scanning is complete (Fig. 1). A wide range of instrumental and laboratory investigations is used in clinical practice. Each has its own advantages and disadvantages. These are important in the differential diagnosis of these complications. Measurement of serum creatinine and calculation of the estimated glomerular filtration rate are standard components of routine monitoring. However, creatinine is a non-specific marker and does not respond immediately to structural damage to the renal parenchyma, which can prevent the problem from being detected straight away [1, 2, 14]. As well as creatinine, modern laboratory diagnostics offer several other biomarkers, including cystatin C, neutrophil gelatinase-associated lipocalin and cell-free DNA derived from the donor. Cystatin C is a more sensitive marker of declining glomerular filtration than creatinine, enabling earlier diagnosis of graft dysfunction. Neutrophil gelatinase-associated lipocalin, in turn, has been established as an early predictor of acute kidney injury. However, a major limitation of both cystatin C and neutrophil gelatinase-associated lipocalin is their lack of specificity, which prevents them from being used for differential diagnosis. In contrast, donor-derived cell-free DNA, also known as a "liquid biopsy", is a highly

specific indicator of active rejection, particularly antibody-mediated rejection. Meta-analyses have shown that an increase in the donor-derived cell-free DNA fraction above 1% clearly correlates with the histological features of rejection. In contrast, this parameter usually remains low in uncomplicated acute tubular necrosis [6]. It is important to note that testing for neutrophil gelatinase-associated lipocalin and donor-derived cell-free DNA is difficult to access in Ukraine due to complicated logistics and high costs.

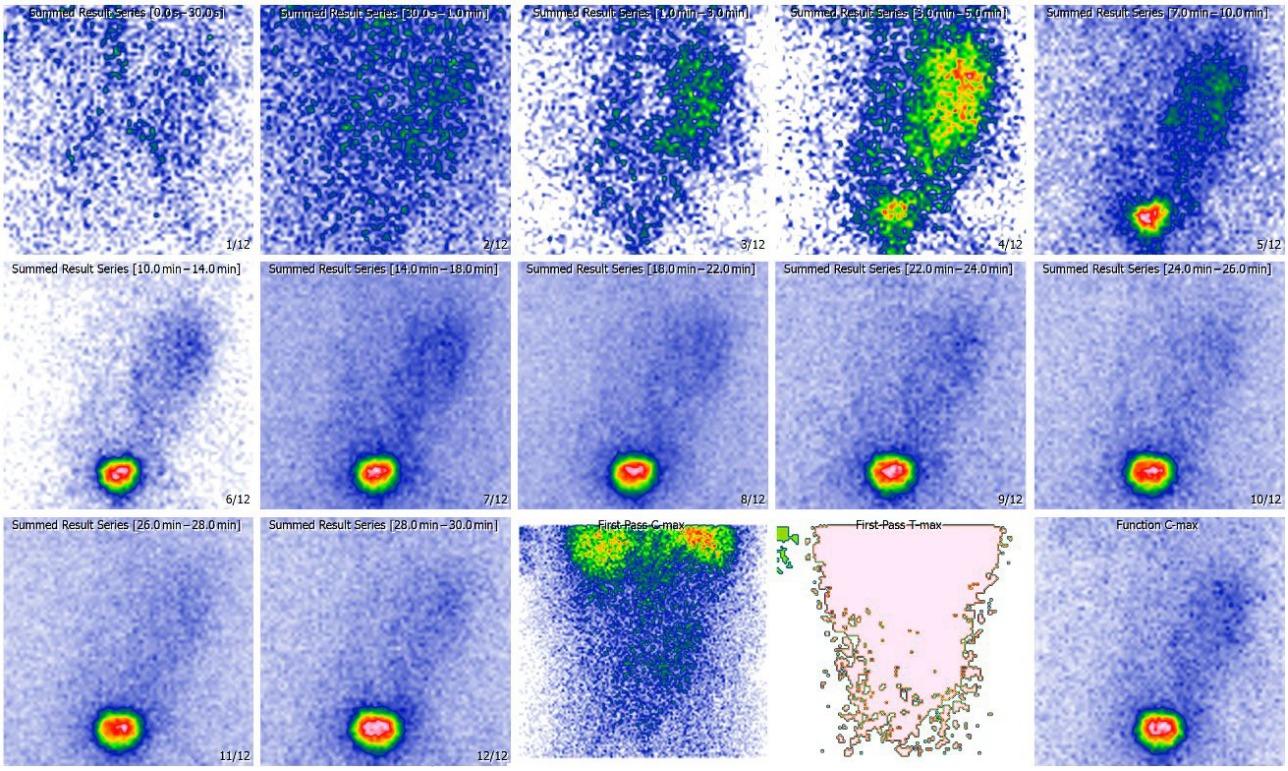

Figure 1. Dynamic renal scintigraphy of a transplanted kidney

Note: Stages 1-12 (shown in the upper and middle rows) represent dynamic images of summed activity from 0 to 30 minutes. Stage 1, corresponding to 0-30 seconds, represents the angiographic phase of graft perfusion. Stages 2-4 (30 seconds to 5 minutes) demonstrate the parenchymal phase, during which peak glomerular filtration of 99mTc-DTPA is reached. Stages 5-12 (7-30 minutes) represent the excretory phase, showing gradual parenchymal clearance and accumulation of the radiopharmaceutical in the urinary bladder. This confirms the absence of urodynamic obstruction. Stages 13-15, shown in the lower right-hand row, represent parametric maps. Stages 13 and 14 (First-Pass C-max and First-Pass T-max, respectively) demonstrate the regions of maximum perfusion amplitude and velocity during the first passage of the bolus. Stage 15, Function C-max, shows the spatial distribution of the most functionally active allograft parenchyma

Source: authors' photo

Ultrasonography, including Doppler ultrasonography, is the preferred imaging method due to its accessibility, lack of radiation exposure and absence of contraindications. It is effective in detecting surgical complications such as urinomas and lymphoceles, as well as in assessing blood flow in major vessels. However, the resistive index, which is used as a marker of parenchymal oedema, depends on the operator and is non-specific. It may be elevated in cases of rejection, acute tubular necrosis, obstruction, and other conditions [3, 12]. High-resolution images are provided by computed tomography, which also enables detailed visualisation of the graft anatomy and surrounding tissues. However, its use is limited by the fact that contrast agents, which are often necessary, can be nephrotoxic and the procedure involves a relatively high radiation dose [16-18]. Magnetic resonance imaging is a safer imaging method. This is particularly true of functional magnetic resonance imaging. The latter is increasingly discussed in the literature. Functional magnetic resonance imaging provides detailed anatomical images as well as information on changes in diffusion, oxygenation, perfusion, metabolism and graft microstructure. However, its use is limited. This is because of the cost of the examination. It is also limited by the shortage of appropriately trained specialists in Ukraine [19]. Ultrasound-guided biopsy remains the gold standard for differential diagnosis, enabling the type of rejection and severity of tubular necrosis to be verified. However, it is an invasive procedure associated with the risk of haemorrhage, arteriovenous fistula formation, and graft loss, which limits its use in serial monitoring [12, 20].

99mTc-DTPA is one of the most commonly used radiopharmaceuticals. It consists of a technetium isotope and diethylenetriaminepentaacetic acid. Glomerular filtration is how it is eliminated, and this allows the glomerular filtration rate to be calculated. It also allows the differential functional and excretory capacity of each kidney to be assessed, and it can be used to identify impaired urinary drainage [5, 21]. Importantly, 99mTc-DTPA is not nephrotoxic. Therefore, it can be used regardless of the functional status of the graft, avoiding the complications associated with certain other diagnostic procedures. According to the latest recommendations of the European Association of Nuclear Medicine, its main uses include the diagnosis of acute and chronic kidney failure, unilateral or bilateral kidney disease (including neoplasms), obstructive uropathy, renovascular hypertension, post-transplant conditions, pyelonephritis, and parenchymal scarring [4, 12].

One of the major advantages of dynamic renal scintigraphy is that it does not require any special preparation from the patient. Patients do not need to follow a special diet or fast, and they can maintain an adequate level of hydration. In kidney transplant recipients, the main focus of diagnosis is differentiating between acute tubular necrosis and graft rejection [5]. This purpose is served by the Hilson perfusion index and the Kirchner function index, or their modifications [8, 22]. The Hilson perfusion index is the ratio of the area under the bolus transit curve for the iliac artery or aorta. This is divided by the area under the renal curve. This is over the interval preceding the peak of the arterial curve. It is calculated using the following formula: HI = Area under the arterial curve / Area under the renal curve ×100. A value below 150 is considered normal, or below 1.5 when modified indices are used [4, 22]. The Kirchner function index is the ratio of the rate of increase in renal activity. This is represented by the slope of the renal curve. It is compared to the rate of increase in activity in the aorta or iliac artery. This is during the first passage of the bolus. It is calculated using the following formula: KI = slope of the renal curve / slope of the aortic curve. The function index is considered normal when its value is above 2.5 [8, 22]. The two indices were shown to be useful in the diagnosis of acute tubular necrosis and allograft rejection. Scintigraphic findings were concordant with biopsy findings in 86% of cases [4, 5, 22]. Acute tubular necrosis is characterised by a reduction in the function index, while the perfusion index remains normal or only slightly elevated. In contrast, acute rejection is characterised by a marked increase in the Hilson index, exceeding 250 when the conventional index is used and 2.5 when the modified index is used, while the Kirchner index decreases sharply to below 1.5 [4, 8, 22].

Analysis of the literature confirms that the differential diagnosis of early complications following kidney transplantation is a significant clinical challenge that requires highly sensitive methods [10-11]. This study's main finding is that dynamic renal scintigraphy with 99mTc-DTPA provides an early, objective assessment of graft haemodynamics at the preclinical stage [14]. The conclusions regarding the appropriateness of routinely using dynamic renal scintigraphy are similar to those of M. Strader & S. Kant [1], who emphasised that conventional markers such as serum creatinine are delayed indicators that respond only after irreversible structural changes have occurred. In contrast, the present study's findings indicate that dynamic renal scintigraphy can detect functional abnormalities immediately. M. Oellerich *et al*. [6] concentrated on the high specificity of liquid biopsy based on donor-derived cell-free DNA for detecting acute rejection when evaluating alternative diagnostic markers. While the authors of this study recognise the high diagnostic value of this laboratory test, their analysis suggests that in settings with limited resources and complex logistics, using readily available 99mTc-DTPA is a more rational and rapid option for routine monitoring.

The findings regarding the benefits of radionuclide imaging are fully consistent with those of I. Ahmad *et al*. [3], who showed that, despite its accessibility, routine Doppler ultrasonography cannot reliably distinguish between acute tubular necrosis and rejection due to the non-specific nature of the resistive index. In contrast, this review shows that dynamic renal scintigraphy can overcome this limitation by visualising the dissociation phenomenon. This is a key pathognomonic feature, where preserved perfusion combined with impaired function clearly indicates tubular necrosis. Furthermore, the authors of this study emphasise that the administration of nephrotoxic contrast agents during the early postoperative period is unacceptable, unlike approaches that promote the use of computed tomography [16, 18]. This makes the use of the functionally safe radiopharmaceutical 99mTc-DTPA a uniquely suitable option [12, 21].

The present findings concerning the choice of radiopharmaceutical are also relevant. They should be compared with the study by D. Theerakulpisut *et al*. [5]. This study found equally high predictive values for both 99mTc-DTPA and the tubule-targeting agent 99mTc-MAG3. However, the authors of the present study emphasise something different. They say that the main aim in the differential diagnosis of acute rejection is the assessment of the haemodynamic phase. By this they mean the first passage of the bolus. This phase depends on the quality of radiopharmaceutical administration rather than its excretory mechanism. The authors of the present study demonstrate that the more cost-effective 99mTc-DTPA can be successfully used to calculate the required Hilson and Kirchner perfusion indices. It remains the radiopharmaceutical of choice for routine screening (Table 1).

Table 1. Comparative characteristics of DTPA and MAG3

Parameter	DTPA	MAG3
Radiopharmaceutical class	Glomerular filtration agent	Tubular excretion agent
Mechanism	Freely filtered by the glomeruli without tubular secretion	Secreted by proximal tubular cells through active transport
Parameters assessed	Glomerular filtration rate, excretion and differential renal function	Renal perfusion, tubular function, excretion and differential renal function
Clinical applications	Obstructive uropathy, postoperative assessment and renal graft evaluation	Obstructive uropathy, for which it is preferred, renal graft evaluation and renal artery stenosis
Advantages	Pure marker of glomerular filtration; low radiation exposure	More effective in kidney failure; effective in obstruction
Limitations	Less effective in severe obstruction because of weak secretion	Slightly higher radiation exposure; more expensive
Routine dose	1-2 mCi (37-74 MBq)	2-4 mCi (74-148 MBq)
Plasma half-life	Approximately 100 minutes	Approximately 15-20 minutes
Principal conclusion	DTPA: filtration and drainage	MAG3: secretion and obstruction

Source: compiled by the authors

Finally, the present findings regarding the necessity of mathematically objectifying scintigraphic images are directly supported by the work of H. Ale Ali & P. Scherer [4], as well as the studies of M. Nechaev [8, 22]. In agreement with these authors, the authors of the present study concluded that visual image assessment alone is insufficient. Only by integrating semi-automated indices can the diagnostic sensitivity reported in the international literature be achieved. The Hilson index above 2.5 indicates rejection, whereas an index below 2.0 combined with a reduced Kirchner index indicates tubular necrosis. This approach provides sensitivities of up to 98% and 87% for ischaemic and immunological complications, respectively [4, 22]. Overall, the comparative analysis confirms that innovative, non-invasive, molecular imaging approaches can substantially reduce the need for traumatic, percutaneous biopsy. According to J.M. Halimi *et al*. [20], this procedure remains associated with a considerable risk of complications.

In summary, the choice of a particular radiopharmaceutical should be based on the principal clinical objectives. It should also take the patient's overall functional status into account. While 99mTc-MAG3 clearly has advantages for visualising the renal parenchyma in cases of severe obstruction or critically impaired excretory function, 99mTc-DTPA remains the optimal first-line tool for routine postoperative screening. Key perfusion parameters, particularly the Hilson and Kirchner indices, can be objectively calculated using the pharmacokinetic properties of 99mTc-DTPA as a pure marker of glomerular filtration. These measurements are essential for rapidly and reliably differentiating immunological complications, such as rejection, from ischaemic complications, such as tubular necrosis. A reliable, non-invasive diagnostic algorithm is provided by a comprehensive analysis of haemodynamic scintigraphic parameters, particularly when integrated with modern laboratory biomarkers. This multimodal approach can significantly improve the clinical management of recipients during the early post-transplant period and reduce the need for high-risk percutaneous biopsy.

CONCLUSIONS

1. Dynamic renal scintigraphy using 99mTc-DTPA is an effective, non-invasive diagnostic method that can detect haemodynamic abnormalities in the allograft at the preclinical stage.

2. The key criterion for scintigraphic differentiation is assessing the relationship between graft perfusion and function. Acute tubular necrosis is characterised by a dissociation phenomenon, with preserved perfusion despite reduced excretory function. In contrast, acute rejection is accompanied by a parallel deterioration in both parameters.

3. Using semi-automated quantitative parameters, particularly the Hilson and Kirchner indices, provides an objective basis for the diagnostic process and demonstrates a strong correlation with biopsy findings.

4. The high sensitivity and specificity of dynamic renal scintigraphy confirm its status as a reliable differential diagnostic tool for the timely identification of ischaemic and immunological graft injury.

5. Using cost-effective, non-nephrotoxic 99mTc-DTPA minimises the need for invasive procedures and facilitates timely selection of an appropriate treatment strategy during the early postoperative period.

Limitations. Firstly, due to the descriptive nature of this narrative review, no formal assessment of the risk of systematic bias was conducted. Second, the literature search was limited to English- and Ukrainian-language publications only, which may have affected the comprehensiveness of the global evidence included.

ACKNOWLEDGEMENTS

None.

FUNDING

During the preparation of this manuscript, no specific funding was received from any public or private organisation.

CONFLICT OF INTEREST

There is no conflict of interest. The authors of the article did not take part in the peer-review process or in editorial decisions regarding their own manuscript.

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Сергій Земсков

Доктор філософії, доктор медичних наук, професор
Національний медичний університет ім. О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-5039-1324

Лариса Натрус

Доктор філософії, доктор медичних наук, професор
Національний медичний університет ім. О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0003-1763-0618

Михайло Ткаченко

Доктор філософії, доктор медичних наук, професор
Національний медичний університет ім. О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0003-4210-1566

Ірина Красюк

Кандидат медичних наук, доцент
Національний медичний університет ім. О. О. Богомольця
01601, бульв. Т. Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-3483-5247

Динамічна реносцинтиграфія з 99mTc-DTPA у диференційній діагностиці гострого тубулярного некрозу та гострого відторгнення ниркового трансплантата в ранньому посттрансплантаційному періоді

Анотація

Актуальність. Трансплантація нирки є визнаним у світі стандартом лікування термінальної стадії ниркової недостатності, проте ранній післяопераційний період часто ускладнюється порушенням функції трансплантата. Найпоширенішими причинами ранньої дисфункції є гострий тубулярний некроз та гостре відторгнення, диференційна діагностика яких залишається складною через схожість клінічної симптоматики та обмеження рутинних методів моніторингу.

Мета. Описовий огляд даних щодо діагностичної точності та можливостей динамічної реносцинтиграфії з 99mTc-DTPA у розрізненні гострого тубулярного некрозу та відторгнення трансплантата.

Матеріали та методи. Пошук релевантних публікацій проводився у міжнародних базах даних PubMed, Scopus, Web of Science та Google Scholar, охоплюючи період переважно з січня 2020 року по січень 2026 року. До аналізу було включено дослідження, що розглядали застосування сцинтиграфії з 99mTc-DTPA у дорослих після алотрансплантації нирки з верифікацією діагнозу шляхом біопсії або клінічного спостереження. Оцінка ризику систематичних похибок формально не проводилась, що розглядається як обмеження даного огляду. У фінальний аналіз було включено 22 джерела. Слід враховувати, що даний огляд обмежувався аналізом англо- та україномовних публікацій, що могло вплинути на повноту охоплення світових даних.

Результати. Аналіз джерел свідчить, що ключовим критерієм сцинтиграфічної диференціації є оцінка співвідношення перфузії та функції трансплантата. Гострий тубулярний некроз характеризується феноменом дисоціації (збережена перфузія на тлі зниженої екскреторної функції), тоді як гостре відторгнення супроводжується симетричним погіршенням гемодинаміки та функції внаслідок підвищення судинного опору. Встановлено, що використання напівавтоматичних кількісних параметрів, зокрема індексів Хілсона та Кіршнера, забезпечує високу кореляцію з результатами біопсії. Згідно з даними літератури, чутливість методики сягає 98 % для діагностики гострого тубулярного некрозу та 87 % для виявлення гострого відторгнення. Економічно доступний 99mTc-DTPA залишається оптимальним агентом для рутинної оцінки перфузійних індексів навіть при зниженій функції трансплантата.

Висновки. Динамічна реносцинтиграфія з 99mTc-DTPA є ефективним неінвазивним методом діагностики, що дозволяє виявляти порушення гемодинаміки алотрансплантата на доклінічному етапі. Використання кількісних індексів перфузії дозволяє об'єктивізувати діагностичний процес, надійно розрізняти ішемічні та імунологічні ускладнення та мінімізувати необхідність проведення інвазивних втручань, сприяючи своєчасному вибору адекватної тактики лікування.

Ключові слова: швидкість клубочкової фільтрації; трансплантація нирки; функціональна візуалізація; посттрансплантаційні ускладнення; дисфункція трансплантата; відторгнення трансплантата; сцинтиграфічний моніторинг.

LITERATURE REVIEWS

Medical Science of Ukraine
Медична наука України

ISSN: 2664-472X
e-ISSN: 2664-4738
Vol. 22, No. 2, 2026

UDC 616.89:616-008.441.13:612.017
DOI: https://doi.org/10.32345/2664-4738.2.2026.20

Journal homepage: https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/
Received: 25.12.2025 Revised: 01.05.2026 Accepted: 28.05.2026 Published: 30.06.2026

Maryna Tsvetkova

Senior Lecturer
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd., Kyiv, Ukraine
https://orcid.org/0000-0002-8796-009x

Nataliia Korzh*

Student
Bogomolets National Medical University
01601, 13 Taras Shevchenko Blvd, Kyiv, Ukraine
https://orcid.org/0009-0007-7846-4576

Pavlo Petrushanko

Postgraduate Student
Private Higher Educational Institution "Kyiv Medical University"
01004, 17-A Velyka Vasylkivska Str., Kyiv, Ukraine
https://orcid.org/0009-0005-0212-9961

Psychoneuroimmunological mechanisms of stress-induced mental and psychosomatic disorders

Abstract

Relevance. Psychosomatic disorders represent a significant medical and biological problem, as their development is linked to the chronic activation of stress-mediating systems, in particular the hypothalamic-pituitary-adrenal axis and immuno-inflammatory mechanisms, which contribute to the development and progression of somatic pathology. Despite a considerable body of research, the pathogenesis of psychosomatic disorders requires an integrative synthesis that takes into account the interaction of neuroendocrine, immunoinflammatory and metabolic mechanisms, in particular neuroinflammation, glucocorticoid resistance, activation of the kynurenine pathway and gut dysbiosis. The relevance of this study stems from the need to systematise these data and develop a comprehensive pathogenetic model that can serve as a basis for improving the diagnosis and treatment of psychosomatic disorders.

Aim. To systematise current scientific data on the psychoneuroimmunological mechanisms underlying the development of stress-induced mental and psychosomatic disorders by analysing the neuroendocrine, immuno-inflammatory, neurotransmitter and microbiome changes that arise under the influence of chronic stress and contribute to the development of psychosomatic pathology.

Materials and methods. The study involved a narrative analysis of current scientific publications in the PubMed, PMC and Scopus databases for the period 2015-2025 (187 identified, 26 included in the final analysis). Methods of systematic analysis, generalisation and comparison of scientific data were employed.

Results. This study systematises an integrative approach to the pathogenesis of psychosomatic disorders, uniting neuroendocrine, immune, metabolic and microbiome mechanisms into a single, interconnected cascade. Key points of convergence (the hypothalamic-pituitary-adrenal axis, indoleamine 2,3-dioxygenase 1, neuroinflammation) have been identified, and the concept of a pathological "vicious circle" that drives the chronicity of the process has been substantiated. It has been shown that chronic stress, via glucocorticoid resistance, neuroinflammation and kynurenine metabolism, forms a self-reinforcing pathological cycle, which underlies the chronicity of psychosomatic disorders.

Suggested Citation:
Tsvetkova M, Korzh N, Petrushanko P. Psychoneuroimmunological mechanisms of stress-induced mental and psychosomatic disorders. Med Sci Ukr. 2026;22(2):186–196. DOI: https://doi.org/10.32345/2664-4738.2.2026.20

*Corresponding author (*nataskorzh@gmail.com*)

Conclusions. Psychosomatic pathology should be regarded as a systemic, multifactorial process in which the interaction of neuroendocrine, immune and microbiome regulation plays a key role.
Practical value. The findings presented here can be used to deepen the understanding of the pathogenesis of psychosomatic diseases and to identify promising therapeutic targets.
Keywords: hypothalamic-pituitary-adrenal axis; glucocorticoid resistance; neuroinflammation; kynurenine pathway; "microbiome-gut-brain" axis.

INTRODUCTION

Psychosomatic and stress-induced mental disorders are one of the most pressing issues in modern medicine. According to the World Health Organisation [1], depression is the leading cause of disability worldwide, whilst anxiety disorders affect over 280 million people. The prevalence of psychosomatic conditions – ranging from irritable bowel syndrome to cardiovascular and endocrine comorbidities – is steadily increasing in the context of chronic social stress, making an understanding of their pathogenetic mechanisms a clinical priority. The central component of the stress response is the hypothalamic-pituitary-adrenal axis (HPA axis). N.W. Churchill *et al*. [2] described glucocorticoids in their work as "final effectors of the stress response", which regulate the transcription of hundreds of genes and determine whether acute stress will progress to a chronic condition. It is precisely the prolonged hyperactivation of the HPA axis, leading to the development of glucocorticoid resistance – a condition in which cortisol loses its anti-inflammatory and inhibitory function – that is now regarded as the key pathogenetic mechanism linking psychological stress to somatic dysfunction. E. Knezevic *et al.* [3] examined how chronic hypercortisolism causes hippocampal atrophy, excitotoxicity via NMDA receptors and suppression of brain-derived neurotrophic factor (BDNF), thereby forming the neurobiological substrate of depression and post-traumatic stress disorder (PTSD). In parallel with neuroendocrine changes during chronic stress, the immune system is activated. C.M. Pariante [4] emphasised in his review that glucocorticoid resistance is a central link between stress and systemic inflammation: when cortisol loses its ability to suppress NF-κB, levels of IL-1β, IL-6 and TNF-α rise steadily, maintaining a chronic inflammatory state. D.L. Wong *et al*. [5] demonstrated that chronic catecholamine activation independently exacerbates oxidative stress in the endothelium and triggers cardiomyocyte apoptosis, which explains the cardiovascular comorbidity associated with depression and PTSD.

An important molecular link between inflammation and neurotransmitter disturbances is the kynurenine pathway of tryptophan metabolism. A.H. Miller & C.L. Raison [6] proposed a concept whereby cytokine-induced activation of indoleamine-2,3-dioxygenase (IDO1) redirects tryptophan away from serotonin synthesis towards the accumulation of neurotoxic metabolites – quinolinic acid and 3-hydroxykinurenine – which directly contributes to cognitive and affective disturbances. A.A. Badawy *et al*. [7] confirmed the clinical significance of this mechanism in a systematic review, noting an increased KYN/Trp ratio in patients with major depressive disorder, PTSD and chronic fatigue syndrome. In current discourse, understanding of the role of the "microbiome-gut-brain" axis (MGBA) in the pathogenesis of stress-related disorders has expanded significantly. In their review, J. Khlevner *et al*. [8] characterised this axis as a multi-level communication system comprising neural (vagus nerve), immune (cytokines, Toll-like receptors), endocrine and metabolic pathways. R.G. Xiong *et al*. [9] found that in depression and anxiety disorders, the microbiome is characterised by a reduction in anti-inflammatory producers of short-chain fatty acids (*Faecalibacterium prausnitzii*, *Roseburia*) and an increase in pro-inflammatory taxa (*Enterobacteriaceae*), whilst dysbiosis and increased intestinal permeability trigger a systemic inflammatory cascade that sustains neuroinflammation.

Despite a significant body of research, an integrative pathogenetic model that unites neuroendocrine, immune, metabolic and microbiome mechanisms into a single interconnected cascade remains insufficiently systematised. In particular, the points of convergence between HPA axis dysfunction, IDO1 activation and dysbiosis – as components of a single "vicious circle" that drives the chronicity of the process – have not been fully described. A. Warren *et al*. [10] emphasised the need to consider these mechanisms holistically, as an isolated analysis of individual links in the pathogenesis does not allow for the identification of optimal therapeutic targets. A. Verma *et al*. [11] also emphasise that stress-induced dysregulation of the microbiome, metabolome and hormonal axis forms a mutually reinforcing cycle that requires a comprehensive therapeutic approach. Thus, the systematisation of current data and the development of a comprehensive pathogenetic model of psychosomatic disorders is a pressing task, both for deepening scientific understanding of the problem and for justifying new diagnostic and therapeutic strategies. The aim of the study was to conduct a comprehensive analysis of current understanding of the psychoneuroimmunological basis of stress-induced mental and psychosomatic disorders, with a focus on determining the role of neuroendocrine dysregulation, the immuno-inflammatory response, neurotransmitter disturbances and changes in the gut microbiome in the pathogenesis of psychosomatic pathology.

MATERIALS AND METHODS

A narrative literature review incorporating elements of a structured search was conducted to identify relevant studies investigating the pathogenetic mechanisms of psychosomatic disorders induced by chronic stress. Three electronic databases were searched: PubMed, PMC, and Scopus. The search strategy was based on the following keywords: "stress-mediating systems", "hypothalamic-pituitary-adrenal axis", "glucocorticoid resistance", "neuroinflammation", "psychoneuroimmunology", "kynurenine pathway", "microbiome-gut-brain axis", and "psychosomatic disorders". These terms were used both individually and in combination using the Boolean operators AND and OR. The search was primarily limited to English-language publications published between 2015 and 2025, yielding an initial total of 187 publications. The selection process was carried out in two stages. In the first stage, the titles and abstracts of all the publications found were independently reviewed by two researchers to assess their relevance to the research question; based on the results of this stage, 64 publications were selected. Studies that clearly did not investigate the neuroendocrine, immune or metabolic mechanisms underlying the development of psychosomatic pathology were excluded. In the second stage, the full texts of 64 potentially suitable articles were obtained and also independently assessed; following a full-text analysis, 26 sources were included in the final dataset. Among the selected publications were: a fundamental review of cortisol physiology by J. Kaur *et al.* [12], as well as works by D.S. Goldstein *et al*. [13-14], devoted to the role of catecholamines in stress responses and their link to neurodegenerative processes. Disagreements regarding the inclusion or exclusion of individual publications were resolved through collegial discussion until a consensus was reached. Articles were included in the analysis provided they met the following criteria: direct investigation of the pathogenetic mechanisms of psychosomatic disorders in the context of the stress response; publication in a peer-reviewed journal indexed in Scopus. Publications with similar or duplicative content were excluded (preference was given to works of higher methodological quality or greater relevance), as were conference abstracts and proceedings, and articles that did not meet the criteria for an evidence base. Following the selection process, a corpus of 26 publications was compiled, on the basis of which an integrative pathogenetic model of psychosomatic disorders was developed using methods of systematic analysis, generalisation and comparison.

RESULTS AND DISCUSSION

A key factor in the development of psychosomatic disorders is the chronic activation of stress-mediating systems, in particular the hypothalamic-pituitary-drenal axis and the sympathoadrenal system [1, 6]. In response to prolonged psycho-emotional stress, the secretion of corticoliberin, adrenocorticotropic hormone and cortisol increases, which is initially of an adaptive nature [12]. Chronic hyperactivation of these systems leads to excessive production of cortisol and catecholamines. The first, immediate "line of defence" against stress is provided by the sympathetic-adrenal system (SAS). A perceived stressor, via the cortical associative areas and the amygdala, activates the hypothalamic preoptic and paraventricular nuclei, from where descending sympathetic pathways reach the adrenal medulla. Chromaffin cells are responsible for a massive release of adrenaline (80-85% of secretion) and noradrenaline (15-20%) into the bloodstream. This response develops within seconds and is known by the classic term "fight-or-flight" [13]. D.L. Wong *et al*. [5] demonstrated that adrenaline not only performs a short-term regulatory function, but, upon chronic activation, becomes a direct factor in tissue damage: it stimulates oxidative stress in the endothelium by increasing the production of reactive oxygen species (ROS), activates NF-κB-mediated inflammatory signalling, accelerates cardiomyocyte apoptosis and enhances platelet aggregation. Furthermore, via β2-receptors, adrenaline suppresses natural killer (NK) cells and alters the cytokine profile, which explains the immunosuppression observed during acute stress. Takotsubo syndrome (stress-induced cardiomyopathy) is an extreme example of the cardiotoxicity of catecholamines: following emotional trauma, a massive release of adrenaline causes transient dysfunction of the left ventricular apex, which clinically resembles acute myocardial infarction. The pathophysiological mechanism involves the direct toxic effect of supraphysiological concentrations of catecholamines and spasm of the small coronary vessels [5].

The second level of the stress response, the HPA axis, is activated more slowly but has longer-lasting effects. In response to stress, neurons in the paraventricular nucleus of the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), which stimulate the corticotropic cells of the pituitary gland to secrete adrenocorticotropic hormone (ACTH). ACTH acts on the zona fasciculata of the adrenal glands, activating the synthesis of cortisol [12]. At the cellular level, cortisol interacts with mineralocorticoid receptors (MRs, high affinity) and glucocorticoid receptors (GRs, lower affinity). MRs are active at basal levels and provide "proactive" inhibition, whilst GRs are activated during stress and provide "reactive" inhibition. In the brain, MRs have a neuroprotective effect, whereas excessive activation of GRs may contribute to neurotoxicity [3]. The genomic action of cortisol is mediated through binding to GRs, their translocation into the nucleus and interaction with glucocorticoid

response elements or transcription factors (NF-κB, AP-1), which alters gene expression (hours) and brings about a large-scale reprogramming of cellular metabolism, the immune response and neuroplasticity. Non-genomic effects occur more rapidly – via membrane receptors and signalling cascades (MAPK/ERK) [2-3]. Under conditions of chronic stress, glucocorticoid resistance develops, manifesting as a reduction in receptor sensitivity to cortisol. Prolonged hypercortisolism leads to a reduction in the density and sensitivity of glucocorticoid receptors in target tissues (the hippocampus, pituitary gland, hypothalamus and immune cells). "Glucocorticoid resistance" ensues – a condition in which, despite elevated cortisol levels, its anti-inflammatory and inhibitory effects on the HPA axis are attenuated. E. Knezevic *et al*. [3] described numerous pathological consequences of chronic hypercortisolism in a systematic review: in hippocampal neurons, excessive activation of the GR leads to hyperexcitation of glutamate NMDA receptors (excitotoxicity), oxidative stress, suppression of neurogenesis in the dentate gyrus, atrophy of dendritic spines and a reduction in hippocampal volume. These changes are well documented in patients with major depressive disorder and PTSD. Concurrently, chronically elevated CRH in the amygdala enhances fear memory and reactivity, forming the neurobiological basis of anxiety.

Another form of dysregulation – hypocortisolism associated with increased sensitivity of the GR – is characteristic of PTSD. C.M. Pariante [4] demonstrated that in PTSD, the number of lymphocytic GR is significantly elevated, whilst daily cortisol excretion is reduced compared with healthy individuals and patients with major depression. This phenomenon is interpreted as compensatory hypersensitivity of the GR following initial stress-induced exhaustion, or as an epigenetic adaptation that reprogrammes the HPA axis to a "conservative" mode following massive stress. It is of fundamental importance that, in PTSD and major depression, dysregulation of the HPA axis occurs in opposite directions, although in both cases it is pathogenic. Regulation of the stress response at the level of the central nervous system (CNS) is mediated through the interaction of the hippocampus, the amygdala and the medial prefrontal cortex (mPFC): the hippocampus is responsible for contextual processing and the inhibition of stress-related memories, the amygdala for the initial assessment of threat and the formation of a fear response, whilst the mPFC provides top-down cognitive control over its activity. Under chronic stress, this system becomes unbalanced: the hippocampus atrophies as a result of glucocorticoid-induced neurotoxicity, the amygdala hypertrophies and becomes hyperreactive, whilst the mPFC loses its ability to effectively inhibit it due to the weakening of inhibitory gamma-aminobutyric acid (GABAergic) projections. As a result, a state of chronic "readiness for danger" develops, characteristic of anxiety disorders, depression and PTSD. Cortisol inhibits the synthesis of brain-derived neurotrophic factor (BDNF), and its reduction in the hippocampus and BDNF is one of the most consistently observed molecular correlates of depression. BDNF is essential for neuronal survival, synaptogenesis and neurogenesis, and the restoration of its levels is considered one of the mechanisms of action of SSRIs, electroconvulsive therapy and physical exercise. Chronic hypercortisolism also disrupts neurotransmitter systems: it reduces the sensitivity of 5-HT1A serotonin receptors, inhibits tryptophan hydroxylase activity, decreases dopamine availability in the mesolimbic system – contributing to anhedonia – and enhances glutamatergic excitation in the hippocampus, leading to the development of excitotoxicity [3]. The interaction between glucocorticoid receptors and the noradrenergic system confers pronociceptive properties on hypercortisolism, which is significant in the development of psychosomatic pain.

As noted by A. Warren *et al.* [10] and D.S. Goldstein *et al*. [13], glucocorticoid resistance leads to a loss of cortisol's anti-inflammatory effect and the activation of systemic inflammation. This is accompanied by increased levels of pro-inflammatory cytokines, in particular interleukin-1β, interleukin-6 and tumour necrosis factor-α [14-16]. Systemic inflammation is associated with the development of neuroinflammation through the activation of microglia – the primary immunocompetent cells of the central nervous system [2, 7, 17]. Activated microglia produce pro-inflammatory mediators, as well as reactive oxygen and nitrogen species, which disrupt neuronal plasticity, synaptic transmission and neurotransmitter balance, as highlighted by H.Y. Tang *et al.* [18], N. Mourtzi *et al*. [19] and G. Turecki *et al.* [20]. It has been established that disruption of glucocorticoid signalling leads to a loss of control over the immune response and the development of systemic inflammation. Activation of microglia and elevated levels of pro-inflammatory cytokines give rise to a state of neuroinflammation, which is key to the development of psychosomatic disorders. Under conditions of chronic stress, cortisol, despite elevated blood levels, gradually loses its ability to suppress inflammation. This occurs through several mechanisms. Firstly, pro-inflammatory cytokines chemically modify the glucocorticoid receptor (GR) in such a way that it is less able to enter the cell nucleus and cannot perform its function. Secondly, cytokines stimulate the formation of an "inactive" form of the GR (the β-isoform), which blocks the function of the main form of the receptor. Thirdly, chronic inflammation activates the NF-κB signalling factor, which competes with the GR for the regulation of the same genes. The result is a pathological vicious cycle (Fig. 1).

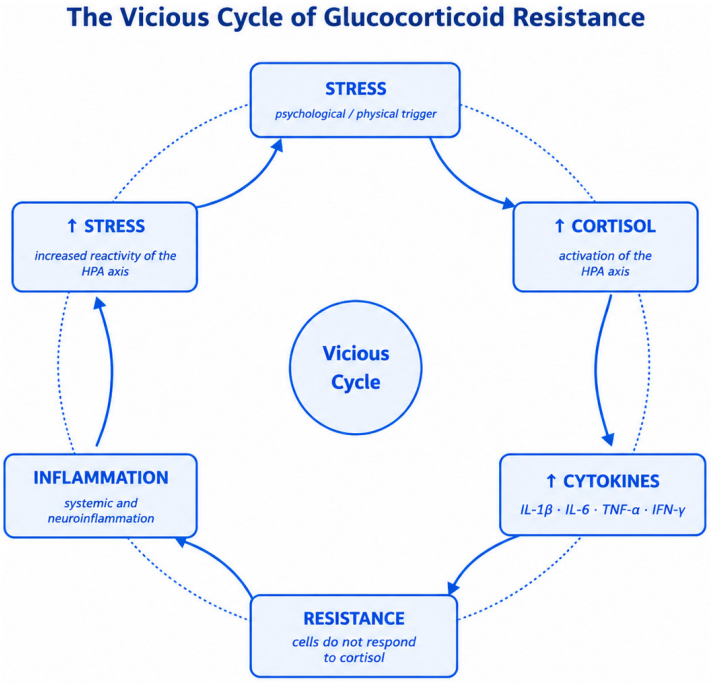

Figure 1. The pathological vicious cycle of glucocorticoid resistance
Source: compiled by the authors based on E. Knezevic *et al*. [3], C.M. Pariante [4], D.S. Goldstein *et al*. [13]

As shown in Figure 1, glucocorticoid resistance develops as a self-perpetuating pathological cycle, in which chronic stress and increased cortisol secretion are accompanied by the activation of pro-inflammatory cytokines, a reduction in the sensitivity of target cells to cortisol, and the subsequent maintenance of neuroinflammation. Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) themselves also activate the HPA axis, stimulating further secretion of CRH by the hypothalamus. They increase the permeability of the blood-brain barrier (BBB) – a protective structure separating the blood from brain tissue – and enter the central nervous system (CNS), where they activate microglia – specialised immune cells of the brain. Activated microglia begin to release substances that damage neurons: excess glutamate (the main excitatory neurotransmitter), free radicals, nitric oxide and other pro-inflammatory molecules. At the same time, it inhibits the function of astrocytes – the "support" cells of neurons that provide them with nourishment and protection – in particular, reducing the production of the neurotrophic factor BDNF [21]. The accumulation of excess glutamate leads to excessive neuronal excitation via NMDA receptors – a process known as excitotoxicity, which is one of the key mechanisms underlying hippocampal neuronal death in depression. It is precisely this mechanism that underpins the action of ketamine: by blocking NMDA receptors, it rapidly eliminates excessive excitation, restores synaptic connections and increases BDNF levels – all within a few hours, significantly faster than conventional antidepressants [3]. The key mechanism linking immune and neurotransmitter changes is the cytokine-induced activation of IDO1, which causes a shift in tryptophan metabolism from the serotonin pathway to the kynurenine pathway [8]. This leads to a reduction in serotonin levels – which are important in the development of affective and somatoform disorders – and to the accumulation of neuroactive metabolites [5, 21-22]. The kynurenine pathway of tryptophan metabolism acts as a molecular link between inflammation and neurotransmitter disturbances. Upon activation of the IDO1 enzyme, tryptophan is redirected from serotonin synthesis towards the formation of neurotoxic metabolites, in particular quinolinic acid [7-6]. Table 1 summarises information on the main metabolites of the kynurenine pathway and their neurobiological role.

Table 1. Density and porosity of studied travertine samples

Metabolite	Mechanism of action	Effect	Clinical significance
Kinurenine (KYN)	Substrate for both branches of the kynurenine pathway (KP); competes with tryptophan (Trp) for transport across the blood–brain barrier (BBB)	Reduces the availability of Trp for serotonin	↑ in cases of depression, sepsis

Table 1. *Continued*

Metabolite	Mechanism of action	Effect	Clinical significance
Quinoline acid (QA)	NMDA receptor agonist; induces oxidative stress through Fe^{2+} chelation	Excitotoxicity, apoptosis of hippocampal neurons	↑ in the CSF of patients with depression, Alzheimer's disease, and Parkinson's disease
Kynurenic acid (KYNA)	NMDA receptor and α7 nicotinic acetylcholine receptor antagonist	Neuroprotection, reduced excitability	Reduced in depression; the primary target of new antidepressants
3-Hydroxykinurenine (3-HK)	Generates reactive oxygen species (ROS); activates neuronal apoptosis	Neurotoxicity	↑ in cases of PTSD and schizophrenia
Picolinic acid (PA)	Neuroprotective and antioxidant; chelates metal ions	Anti-inflammatory, anti-apoptotic	↓ in cases of Alzheimer's disease

Note: ↑ – an increase in the level or activity of the relevant metabolite/parameter; ↓ – a decrease in the level or activity
Source: compiled by the authors based on A.H. Miller & C.L. Raison [6], A.A. Badawy *et al*. [7], K. Ogyu *et al*. [16]

IDO1 represents a key point of convergence between the HPA stress response, immune activation, and neurochemical alterations. Pro-inflammatory cytokines, particularly IFN-γ and IL-6, stimulate IDO1 activity, whereas cortisol released during the stress response initially suppresses IDO1 as part of its anti-inflammatory action. However, under conditions of chronic inflammation and glucocorticoid resistance, this inhibitory effect is lost. Consequently, persistent IDO1 hyperactivation reflects the simultaneous dysregulation of both neuroendocrine and immune regulatory systems. A clinical study by A.H. Miller & C.L. Raison [6] confirmed that kynurenine concentrations and the KYN/Trp ratio – a recognised marker of IDO1 activity – are significantly elevated in patients with major depressive disorder, PTSD, chronic fatigue syndrome, and in patients with cancer receiving cytokine-based immunotherapy. Notably, administration of IFN-α for chronic hepatitis C induces a clinical syndrome resembling major depressive disorder in a proportion of patients, predominantly through activation of the IDO1-dependent kynurenine pathway. Quinolinic acid activates NMDA receptors and promotes excitotoxic neuronal injury, while 3-hydroxykynurenine possesses potent pro-oxidant properties that further enhance neuronal damage and sustain neuroinflammation [8,20]. Together, these mechanisms establish the pathological vicious cycle of "neuroinflammation–neurotoxicity" (Fig. 2).

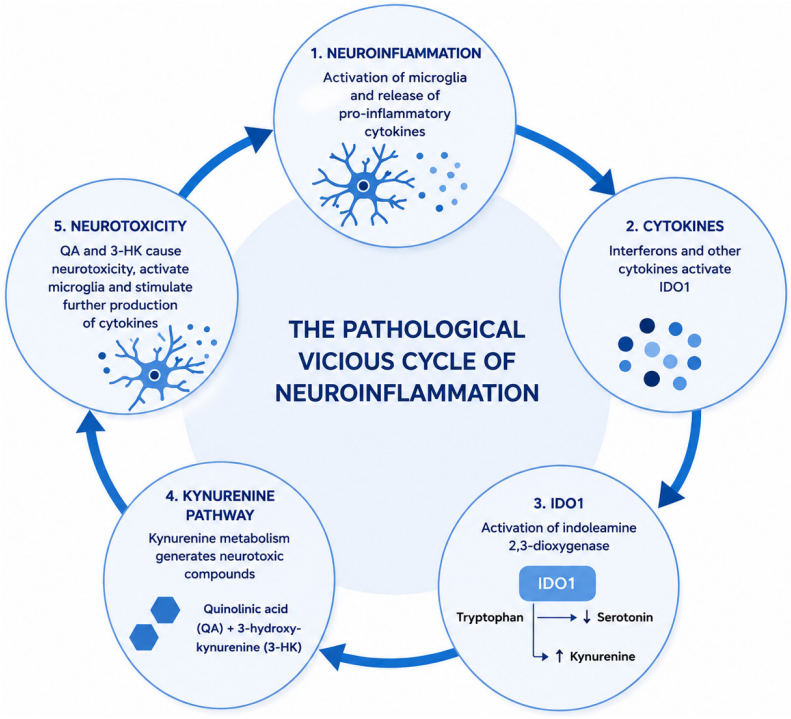

Figure 2. The pathological vicious cycle of "neuroinflammation–neurotoxicity"
Source: compiled by the authors based on A.H. Miller & C.L. Raison [6], A.A. Badawy *et al*. [7]

At the same time, it should be noted that activation of the kynurenine pathway is not a universal marker of depressive disorders: an increased KYN/Trp ratio and IDO1 activity are not observed in all patients with major depressive disorder, and their severity varies considerably depending on the degree of inflammation, comorbid somatic conditions and the study methodology. This limits the consideration of the kynurenine pathway as the sole or obligatory pathogenetic mechanism of depression and points to the need for further stratification of patients into biological subtypes [16-17]. The integrative model presented in Figure 3 illustrates the sequence of pathogenetic events from the primary trigger to the final clinical outcome.

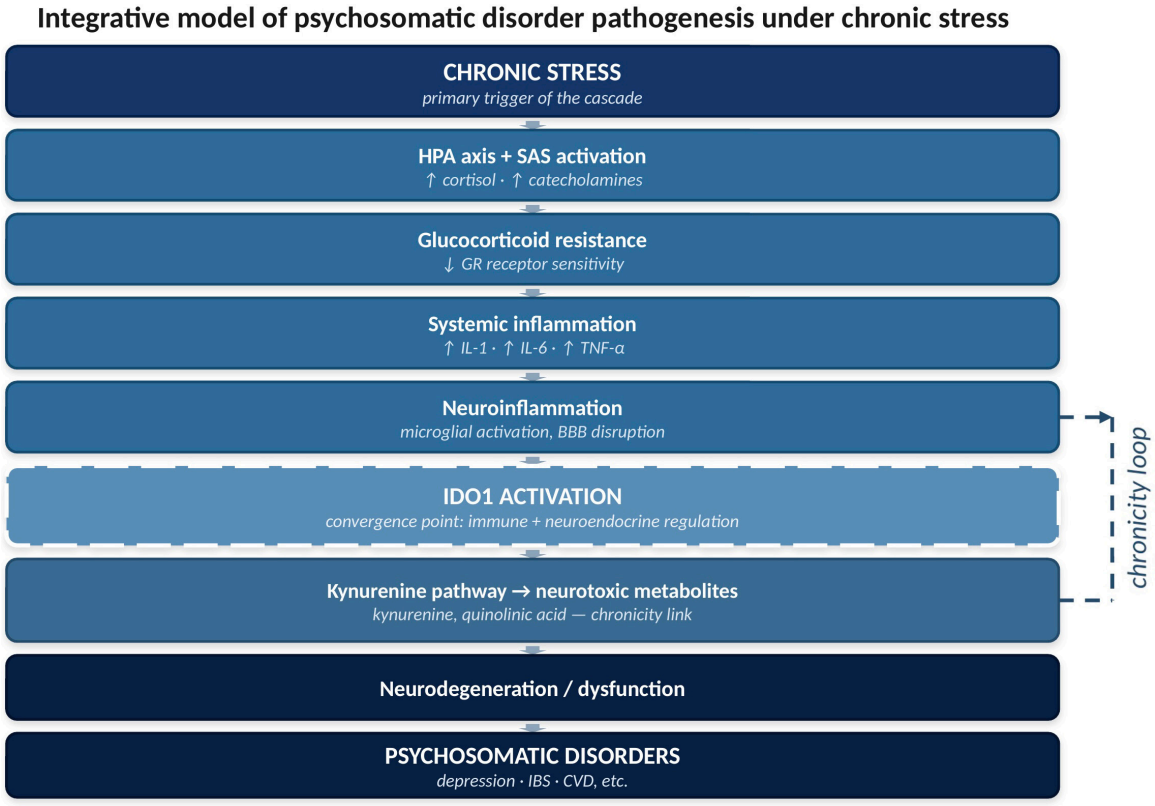

Figure 3. An integrative model of the pathogenesis of psychosomatic disorders in chronic stress
Source: compiled by the authors based on E. Knezevic *et al*. [3], C.M. Pariante [4], A.H. Miller & C.L. Raison [6]

The primary component of the model is chronic stress, which triggers a cascade through the activation of the HPA axis and the SAS, accompanied by increased levels of cortisol and catecholamines. The intermediate components of the model develop sequentially: glucocorticoid resistance (reduced receptor sensitivity to cortisol), loss of immune control, systemic inflammation (elevated IL-1, IL-6, TNF-α) and microglial activation with disruption of the blood-brain barrier, which together constitute a state of neuroinflammation. The key point of convergence in the model is the activation of IDO1, which integrates the immune (cytokine-dependent) and neuroendocrine (cortisol-dependent) signalling pathways, switching tryptophan metabolism to the kynurenine pathway. This forms an intermediate link in the chronicisation process: the accumulation of neurotoxic metabolites (kinurenine, quinolinic acid) sustains and exacerbates neuroinflammation, creating a self-reinforcing cycle – it is precisely this cyclical nature, rather than a linear sequence, that determines the chronic and progressive nature of the pathology. The final components of the model are neurodegeneration/dysfunction and the psychosomatic disorders themselves (depression, IBS, cardiovascular diseases, etc.). Based on the logic of the model, potential therapeutic targets include: glucocorticoid receptors (restoration of sensitivity), pro-inflammatory cytokines (anti-cytokine therapy), the IDO1 enzyme (IDO1 inhibitors) and the gut microbiome (probiotic correction of dysbiosis), as intervention at the convergence points is theoretically capable of breaking the self-perpetuating cycle of chronicity more effectively than targeting individual peripheral links in the cascade. An additional factor is the state of the gut microbiome [23-24]. Dysbiosis is accompanied by increased intestinal barrier permeability and the translocation of lipopolysaccharides into the bloodstream, which activates Toll-like receptors and enhances cytokine production, thereby sustaining systemic and neuroinflammation [4, 11, 25].

The concept of the MGBA axis has evolved from a hypothesis into a well-established neurobiological paradigm. It is a multi-level communication system comprising a neural channel involving the vagus nerve and the enteric nervous system, an immune channel involving cytokines, Toll-like receptors and microglial activation, an endocrine pathway involving hormones and neuropeptides, notably serotonin, peptide YY, GLP-1 and melatonin, as well as a metabolic pathway represented by short-chain fatty acids and other microbial metabolites [11]. The microbiome weighs approximately 1-2 kg, and the number of microbial cells is roughly equal to the number of cells in the body. Around 90-95% of the body's serotonin is synthesised in the gut by enterochromaffin cells – primarily under the regulatory influence of gut bacteria and their metabolites, but not directly by the bacteria themselves. The gut microbiome is also involved in the synthesis of GABA, acetylcholine, noradrenaline and dopamine in quantities sufficient for local neuroregulation. Furthermore, gut bacteria are the principal producers of short-chain fatty acids, which perform numerous systemic physiological functions and act as histone deacetylase inhibitors, thereby serving as important epigenetic regulators [23]. Psychological stress and elevated cortisol alter the composition of the microbiome through several mechanisms. Sympathetic activation reduces blood flow to the gut and the secretion of protective mucus, which suppresses the commensal microflora. Cortisol increases intestinal permeability by disrupting tight junctions in enterocytes, in particular by reducing levels of claudin-1 and ZO-1, as a result of which bacterial antigens, such as lipopolysaccharide, enter the bloodstream and activate Toll-like receptor 4, triggering systemic inflammation. Catecholamines further stimulate the growth of pathogenic bacteria, notably Escherichia and Salmonella [19].

The microbiome's feedback effect on the hypothalamic-pituitary-adrenal axis is mediated via microbial metabolites of tryptophan and short-chain fatty acids, which regulate serotonin secretion by enteroendocrine cells and influence signalling via the vagus nerve to the hypothalamus. Bacterial lipopolysaccharides are also capable of stimulating the secretion of corticotropin-releasing hormone. Certain strains of *Lactobacillus* and *Bifidobacterium* produce GABA and reduce cortisol levels during stress [23]. A systematic review by R.G. Xiong *et al.* [9] showed that in depression and anxiety disorders, the microbiome is characterised by a reduction in anti-inflammatory producers of short-chain fatty acids, such as *Faecalibacterium prausnitzii* and *Roseburia*, and an increase in pro-inflammatory taxa, particularly Enterobacteriaceae. A reduction in *Faecalibacterium* is one of the most consistently reported markers of depression. Increased intestinal permeability during chronic stress triggers a systemic inflammatory cascade, involving the activation of Toll-like receptor 4, the nuclear factor NF-κB, the production of pro-inflammatory cytokines and the subsequent activation of microglia, leading to the development of neuroinflammation. The "microbiota-inflammasome-brain" theory highlights the role of the NLRP3 inflammasome as an additional mechanism in depression, particularly in patients with inflammatory bowel disease. Therapeutic data from A. Icenhour *et al.* [23] demonstrated that probiotics, specifically *Lactobacillus helveticus* R0052 in combination with *Bifidobacterium longum* R0175, reduce cortisol levels and symptoms of anxiety and depression, whilst the use of *Lactobacillus plantarum* JYLP-326 and *Bifidobacterium breve* CCFM1025 enhances the efficacy of standard pharmacotherapy, accompanied by normalisation of the microbiome and tryptophan metabolism. However, the clinical evidence base regarding the efficacy of probiotics in psychiatry remains inconsistent: the results of individual randomised trials are contradictory, the effects are often strain-specific and not transferable to other probiotic preparations, and most studies have small sample sizes and short follow-up periods. Thus, the role of probiotics as an adjunctive therapy for mental disorders requires confirmation in larger-scale and methodologically sounder clinical trials before they can be recommended for widespread clinical use [9, 23].

Irritable bowel syndrome is the most common functional gastrointestinal disorder, with a prevalence of 10-15% and a higher incidence in women; it is characterised by chronic abdominal pain, bowel dysfunction and bloating without structural abnormalities. According to the Rome IV criteria and the DGBI concept, IBS is regarded as a disruption of the brain-gut axis, rather than a purely "psychological" or "organic" disease. Psychological stress is a trigger for flare-ups in over 70% of patients; at the same time, IBS itself perpetuates chronic stress via a bidirectional loop. Early childhood stress is associated with the development of IBS through epigenetic changes in the HPA axis, in particular NR3C1 methylation [18]. Studies by A. Icenhour *et al*. [23] and L. Fardet *et al*. [24] demonstrated hyperreactivity of the HPA axis in IBS: an increased ACTH response to CRH, reduced activation of the medial prefrontal cortex and an enhanced intestinal motor response, which is associated with visceral hypersensitivity. CRH and cortisol accelerate intestinal transit, activate mast cells, increase intestinal permeability and alter the microbiome, thereby promoting microinflammation. An increase in CRH-positive neurons in the submucosal plexus has also been observed, indicating local hyperactivation of the CRH system [18]. Thus, the pathogenesis of psychosomatic disorders involves an interaction of neuroendocrine, immune and metabolic mechanisms, at the centre of which lies a vicious circle of glucocorticoid resistance, chronic inflammation, activation of the kynurenine pathway and the neurotoxic effects of its metabolites [4, 6, 9]. This is consistent with

current concepts in psychoneuroimmunology, notably those of A. Farzi *et al*. [25] and X. Gong *et al.* [26], and justifies the need for an integrative approach to therapy. Chronic neuroinflammation also causes metabolic changes in the CNS through the activation of IDO1, which shifts tryptophan metabolism towards the kynurenine pathway, leading to the accumulation of neurotoxic metabolites that further activate microglia and perpetuate the pathological "vicious circle" of neuroinflammation and neurotoxicity.

CONCLUSIONS

1. Based on a review of the literature, this study systematises current understanding of the role of stress-mediating systems – the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal system – in the development of psychosomatic disorders, which manifest through neuroendocrine, immune and metabolic mechanisms.

2. A review of the literature has shown that a key link in the pathogenesis is the dysregulation of glucocorticoid signalling in the form of glucocorticoid resistance, which leads to a loss of control over the inflammatory response and the development of systemic inflammation.

3. According to the literature, neuroinflammation acts as a central pathogenetic mechanism, arising as a result of microglial activation, increased levels of pro-inflammatory cytokines and impaired blood-brain barrier permeability.

4. An analysis of current sources provides grounds for asserting that the kynurenine pathway of tryptophan metabolism, via IDO1 activation, is a key point of convergence between the immune and neuroendocrine systems, contributing to the accumulation of neurotoxic metabolites and the development of cognitive and affective disorders.

5. Based on a review of the literature, the role of the microbiome-gut-brain axis as an important modifier of stress-induced changes has been substantiated, through its influence on intestinal barrier permeability, the production of lipopolysaccharides and the activation of systemic inflammation.

6. Based on a synthesis of scientific data, an integrative pathogenetic model has been proposed that unites hyperactivation of the HPA axis, neuroinflammation, kynurenine metabolism, epigenetic changes and microbiome dysbiosis into a single interconnected cascade.

7. Based on a review of the literature, a pathological "vicious circle" has been identified, in which chronic stress, via glucocorticoid dysfunction and immune activation, sustains a self-reinforcing system of neuroinflammation that underlies the chronicity of psychosomatic disorders.

8. An analysis of the current scientific literature supports the need to view psychosomatic pathology as a systemic, multifactorial process in which the interaction of neuroendocrine, immune and microbiome regulation plays a key role.

Limitations of the study. The study has a number of limitations. Firstly, the narrative nature of the review, which incorporates elements of a systematic search, does not rule out subjectivity in the selection and interpretation of sources. Secondly, a significant proportion of the mechanisms analysed (in particular, the role of IDO1, the microbiome and epigenetic changes) have been studied predominantly in animal models or in small clinical samples, which limits the direct transfer of findings to clinical practice. Thirdly, the heterogeneity of the nosological groups (depression, PTSD, IBS, cardiovascular disorders), which were considered collectively within the psychosomatic model, complicates the formulation of universal pathogenetic patterns.

Prospects for further research. Promising areas for further research include: conducting systematic reviews and meta-analyses for individual nosological groups, taking into account the specific nature of their pathogenetic mechanisms; clinical validation of the proposed integrative model through multicentre cohort studies; investigating IDO1 and metabolites of the kynurenine pathway as potential biomarkers of severity and prognosis in psychosomatic disorders; and studying probiotic and targeted psychopharmacological interventions aimed at key convergence points in the described pathogenetic cascade.

ACKNOWLEDGEMENTS

None.

FUNDING

This study forms part of the planned research project of the Department of Pathophysiology at the Bogomolets National Medical University entitled "Pathogenetic mechanisms and rationale for the correction of organ damage induced by external factors affecting the organism", state registration No. 0126U001773.

CONFLICT OF INTEREST

None.

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Марина Цвєткова
Старший викладач
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0000-0002-8796-009x

Наталія Корж
Студент
Національний медичний університет імені О. О. Богомольця
01601, бульвар Тараса Шевченка, 13, м. Київ, Україна
https://orcid.org/0009-0007-7846-4576

Павло Петрушанко
Аспірант
Приватний вищий навчальний заклад «Київський медичний університет»
01004, вул. Велика Васильківська, 17-А, м. Київ, Україна
https://orcid.org/0009-0005-0212-9961

Психонейроімунологічні механізми стрес-індукованих психічних і психосоматичних розладів

Анотація
Актуальність. Психосоматичні розлади становлять значущу медико-біологічну проблему, оскільки їхній розвиток пов'язаний із хронічною активацією стрес-реалізуючих систем, зокрема гіпоталамо-гіпофізарно-надниркової осі та імунозапальних механізмів, що сприяють формуванню й прогресуванню соматичної патології. Попри значний обсяг досліджень, патогенез психосоматичних розладів потребує інтегративного узагальнення з урахуванням взаємодії нейроендокринних, імунозапальних і метаболічних механізмів, зокрема нейрозапалення, глюкокортикоїдної резистентності, активації кінуренінового шляху та дисбіозу кишечника. Актуальність дослідження зумовлена необхідністю систематизації цих даних і формування цілісної патогенетичної моделі, що може слугувати основою для вдосконалення діагностики й терапії психосоматичних розладів.
Мета. Систематизувати сучасні наукові дані щодо психонейроімунологічних механізмів розвитку стрес-індукованих психічних і психосоматичних розладів шляхом аналізу нейроендокринних, імунозапальних, нейромедіаторних та мікробіомних змін, які виникають під впливом хронічного стресу та беруть участь у формуванні психосоматичної патології.
Матеріали та методи. У дослідженні проведено наративний аналіз сучасних наукових публікацій у базах даних PubMed, PMC, Scopus за 2015-2025 роки (187 знайдених, 26 включено до фінального аналізу). Використано методи системного аналізу, узагальнення та порівняння наукових даних.
Результати. У роботі систематизовано інтегративних підхід до патогенезу психосоматичних розладів, що об'єднує нейроендокринні, імунні, метаболічні та мікробіомні механізми в єдиний взаємопов'язаний каскад. Виділено ключові точки конвергенції (гіпофізарно-надниркова вісь, індоламін-2,3-діоксигеназа 1, нейрозапалення) та обґрунтовано концепцію патологічного «порочного кола», що забезпечує хронізацію процесу. Показано, що хронічний стрес через глюкокортикоїдну резистентність, нейрозапалення та кінуреніновий метаболізм формує самопосилюване патологічне коло, яке є основою хронізації психосоматичних розладів.
Висновки. Психосоматична патологія має розглядатися як системний мультифакторний процес, де ключову роль відіграє взаємодія нейроендокринної, імунної та мікробіомної регуляції.
Практична цінність. Отримані узагальнення можуть бути використані для поглиблення розуміння патогенезу психосоматичних захворювань та визначення перспективних терапевтичних мішеней.
Ключові слова: гіпоталамо-гіпофізарно-наднирникова вісь; глюкокортикоїдна резистентність; нейрозапалення; кінуреніновий шлях; вісь «мікробіом – кишківник – мозок».

MEDICAL SCIENCE OF UKRAINE

Vol. 22, No. 2
2026

Executive Secretary:
Iana Ushko
Technical secretary:
Nina Vasko

Approved for publication 28.05.2026
Format 60×84/8
Conventional printed sheets 23
Circulation 100 copies

Publisher: Bogomolets National Medical University
01601, 13 T. Shevchenko Blvd., Kyiv, Ukraine
E-mail: msu@medjournal.org.ua
https://nmuofficial.com/zhurnal-medychna-nauka-ukrayiny/