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THE IMPACT OF AMINO ACIDS ON CHANGES IN FLUID AND FAT TISSUE CONTENT IN RATS WITH TYPE 2 DIABETES MELLITUS

Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine

UDC 616.379-008.64-018.2-074:547.466]-092.9

M. I. Isachenko, O. V. Melnikova, O. V. Khorolets

THE IMPACT OF AMINO ACIDS ON CHANGES IN FLUID AND FAT TISSUE CONTENT IN RATS WITH TYPE 2 DIABETES MELLITUS

Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine

The **aim of the study** was to determine the body composition of rats with experimental type 2 diabetes mellitus, and to assess the impact of amino acid correction on these parameters using bioelectrical impedance analysis.

Materials and methods. Type 2 diabetes mellitus was induced with streptozotocin (30 mg/kg) in rats with insulin resistance. Two experimental subgroups received L-arginine or N-acetyl-L-cysteine, while the diabetic control group received drinking water. Glucose levels, body weight, and body composition were measured.

Results. Streptozotocin administration caused persistent hyperglycemia and body mass reduction, primarily due to fat loss, despite a slight increase in lean body mass. However, the lean body mass remained lower than in the control group. These changes led to overall dehydration caused by reduced extracellular and intracellular fluid volumes, while their ratio was preserved. L-arginine and N-acetyl-L-cysteine reduced glucose levels by 14 % and 13 %, respectively, compared to the untreated diabetic group. Despite the reduction in glucose levels, all diabetic subgroups experienced progressive dehydration, without significant differences in total body weight, fat, or lean body mass mass. The fat-to-lean mass ratio in amino acid-treated groups was 1:5, significantly different from the 1:6 ratio observed in untreated diabetic rats.

Conclusion. Modeling type 2 diabetes mellitus in rats with insulin resistance leads to changes in body composition in rats, including fat mass loss and general dehydration. Amino acid correction reduces glucose levels but does not prevent alterations in water and fat metabolism.

Keywords: bioimpedance analysis of body composition, type 2 diabetes mellitus, L-arginine, N-acetyl-L-cysteine, rats.

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М. І. Ісаченко, О. В. Мельнікова, О. В. Хоролець

ВПЛИВ АМІНОКИСЛОТ НА ЗМІНИ ВМІСТУ РІДИНИ ТА ЖИРОВОЇ ТКАНИНИ У ЩУРІВ ІЗ ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ

Запорізький державний медико-фармацевтичний університет, Запоріжжя, Україна

Метою дослідження було визначення складу тіла щурів з експериментальним цукровим діабетом 2-го типу (ЦД2), а також оцінка впливу корекції амінокислотами на ці показники за допомогою біоімпедансного аналізу.

Для реалізації мети тваринам проводили визначення концентрації глюкози, маси тіла й біоімпедансний аналіз складу тіла.

Моделювання ЦД2 на фоні інсулінорезистентності призводить до змін у складі тіла щурів, включно з втратою жирової маси та загальною дегідратацією. Корекція амінокислотами знижує рівень глюкози, але не попереджає змін у водному та жировому обміні.

Ключові слова: біоімпедансний аналіз складу тіла, цукровий діабет 2-го типу, L-аргінін, N-ацетил-L-цистеїн, щури.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine disorders worldwide, characterized by insulin resistance and impaired insulin secretion [1]. According to data from the World Health Organization, the number of people suffering from this condition is growing year by year, driven by lifestyle changes, particularly insufficient physical activity, unhealthy diets, and rising obesity rates among the population [2].

In the search for new approaches to the treatment and management of T2DM and its complications, researchers are focusing on various pharmacological agents, including amino acids (AA) [3], the most promising of which are L-arginine [4] and N-acetyl-L-cysteine [5]. These compounds demonstrate potential in regulating glucose metabolism, reducing insulin resistance, and improving pancreatic β-cell function [4; 5]. Experimental studies investigating the efficacy of amino acids are important for determining their role in the treatment of T2DM, as they

may offer new strategies for disease management and improving patient condition [6].

One of the common methods for assessing the metabolic status of patients with T2DM is bioelectrical impedance analysis of body composition (BIA) [7]. This method provides an accurate determination of the percentage ratio between muscle and fat mass, as well as the body's hydration level. BIA provides valuable information about changes in the bodies of patients with diabetes that may be associated with the development of complications or the effectiveness of treatment [8].

Studies conducted on animals, such as rats, also play an important role in investigating the mechanisms of T2DM, allowing researchers to detect changes in metabolism and assess the impact of various therapeutic interventions on body composition [9]. Due to its sensitivity and accuracy, BIA can help detect early signs of metabolic disorders, which is critically important for developing new strategies for the treatment and prevention of diabetes [10].

Based on the above, **the aim of the study** was to determine the body composition of rats with experimental type 2 diabetes mellitus, as well as to evaluate the impact of amino acid correction on these parameters using bioelectrical impedance analysis.

Materials and Methods

All studies were conducted at the Educational and Research Medical Laboratory Center with a vivarium at Zaporizhzhia State Medical and Pharmaceutical University (Certificate of Technical Competence No. 181/23 issued by the Ministry of Health of Ukraine on December 21, 2023, valid until December 20, 2028), in accordance with the "General Ethical Principles of Animal Experiments" approved by the 3rd National Congress (Kyiv, 2007), and the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes" (Strasbourg, 1986). During the experiment, the Law of Ukraine "On the Protection of Animals from Cruel Treatment" No. 27, Art. 230, 2006, as amended by Law No. 1759-VI (1759-17) of December 15, 2009, Information of the Verkhovna Rada of Ukraine, 2010, No. 9, Art. 76, General Ethical Principles of Animal Experiments (First National Congress on Bioethics, September 20, 2001, Kyiv), Ethical Principles of Animal Experiments (I National Congress on Bioethics, September 20, 2001, Kyiv), Code of Ethics for Scientists of Ukraine (National Academy of Sciences of Ukraine, 2009), and the approval of the Local Bioethics Committee at ZSMPhU (Protocol No. 2 dated March 15, 2023). The study was conducted as part of ZSMPhU's initiative-based research project on "Pathogenesis and Pathomorphology of Endocrine, Cerebrovascular, Neoplastic, and Non-neoplastic Diseases in Patients and in Experiments" (State registration number 0125U002639), duration: 2025-2029.

Study design

Type 2 diabetes mellitus was induced in normoglycemic, normotensive male Wistar rats aged 16–20 months, which were divided into 2 experimental groups and 3 subgroups (Fig. 1).

Before the induction of T2DM, male Wistar rats with normal blood pressure and glucose levels were subjected to a model of insulin resistance using the appropriate method [11], followed by adherence to the described diet throughout the experiment.

To induce T2DM, a single dose of streptozotocin (Streptozotocin, S0130-1G, Sigma-Aldrich) in 50 mM sodium citrate buffer (pH 4.5) at a dose of 30 mg/kg intraperitoneally, followed by drinking glucose solution according to the following schedule: day 1 – 20 % solution, days 2–3 – 10 % solution, days 4–5 – 5 % solution, and from day 6 onward – drinking pure water. Rats in the control group received only citrate buffer intraperitoneally in the same volume. Two weeks after streptozotocin administration, only animals with a glucose concentration > 15 mmol/L in a blood sample from the tail vein were included in the experiment. Measurements were performed using a Contour Plus glucometer (BAYER CONSUMER CARE AG, Switzerland) and Contour Plus test strips.

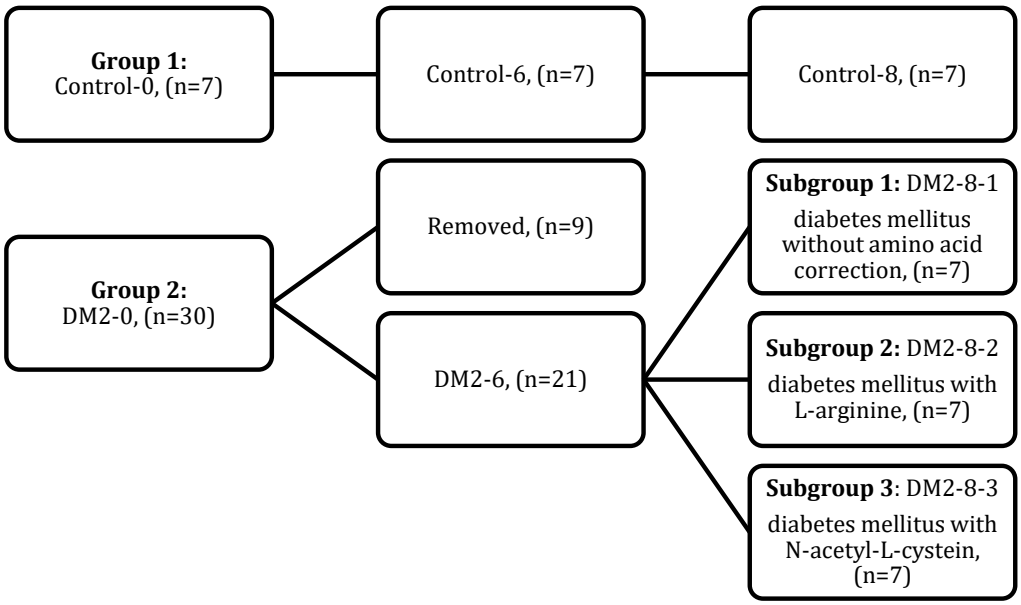

Fig. 1. Study design

The animals were then kept for another 4 weeks under standard conditions with blood glucose monitoring every 2 weeks. Starting from week 7, the rats were divided into 3 subgroups. Subgroup DM2-8-1 consisted of rats with T2DM without amino acid correction; subgroup DM2-8-2 consisted of rats with T2DM to which a solution of L-arginine (2-amino-5-guanidinovaleric acid, C6H14N4O2, CHDA, China) at a dosage of 1.5 g/kg/L per day for 2 weeks, and subgroup 3 – DM2-8-3 – consisted of T2DM rats treated with N-acetyl-L-cysteine (N-acetyl-L-cysteine, C5H9NO3S, China) at the same dosage.

Methodology for conducting bioelectrical impedance analysis of body composition

Prior to performing the bioelectrical impedance analysis (BIA), it was mandatory to enter the animals' biometric data (body weight in grams and rectoanal length in centimeters) into the Vet BIS1 impedance analyzer (ImpediVet, Australia) in accordance with the manufacturer's instructions [12]. The study methodology is detailed in previous articles [11; 13]. The calculated body composition parameters were: total body water (TBW) volume, in milliliters and as a percentage of body weight; extracellular fluid (ECF) and intracellular fluid (ICF) in milliliters and as a percentage of BW; lean body mass (LBM) and fat body mass (FBM) in grams and as a percentage of body weight (Fig. 2) [13]. For anesthesia of the animals, "Medison" (medetomidine hydrochloride) was used, followed by administration of its antidote – "Reverson" (atipamezole hydrochloride) – after the study was completed.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) in the Statistica software (license No. JPZ804I382130ARCN10-J). Continuous variables are presented as the mean (M) ± standard error of the mean (m). All parameters were compared using one-way ANOVA, followed by Tukey's two-sided post-hoc test for multiple comparisons when significant. A two-sided p-value < 0.05 was considered statistically significant for all tests.

Research results and their discussion

The results of the blood glucose concentration measurements in rats of the experimental groups and subgroups are presented in Figure 3 (Fig. 3A–B).

In rats of the DM2 group, a statistically significant increase in glucose concentration was observed compared to control indices at weeks 2, 4, and 6 of the study (Fig. 3A). Administration of L-arginine to rats of the DM2-8-2 subgroup had a significant effect on glucose concentration, leading to a 14 % reduction compared to the untreated DM2-8-1 subgroup, while in the DM2-8-3 subgroup treated with N-acetyl-L-cysteine, only a tendency toward a 13 % decrease was observed (Fig. 3B).

Within 5 weeks following streptozotocin administration to rats with diabetes mellitus, no statistically significant changes in body weight were observed compared to the control group, and neither amino acid had a statistically significant effect on body weight at weeks 7 and 8 of the experiment (Table 1).

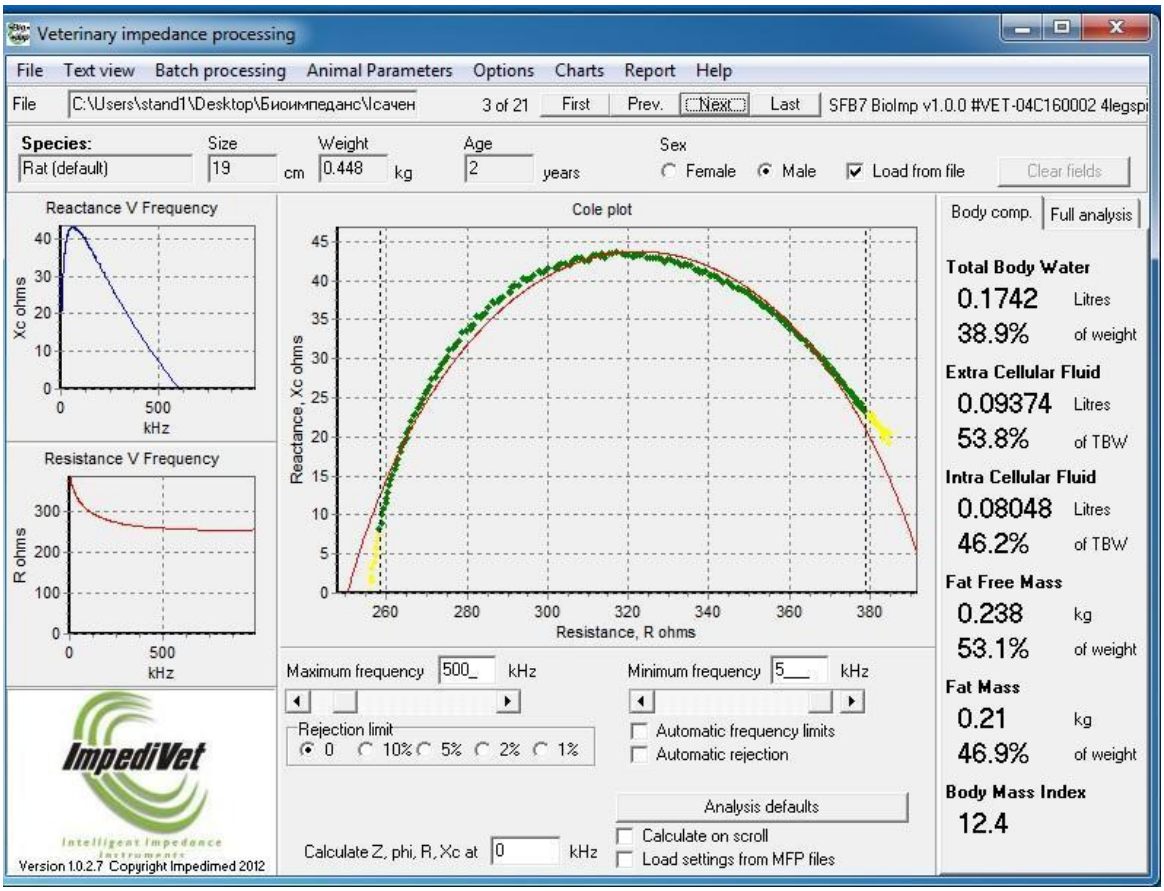

Fig. 2. Analysis of body composition in rats from the T2DM group after Phase 1 and before streptozotocin administration

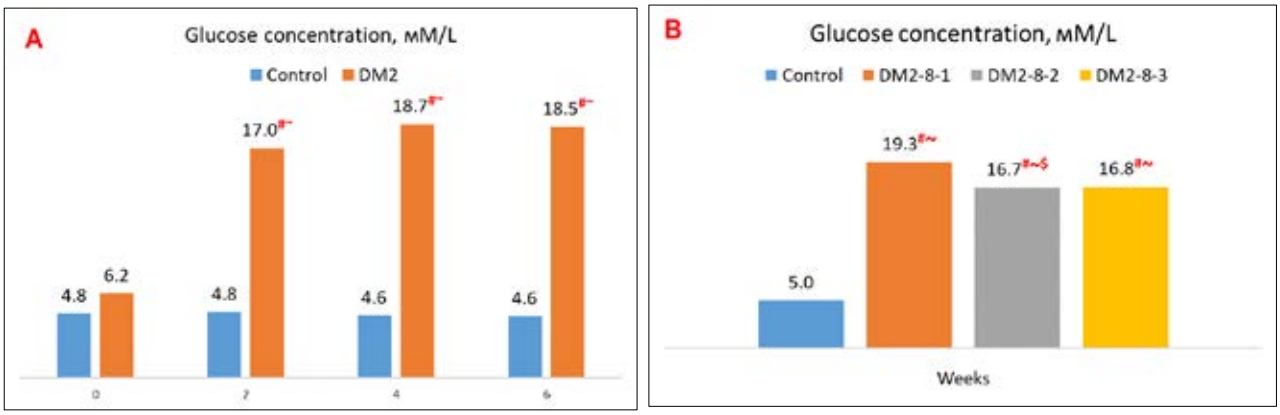

Fig. 3. Changes in glucose concentration in rats from the experimental groups, M ± m

Note 1: # – statistically significant difference in DM2 values compared to those of the control group at the corresponding time point ($p < 0.05$).

Note 2: ~ – statistically significant difference in group parameters at weeks 6 and 8 compared to those of the same group at week 0 ($p < 0.05$).

Note 3: $ – statistically significant difference in parameters of subgroups DM2-8-2 and DM2-8-3 compared to parameters of subgroup DM2-8-1 ($p < 0.05$)

Table 1

Body composition parameters in rats of the experimental groups, M ± m

Groups		0 weeks		6 weeks		8 weeks			
Parameters		Control	DM2	Control	DM2	Control	DM2-8-1	DM2-8-2	DM2-8-3
Rat body mass	g	324 ± 4	352 ± 7#	367 ± 4~	352 ± 6#	377 ± 5~	359 ± 13	362 ± 11	362 ± 11
TBW	ml	0.177 ± 0.007	0.167 ± 0.004	0.211 ± 0.007~	0.160 ± 0.003#	0.212 ± 0.002~	0.137 ± 0.006#~	0.138 ± 0.005#~	0.139 ± 0.003#~
	%	54.5 ± 1.8	47.5 ± 0.7#	57.4 ± 1.3	45.6 ± 0.5#~	56.1 ± 0.5	38.1 ± 0.3#~	38.0 ± 0.6#~	38.4 ± 0.3#~
ECF	ml	0.082 ± 0.003	0.069 ± 0.002#	0.097 ± 0.003~	0.075 ± 0.002#~	0.096 ± 0.001~	0.068 ± 0.003#	0.070 ± 0.002#	0.072 ± 0.002#
	%	46.5 ± 0.7	41.6 ± 1.2#	45.8 ± 0.5	47.1 ± 0.7~	45.2 ± 0.7	49.6 ± 1.6#~	50.8 ± 0.7#~	51.6 ± 0.5#~
ICF	ml	0.095 ± 0.004	0.098 ± 0.003	0.111 ± 0.003~	0.085 ± 0.002#~	0.116 ± 0.002~	0.069 ± 0.004#~	0.068 ± 0.003#~	0.067 ± 0.001#~
	%	53.5 ± 0.7	58.4 ± 1.2#	54.2 ± 0.5	52.9 ± 0.7~	54.8 ± 0.7	50.4 ± 1.6#~	49.2 ± 0.7#~	48.4 ± 0.5#~
FBM	g	0.048 ± 0.001	0.129 ± 0.003#	0.057 ± 0.002~	0.062 ± 0.002~	0.055 ± 0.002~	0.052 ± 0.003~	0.057 ± 0.002~	0.060 ± 0.003~
	%	14.8 ± 0.3	36.7 ± 0.5#~	15.4 ± 0.3	17.6 ± 0.5#~	14.5 ± 0.5	14.6 ± 0.5~	15.6 ± 0.5~	16.6 ± 0.6~$
LBM	g	0.276 ± 0.005	0.223 ± 0.005#	0.312 ± 0.004~	0.290 ± 0.005#~	0.323 ± 0.004~	0.307 ± 0.01~	0.306 ± 0.010~	0.301 ± 0.009#~
	%	85.2 ± 0.3	63.3 ± 0.5#	84.6 ± 0.3	82.4 ± 0.5#~	85.5 ± 0.5	85.4 ± 0.5~	84.4 ± 0.5~	83.4 ± 0.6#~$

Note 1: # – statistically significant difference in the indicators of group DM2 compared to those of the control group at the corresponding time point ($p < 0.05$).

Note 2: ~ – statistically significant difference in the indicators of the groups at weeks 6 and 8 compared to the indicators of the same group at week 0 ($p < 0.05$).

Note 3: $ – statistically significant difference in the indicators of the subgroups DM2-8-2 and DM2-8-3 weeks compared to the indicators of subgroup DM2-8-1 ($p < 0.05$).

As we noted earlier, prior to the induction of T2DM in rats of the DM2-0, obesity had developed, that was accompanied by changes in body composition, a relative deficiency of TBW due to extracellular dehydration, and a redistribution of fluid resulting in intracellular hyperhydration (week 0 values) (Table 1) [11].

Six weeks of T2DM led to a statistically significant 7 % loss in LBM compared to the control group, while changes in FBM showed no significant differences, with the FBM:LBM ratio returning to near-control levels – 1:5. When compared to the animals' condition prior to streptozotocin administration, the changes were more pronounced: a decrease in FBM by a 52 % accompanied by a 30 % increase in LBM. Hyperglycemia, which persisted for 6 weeks, led to generalized dehydration (a 24 % decrease in absolute TBW and a 21 % decrease in relative indicator compared to the control group). These changes occurred due to the loss of both ECF and ICF, with their ratio to TBW remaining within the normal range (1.0 : 1.1) (see Table 1).

The addition of amino acids to drinking water for two weeks had no statistically significant effect on the absolute

values of FBM and LBM in rats of the DM2-8-2 and DM2-8-3 subgroups compared to rats that drank pure water (DM2-8-1) (see Table 1). Analysis of the relative values of FBM and LBM in animals who were administered N-acetyl-L-cysteine (DM2-8-3) revealed a significant decrease in FBM accompanied by an increase in LBM compared to rats without correction (DM2-8-1), but the ratio of FBM to LBM in both treatment subgroups remained at the same level –1:5 versus 1:6 in the DM2-8-1 rats (see Table 1).

Analysis of body water at week 8 revealed a progression of overall dehydration in all three subgroups, with no statistically significant differences when comparing them to one another (see Table 1). The observed changes were caused by an absolute decrease in both ECF and ICF, with no statistically significant influence of amino acids on the studied parameters. A comparison of relative indices revealed a redistribution of fluid relative to TBW toward extracellular hyperhydration. This altered the ECF:ICF ratio, which was 1.0:1.0 in all three subgroups (see Table 1).

In recent years, L-arginine has attracted significant attention as a potential agent for metabolic disorders correction in patients with T2DM [6]. L-arginine is an amino acid that performs several important functions in the body. Studies have shown that L-arginine can lower blood glucose level, which is crucially important for managing this disease. It promotes vasodilation via nitric oxide (NO) that improves glucose uptake by cells. In addition, L-arginine can stimulate insulin secretion by pancreatic β-cells and increase tissue sensitivity to insulin, that contributes to blood glucose decrease [4]. L-arginine may also influence lipid metabolism and inflammatory processes, which often accompany T2DM. Reducing the intensity of inflammation may decrease insulin resistance and improve patients' overall metabolic status. Studies have shown that patients receiving L-arginine demonstrated a significant reduction in HbA1c levels, which is an important indicator of long-term glycemic control [14].

N-acetyl-L-cysteine is also gaining attention as a potential glucose-lowering agent. This compound, known for its antioxidant properties, may significantly influence glucose metabolism and overall health in patients [5]. One of its key mechanisms of action is the ability to increase glutathione levels, a potent antioxidant that protects cells from oxidative stress, and may enhance cellular insulin sensitivity [6]. It has been established that N-acetyl-L-cysteine can modulate glucose metabolism by regulating the activity of enzymes involved in glycolysis and gluconeogenesis. This effect may lead to a reduction in endogenous glucose production in the liver and improving glucose utilization in peripheral tissues [15]. However, our study revealed only a trend toward a decrease in glucose concentration, which is likely due to an insufficient duration of administration or an inappropriate dose.

It is worth noting that, despite the promising findings, research on L-arginine and N-acetyl-L-cysteine in the context of T2DM are currently in the early stages of investigation. Further clinical and experimental studies are required to elucidate their potential mechanisms of action on the pathogenesis of T2DM, as well as to determine optimal dosing regimens, treatment duration, and potential side effects.

The use of BIA provides new opportunities for assessing metabolic changes in body composition in the context of T2DM [7]. The value of this method is based on its low invasiveness and greater informativeness compared to classical mass spectrometry, which allows for the in vivo assessment of changes in metabolic direction in rats in stage 2 following streptozotocin administration. In our experiment, it was found that over 6 weeks, body weight did not change significantly relative to the control and baseline values in the T2DM group of rats. However, the ratio of FBM to LBM changed from 1:2, indicating marked obesity in the animals, and after the induction of hyperglycemia, this ratio shifted to 1:5 due to a predominant loss of fat mass. One of the likely causes of FBM loss is enhanced lipid catabolism, resulting from the use of lipids as a primary energy source. Although such changes may seem positive, they actually indicate metabolic disturbances resulting from endocrine dysregulation [16]. This leads to an increase in free fatty acid levels and triggers inflammatory processes, which, in turn, exacerbate insulin resistance and complicate glucose control. Inflammation may also intensify catabolic processes in muscles, potentially leading to further loss of muscle mass [16]. On the other hand, monitoring body fat reduction may play an important role in a comprehensive approach to T2DM therapy promoting improved insulin sensitivity and enhancing carbohydrate metabolism [17].

In addition, BIA can help detect changes in hydration levels, which is critically important for correcting fluid and electrolyte imbalances and optimizing therapeutic strategies. One of the main causes of dehydration in rats with T2DM is a disruption of glucose-insulin balance. High blood glucose levels lead to osmotic diuresis and glucosuria, which, in turn, result in dehydration. This condition may have serious consequences, including a decrease in circulating blood volume, electrolyte imbalance, and impaired organ function. Moreover, dehydration can result in increased plasma sodium levels, which may impair tissue sensitivity to insulin. This complicates glycemic control and may lead to further progression of T2DM [16].

Conclusions

1. The administration of streptozotocin to insulin-resistant rats induces persistent hyperglycemia, which leads to a decrease in body weight compared to baseline values; however, this difference was not statistically significant compared to the control group. The weight loss occurred due to a reduction in adipose tissue accompanied by an increase in lean body mass; nevertheless, when compared to the control group, this proportion was lower. These changes led to general dehydration due to a decrease in the volume of extracellular and intracellular fluid while maintaining their ratio.

2. Administration of L-arginine led to a 14 % decrease in glucose concentration compared to the subgroup of rats with untreated diabetes; however, administration of N-acetyl-L-cysteine was accompanied only by a tendency toward a decrease. At the same time, progression of total, extracellular, and intracellular dehydration was observed in

all 3 subgroups, without a significant effect on body weight, fat mass, and lean body mass. The fat-to-lean body mass ratio in both subgroups receiving amino acids remained at the same level – 1:5 that differed significantly from the 1:6 ratio in the subgroup of rats without amino acid administration.

3. Modeling of type 2 diabetes mellitus against a background of insulin resistance leads to changes in the body composition of rats, including loss of fat mass and general dehydration. Correction with amino acids reduces glucose levels but does not prevent changes in water and fat metabolism.

Conflict of Interest
None declared.
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INVESTIGATION OF THE IMMUNOMODULATORY EFFECTS OF GABAPENTIN ON MAMMALIAN MACROPHAGE CELLS

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INVESTIGATION OF THE IMMUNOMODULATORY EFFECTS OF GABAPENTIN ON MAMMALIAN MACROPHAGE CELLS

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Background. Recent research has increasingly highlighted the intricate crosstalk between the immune and nervous systems, particularly in the context of neurological pathogenesis. Gabapentin, a structural analogue of γ-aminobutyric acid (GABA) conventionally prescribed for epilepsy and neuropathic pain, is now gaining attention for its potential immunomodulatory properties. While it is well established that the nervous, endocrine, and immune systems coordinate through a complex network of shared signaling molecules, the specific impact of gabapentin on macrophages – the primary effectors of innate immunity that also orchestrate adaptive responses via antigen presentation – remains poorly understood.

Methods. To elucidate gabapentin's immunomodulatory capabilities, the murine macrophage cell line J774.2 was exposed to varying concentrations of the drug in the presence or absence of lipopolysaccharide (LPS). Following treatment, the secretion profiles of major inflammatory cytokines, specifically IL-6, TNF-α, IL-12p40, and GM-CSF, were quantified utilizing enzyme-linked immunosorbent assays (ELISA).

Results. Our analyses revealed that gabapentin exerted a significant, dose-dependent suppressive effect on the production of IL-6, TNF-α, and IL-12p40 in LPS-stimulated macrophages. Conversely, the secretion of GM-CSF remained largely unaffected. Importantly, none of the tested concentrations induced cytotoxicity, demonstrating that gabapentin effectively dampens the release of pro-inflammatory cytokines without compromising overall macrophage viability.

Conclusion. In summary, this study provides compelling evidence for the selective anti-inflammatory and immunomodulatory actions of gabapentin on macrophages. These findings broaden our understanding of gabapentin's pharmacological profile beyond its classical neurological applications, underscoring its potential therapeutic value in the clinical management of neuroinflammatory and immune-mediated conditions.

Keywords: ınflammation, ımmunomodulator, gabapentin, cytokine, neuroimmune interaction.

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ДОСЛІДЖЕННЯ ІМУНОМОДУЛЮЮЧИХ ЕФЕКТІВ ГАБАПЕНТИНУ НА КЛІТИНИ МАКРОФАГІВ ССАВЦІВ

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Останнім часом зростає інтерес до взаємодії імунної та нервової систем. Габапентин – структурний аналог γ-аміномасляної кислоти, що широко застосовується для лікування нейропатичного болю та епілепсії, – розглядається як потенційний імуномодулюючий агент. Водночас його вплив на клітини вродженого імунітету, зокрема макрофаги, залишається недостатньо вивченим. у цьому дослідженні макрофаги миші лінії J774.2 обробляли різними концентраціями габапентину за наявності або відсутності ліпополісахариду. Рівні прозапальних цитокінів (IL-6, TNF-α, IL-12p40, GM-CSF) визначали методом імуноферментного аналізу. Встановлено, що габапентин дозозалежно знижує продукцію IL-6, TNF-α та IL-12p40 у LPS-стимульованих макрофагах, не впливаючи на рівень GM-CSF і життєздатність клітин. Отримані результати свідчать про протизапальні та імуномодулюючі властивості габапентину й розширюють уявлення про можливості його застосування за імунозалежних і нейрозапальних станів.

Ключові слова: запалення, імуномодулятор, габапентин, цитокіни, нейроімунна взаємодія.

Introduction

Gabapentin is a structural analogue of a structural analogue of γ-aminobutyric acid (GABA) and is primarily prescribed for the treatment of neuropathic pain, partial seizures, and postherpetic neuralgia [1]. Although its mechanism of action is not fully understood, gabapentin binds to the α2δ subunit of voltage-gated calcium channels in the central nervous system, thereby modulating neurotransmitter release [2]. Despite its favorable efficacy in various neurological disorders, gabapentin has been associated with adverse effects such as dizziness, fatigue, and more recently, immunological alterations [3]. There is growing clinical and experimental interest regarding its impact on immune cells, as some reports suggest gabapentin may suppress cytokine production or modulate inflammatory responses [4].

Our study aims to investigate the potential immunomodulatory effects of gabapentin on macrophage cells, which play a central role in both innate and adaptive immunity. Macrophages, which are differentiated from circulating monocytes, are essential in host defense through their roles in antigen presentation, phagocytosis, and cytokine secretion [5–7]. Their interaction with pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), initiates signaling cascades leading to the release of pro-inflammatory cytokines including IL-6, TNF-α, and IL-12 [8; 9]. Modulation of these cytokines may reflect the drug's influence on immune activation or suppression.

Since gabapentin's direct effects on immune cells, particularly macrophages, remain poorly understood, our study addresses a crucial knowledge gap. We hypothesize that gabapentin, upon exposure to activated macrophage cells, may alter cytokine production levels in response to LPS stimulation. Considering the role of macrophages in inflammatory and neuroimmune interactions, understanding these effects may provide insights into gabapentin's broader impact on the immune system and potentially inform its long-term safety profile in vulnerable patient populations.

Materials and Methods

2.1. Cell culture and drug treatment

Gabapentin (P4666, Sigma-Aldrich, USA) was obtained from Sigma-Aldrich, and murine macrophage cell line J774.2 were sourced from the American Type Culture Collection (ATCC). All procedures were carried out under BSL2 aseptic conditions to prevent contamination. The compound was dissolved in sterile distilled water to a final concentration of 10 mg/mL. J774 macrophage cells were cultured in Roswell Park Memorial Institute 1640 medium (RPMI 1640; 11875093, Thermo Scientific, USA) supplemented with 10 % fetal bovine serum (FBS; A5209501, Thermo Scientific, USA) and 1 % antibiotic solution (100 µg/mL streptomycin and 100 µg/mL penicillin; 15140122, Thermo Scientific, USA) [10; 11]. The cells were plated in 24-well plates at a density of 10^6 cells per well and allowed to adhere for 24 hours at 37 °C in a humidified 5 % CO_2 incubator. Subsequently, the cells were treated with 1, 5, and 10 µg/mL concentrations of gabapentin, either alone or in combination with 1 µg/mL lipopolysaccharide (LPS; L5293, Sigma-Aldrich, USA). The negative control group consisted of cells maintained in culture medium without any treatment.

2.2. Cell Viability Assay

Cell viability was assessed using Trypan Blue exclusion staining. For this, an equal volume of Trypan Blue solution was mixed with the cell suspension. The mixture was then loaded onto a hemocytometer, and both stained (non-viable) and unstained (viable) cells were counted. Viability was calculated by subtracting the number of blue-stained cells from the total cell count, dividing the result by the total, and multiplying by 100 to obtain a percentage. All experiments were carried out in triplicate, including three biological replicates. Statistical significance was analyzed using the Student's t-test in GraphPad Prism version V.

2.3. The determination of immunomodulatory activity

After a 24-hour incubation with different gabapentin concentrations, cell culture supernatants were collected. Cytokine quantification was performed using ELISA kits from BD Biosciences (CA, USA), specifically IL-12p40 (Cat. No. 555220), GM-CSF (Cat. No. 555126), TNF-α (Cat. No. 555212), and IL-6 (Cat. No. 555183). In brief, ELISA plates were pre-coated with specific monoclonal antibodies for each cytokine and incubated overnight. After incubation, the collected supernatants were transferred into the antibody-coated wells and further incubated for 24 hours. Following this, the wells were emptied, and 100 µL of TMB substrate (555214, BD Biosciences, USA, USA) was added for 1 hour. To terminate the colorimetric reaction, 1 M sulfuric acid (339741, Sigma-Aldrich, USA) was applied. Absorbance was then read at 450 nm using an ELISA microplate reader (BioTek® 800 TS Absorbance Reader, USA). Cytokine concentrations were calculated by comparing the absorbance values with a standard curve. For statistical analysis, the Student's t-test was performed using GraphPad Prism Version 10.0 [10; 11].

Ethical considerations

This study was conducted using established murine macrophage cell lines (J774.2) obtained from a certified cell repository. No human participants or experimental animals were involved in this research. Therefore, approval from an institutional ethics committee was not required. All animal experiments were conducted in accordance with the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) and applicable ethical guidelines.

Research results and their discussion

3.1. Gabapentin was used at non-cytotoxic concentrations

Trypan Blue staining was performed to assess the viability of J774.2 macrophages following exposure to varying concentrations of gabapentin, with or without LPS stimulation (Fig. 1). No significant differences in cell viability were observed between treated and untreated groups at concentrations ranging from 1 to 10 µg/mL. Therefore, these doses were deemed non-cytotoxic for the cells.

3.2. Gabapentin had anti-inflammatory effects on J774.2 cells

Immunomodulation refers to the ability of a compound to alter immune cell activity by enhancing or suppressing the production of pro- or anti-inflammatory cytokines. To assess the immunomodulatory potential of Gabapentin on macrophages, cytokine levels of IL-6 (Fig. 2), TNF-α (Fig. 3), IL-12p40 (Fig. 4), and GM-CSF (Fig. 5) were measured in J774.2 cells. Upon LPS stimulation, the levels

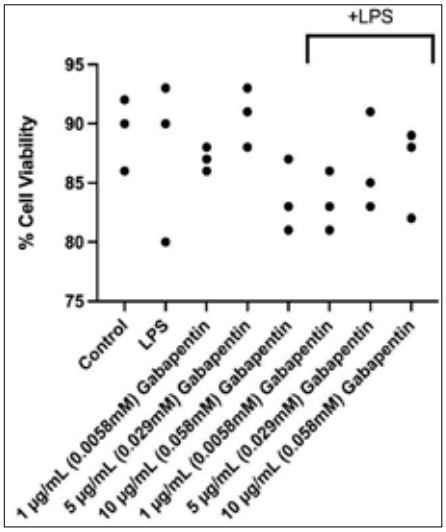

Fig. 1. The cell viability results upon incubation with Gabapentin

of IL-6, TNF-α, and IL-12p40 showed a marked increase, confirming the activation of the inflammatory response. However, Gabapentin treatment – especially at higher concentrations – resulted in a significant, dose-dependent decrease in cytokine production. Notably, cells treated with Gabapentin alone did not show any significant cytokine elevation, indicating that the drug itself does not provoke inflammation. These findings suggest that Gabapentin can attenuate LPS-induced inflammatory signaling in macrophages, supporting its potential role as an anti-inflammatory agent with immunomodulatory properties.

Gabapentin, initially developed for neuropathic pain and seizure control, is gaining increasing attention for its potential immunomodulatory effects beyond the central nervous system [12; 13]. As neuroinflammation has been identified as a key contributor to many neuropsychiatric and neuropathic disorders, exploring how gabapentin influences immune cell function is crucial to understanding its broader therapeutic utility.

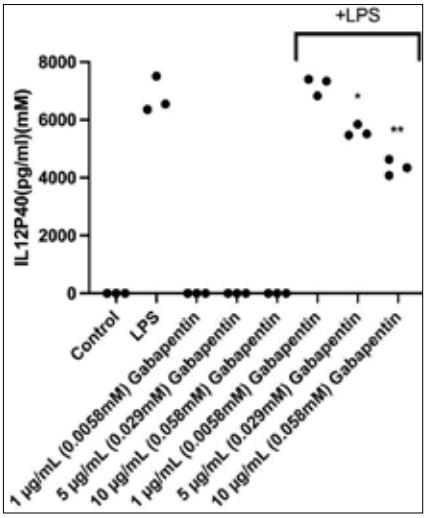

Fig. 4. The production levels of IL-12p40 in J774.2 cells in the presence of in the presence or absence of LPS (* – p < 0.001, ** – p < 0.0005, N = 3)

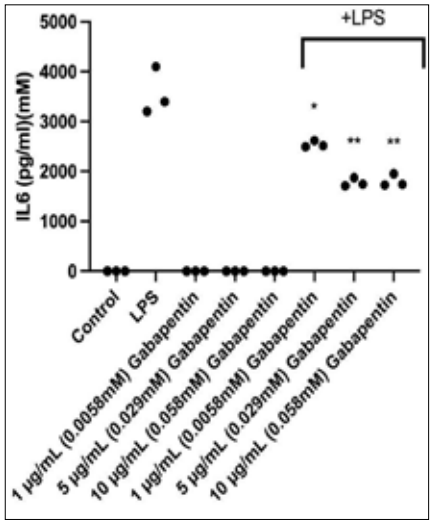

Fig. 2. The production levels of IL-6 in J774.2 cells in the presence of in the presence or absence of LPS (* – p < 0.001, ** – p < 0.0005, N = 3)

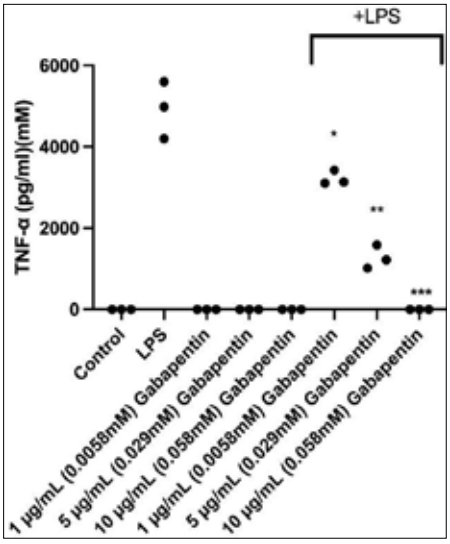

Fig. 3. The production levels of TNF- α in J774.2 cells in the presence of in the presence or absence of LPS (* – p < 0.001, ** – p < 0.0005, * – p < 0.0001, N = 3)**

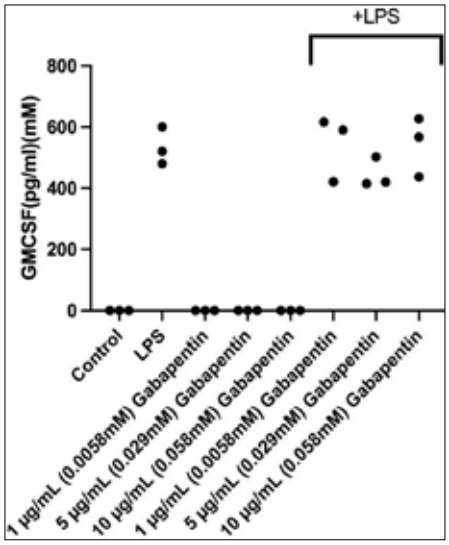

Fig. 5. The production levels of GM-CSF in J774.2 cells

in the presence of in the presence or absence of LPS

In this study, we investigated the effect of gabapentin on LPS-induced cytokine production in the murine macrophage cell line J774.2. Using ELISA, we quantified the levels of IL-6, TNF-α, IL-12p40, and GM-CSF. As expected, LPS stimulation led to a marked increase in IL-6, TNF-α, and IL-12p40 levels, confirming macrophage activation. Co-treatment with gabapentin resulted in a dose-dependent suppression of these cytokines, with the most significant inhibition observed at 10 μg/mL. In contrast, GM-CSF levels remained unchanged across all conditions, suggesting a selective modulation of inflammatory pathways.

IL-6, a key mediator of the acute phase response and chronic inflammation [9], was significantly reduced at the highest gabapentin dose, while lower concentrations (1 and 5 μg/mL) showed more moderate effects. These results support earlier findings that gabapentin may downregulate IL-6 via glial and macrophage pathways [14].

Similarly, TNF-α, which plays a central role in initiating inflammatory cascades [15], showed a significant dose-dependent decline, with 10 μg/mL gabapentin producing the most pronounced reduction. This is consistent with previous in vitro studies demonstrating gabapentin's ability to suppress TNF-α in activated macrophages [15].

Gabapentin also suppressed IL-12p40, a subunit of IL-12 and IL-23 involved in Th1 immune responses and autoimmune pathogenesis [16]. The downregulation of IL-12p40 suggests that gabapentin may attenuate Th1-driven inflammation, further supporting its potential in modulating cellular immunity.

In contrast, GM-CSF, a critical hematopoietic growth factor and cytokine essential for macrophage differentiation and survival, did not exhibit significant changes upon gabapentin treatment. The consistent GM-CSF levels across all doses indicate that gabapentin does not interfere with macrophage proliferation or viability, and its immunomodulatory effects are likely limited to inflammatory signaling rather than affecting cellular maintenance pathways [8].

Conclusions

In summary, our findings reveal that gabapentin can selectively inhibit pro-inflammatory cytokines such as IL-6, TNF-α, and IL-12p40 in LPS-stimulated macrophages, while leaving homeostatic cytokines like GM-CSF unaffected. These data highlight gabapentin's potential as an anti-inflammatory agent in immune-mediated or neuroinflammatory conditions. Future work should explore the underlying molecular mechanisms – particularly involving NF-κB or MAPK pathways – to further clarify gabapentin's role in immune regulation.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

BY, EA, and FA conceptualized the study. BY, EA, and FA conducted the experiments, FA supplied the drug molecules. BY, EA, and FA analyzed the data, wrote the manuscript, read and approved the final version of the manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

Not applicable.

Consent to participate

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Consent to publish

Not applicable.

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ДІАГНОСТИКА, ФАКТОРИ РИЗИКУ ТА БАГАТОФАКТОРНА МОДЕЛЬ ПРОГНОЗУВАННЯ ТЯЖКОГО ПЕРЕБІГУ ЛЕПТОСПІРОЗУ

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ДІАГНОСТИКА, ФАКТОРИ РИЗИКУ ТА БАГАТОФАКТОРНА МОДЕЛЬ ПРОГНОЗУВАННЯ ТЯЖКОГО ПЕРЕБІГУ ЛЕПТОСПІРОЗУ

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Проаналізовано клінічні та лабораторні дані 60 пацієнтів із лептоспірозом. За допомогою багатофакторного регресійного підходу оцінено різні параметри хворих для виявлення незалежних предикторів тяжкості перебігу інфекції.

Ідентифіковано ключові предиктори тяжкого перебігу лептоспірозу. До них належать: сезонність, початковий діагноз, блювання, біль у литкових м'язах, серовар лептоспір, вік пацієнта, час початку антибіотикотерапії, розміри печінки та селезінки, кількість паличкоядерних лейкоцитів, величина ШОЕ, наявність олігоанурії, кількість еритроцитів і білка в сечі.

Розроблені алгоритм і математична модель дають можливість вчасно оцінити ризик розвитку тяжкого перебігу лептоспірозу, призначити адекватну терапію і запобігти несприятливим наслідкам, знизити летальність.

Ключові слова: лептоспіроз, діагностика, прогнозування, багатофакторна модель.

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DIAGNOSIS, RISK FACTORS, AND MULTIFACTORIAL MODEL FOR PREDICTING SEVERE LEPTOSPIROSIS

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Introduction. Leptospirosis is a common zoonotic infection with high mortality. Despite increasing incidence, diagnosis and severity assessment remain inadequate due to varied clinical signs and limitations of current diagnostic methods.

The aim of this study was to stratify the risk coefficient for an unfavorable course of leptospirosis based on a developed mathematical prediction model.

Materials and methods. Clinical and laboratory data from 60 leptospirosis patients were analyzed using multifactorial regression to identify independent predictors of severe disease.

Results. Significant predictors of severe leptospirosis included: seasonality, initial diagnosis, vomiting, calf pain, serovar type, age, delayed antibiotic therapy, hepatosplenomegaly, neutrophil count, ESR, and urinary changes (diuresis, erythrocytes, protein). The regression model showed high prognostic value for early detection of patients at risk of severe disease.

Conclusions. The proposed algorithm and model enable reliable early assessment of severe leptospirosis risk, support timely treatment, and help prevent complications and reduce mortality.

Keywords: leptospirosis, diagnosis, prediction, multifactorial model.

Вступ

Лептоспіроз – одна з найпоширеніших у світі зоонозних інфекцій, що становить загрозу здоров'ю та життю людей і є тягарем для глобальної охорони здоров'я. Щорічно реєструється близько 1,03 млн випадків захворювання, з них 58 900 завершуються летально. Особливо висока захворюваність на лептоспіроз відзначається в країнах Латинської Америки та Південно-Східної Азії [1–3].

Натепер в Україні проблема лептоспірозу надзвичайно актуальна. Епідеміологічна ситуація в країні значно ускладнилася з початком широкомасштабної війни. Суттєво підвищився ризик інфікування лептоспірами не лише цивільних людей, а й військовослужбовців,

особливо в прифронтових регіонах через неможливість дотримуватися санітарних норм, потенційний контакт із гризунами, які є джерелом і резервуаром збудників, користування водою з відкритих водойм, забруднених сечею гризунів, тощо [4–6].

За перші вісім місяців 2024 року в Україні зареєстрували 230 випадків лептоспірозу, що на 63 % більше порівняно з аналогічним періодом 2023 року. Особливо високі показники захворюваності були в серпні (83 випадки). Регіонами з найбільшою кількістю хворих стали Чернігівська та Тернопільська області [7].

Клінічні прояви лептоспірозу надзвичайно різноманітні – від легкого катару верхніх дихальних шляхів до тяжких форм із гострою нирковою недостатністю, інтенсивною жовтяницею та вираженим геморагічним синдромом, що в 10–15 % випадків завершується летально [1; 8; 9]. В Україні захворювання має тяжкий перебіг у понад 70 % госпіталізованих хворих і може потребувати реанімаційного втручання. Летальність від лептоспірозу становить близько 20 % [7].

Сучасна лабораторна діагностика лептоспірозу ґрунтується на серологічних тестах, зокрема реакції аглютинації-лізису (РАЛ) із лептоспірами, і молекулярно-генетичних методах, як-от полімеразна ланцюгова реакція (ПЛР) [10–11].

Швидке виявлення хворих із високим ризиком тяжкого перебігу лептоспірозу є надзвичайно важливим, оскільки такі пацієнти потребують негайної інтенсивної терапії та постійного моніторингу. Фактори, відповідальні за можливий розвиток тяжких форм лептоспірозу, наразі чітко не встановлені [12–13]. На думку багатьох клініцистів, вони пов'язані як із збудником (вірулентність штаму *Leptospira*, величина інфікувальної дози та ін.), так і з господарем (генетична схильність, супутні захворювання тощо).

Натепер, за даними багатьох зарубіжних науковців, машинне навчання (МН) і глибоке навчання (ГН) стали потужними інструментами у сфері виявлення та лікування різних захворювань [14]. МН передбачає навчання комп'ютерів застосовувати минулий досвід для вирішення нових проблем, використовуючи алгоритми, які дають можливість машині виявляти закономірності, на підставі отриманих даних прогнозувати й виробляти обґрунтовані рішення.

Щодо лептоспірозу, то МН може аналізувати епідеміологічну ситуацію щодо хвороби на певній території, великі об'єми клінічних і лабораторних даних, щоб виявити закономірності та взаємозв'язки, яких не знаходять за допомогою традиційних статистичних методів [14–16]. Ця можливість є особливо цінною в умовах обмеженого доступу до сучасних методів специфічної діагностики хвороби, оскільки дає змогу раніше й точніше встановити діагноз лептоспірозу, скорочуючи час до призначення адекватного лікування, що покращить його результати.

Моделювання можливості розвитку тяжких форм лептоспірозу є перспективним напрямом у клінічній інфектології. Розробка й застосування прогностичних моделей дають змогу ідентифікувати пацієнтів із високим ризиком розвитку ускладнень ще на ранніх стадіях захворювання, що має вирішальне значення для своєчасної оптимізації терапії. Такі моделі зазвичай ґрунтуються на багатофакторному аналізі, що охоплює епідеміологічні дані, клінічні прояви, лабораторні показники та демографічні характеристики пацієнтів. Використання статистичних методів, як-от множинний регресійний аналіз, дає можливість кількісно оцінити вплив кожного фактора ризику на ймовірність розвитку несприятливого перебігу інфекції [16; 17]. Прогностичні моделі сприяють підвищенню точності діагностики лептоспірозу, індивідуалізації лікування та, як наслідок, зниженню показників захворюваності та смертності від цієї хвороби.

Мета. Метою дослідження була стратифікація коефіцієнта ризику несприятливого перебігу на ранніх стадіях лептоспірозу (КРНПЛ) на основі розробленої математичної моделі прогнозування.

Матеріали та методи дослідження

Проаналізовано 60 медичних карт стаціонарного хворого пацієнтів із лептоспірозом середнього та тяжкого ступенів, які з 2020 по 2025 рік перебували на стаціонарному лікуванні в інфекційних відділеннях КНП «Тернопільський регіональний фтизіопульмонологічний медичний центр» ТОР і КНП «Тернопільська міська клінічна лікарня швидкої допомоги», а також у нефрологічному та реанімаційному відділеннях КНП «Тернопільська обласна клінічна лікарня» ТОР. Включення пацієнтів у дослідження здійснювали за критеріями, що забезпечували однорідність вибірки за тяжкістю хвороби, підтвердженої специфічними лабораторними методами.

Це дослідження проведено після схвалення комітетом з етики людини ТНМУ імені І. Я. Горбачевського МОЗ України (протокол № 14 від 23 листопада 2021 р.). Пацієнти надали інформовану згоду на обробку їх персональних даних.

Статистичну обробку отриманих результатів дослідження здійснювали з використанням статистичного пакета Statistica 10.0 і табличного редактора Microsoft Excel 2007.

Як математичну модель було застосовано метод регресійного аналізу [16], який дає можливість за даними коефіцієнтів регресії та значень факторів ризику, що мають статистично достовірний вплив на несприятливий перебіг лептоспірозу, виявити залежність між ними та спрогнозувати ймовірності розвитку тяжких форм хвороби з можливим летальним наслідком.

Для оцінювання якості регресійної моделі було ретельно проаналізовано залишкові відхилення. Зокрема, для перевірки нормальності розподілу залишкових відхилень побудовані їх гістограма, а також нормально-ймовірнісний графік. Це є критично важливим для підтвердження коректності застосування регресійного аналізу. Для перевірки незалежності залишкових відхилень від прогнозованих значень і виявлення потенційних закономірностей, що могли б вказувати на порушення припущень моделі, створювали діаграму розсіювання. Додаткову оцінку якості математичної моделі проводили за допомогою аналізу коефіцієнта детермінації Нейджелкерка (R2) [17]. Цей показник характеризує частку дисперсії залежної змінної і є важливим кри-

терієм пояснювальної здатності моделі. Прийнятність моделі для прогнозування КРНПЛ оцінювали за допомогою дисперсійного аналізу (ANOVA), який дає змогу визначити статистичну значущість моделі загалом та її здатність пояснювати варіабельність залежної змінної.

Результати дослідження та їх обговорення

Хворі були госпіталізовані здебільшого на 4–9-й день недуги – 32 пацієнти (53,3 %), 16(26,7 %) – до 4-го дня, а решта – 12 осіб (20,0 %) – після 10-го дня від початку захворювання.

Серед госпіталізованих чоловіки становили більшість – 48 осіб (80,0 %), жінок було 12(20,0 %). Цей гендерний розподіл відповідає епідеміологічним особливостям лептоспірозу, який частіше реєструється в чоловіків через їх професійну діяльність або хобі, пов'язані з контактом із забрудненою водою та ґрунтом. Розподіл за місцем проживання був майже рівномірним: 52,0 % пацієнтів проживали в сільській місцевості, а 48,0 % – у містах. Хворі були віком від 18 до 69 років, тобто належали до найбільш активної та працездатної частини населення, яка схильна до інфікування лептоспірами (рис. 1).

Випадки лептоспірозу реєстрували переважно в літньо-осінній період. Найвищу захворюваність відзначали від серпня по листопад – 60,0 % випадків. Це можна пояснити підвищеною активністю населення та більшою імовірністю контактувати з джерелами збудника, потенційно зараженими водоймами тощо.

У подальшому в пацієнтів з'ясовували можливі шляхи зараження лептоспірами. Часто в однієї особи таких шляхів було декілька. Встановлено, що основним можливим шляхом інфікування (80,0 % випадків) під час виконання господарських робіт був контакт із предметами, забрудненими сечею гризунів. Іншими можливими шляхами зараження були купання у водоймах і риболовля (по 20,0 % випадків), укуси гризунів і перебування в польових умовах, де були гризуни (по 8,0 %). Важливо відзначити, що у 36,0 % хворих виявлено пошкодження шкіри рук, які могли слугувати вхідними воротами для лептоспір.

Хворі (60,0 %) мали таку супутню патологію: метаболічна кардіоміопатія, хронічний панкреатит із порушенням секреторної функції, гіпохромна анемія, артеріальна гіпертензія, хронічний гепатит, цукровий діабет II типу.

Клінічний перебіг захворювання демонстрував значний поліморфізм. у 32,0 % випадків спостерігали типовий варіант – поєднання гарячки, диспепсичних проявів, болів у литкових м'язах та ознак ренального або гепаторенального синдрому. Натомість у 68,0 % пацієнтів захворювання імітувало інші патологічні стани, що ускладнювало своєчасну діагностику. Зокрема, у 28,0 % хворих лептоспіроз перебігав на кшталт гострого респіраторного захворювання (ГРЗ), у 20,0 % – пневмонії, у 12,0 % – вірусного гепатиту, у 4,0 % – нефропатії та у 4,0 % випадків – патології шлунково-кишкового тракту.

Найчастішими зареєстрованими в пацієнтів симптомами були: гарячка (92,0 %), загальна слабість (88,0 %), болі в литкових м'язах (68,0 %), диспепсичні прояви (нудота, блювання, біль у животі, 44,0 %), темно-коричневий колір сечі (48,0 %), жовтяниця (30,0 %), сухість у роті (36,0 %) і головний біль (24,0 %). З боку сечовидільної системи у 60,0 % хворих відзначали олігоанурію, а у 8,0 % осіб під час госпіталізації спостерігали поліурію. Збільшення печінки діагностовано в усіх пацієнтів, селезінки – у 34(56,7 %). у 15(25 %) хворих були прояви геморагічного синдрому – петехії на шкірі та крововиливи в місцях ін'єкцій та кон'юнктиви, носові кровотечі, а також порушення згортання крові.

У загальному аналізі крові відзначали лейкоцитоз до 27,39 × 10^{12} 1/л, паличкоядерний зсув – у 40 осіб (66,7 %), тромбоцитопенію – у 15(25 %), суттєво збільшену ШОЕ до 52 мм/год – у 50 %. Рівень сечовини в крові в обстежених був від 7,3 до 41,2 ммоль/л, креатиніну – від 117 до 892 мкмоль/л. у 18(30 %) пацієнтів діагностували жовтяничну форму лептоспірозу. Під час госпіталізації рівень білірубіну в крові пацієнтів становив від 40 до 429 мкмоль/л, переважно за рахунок прямої фракції, водночас активність АлАТ і АсАТ

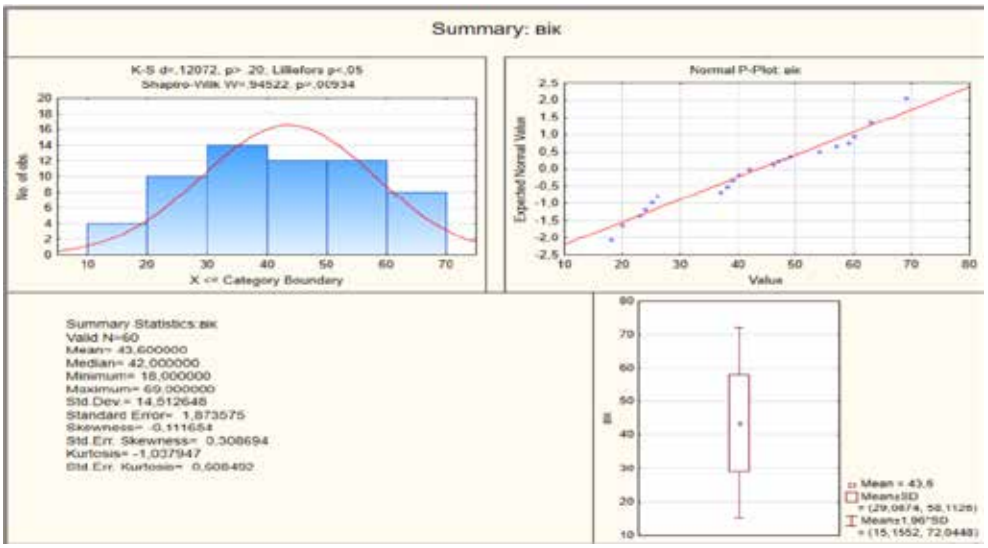

Рис. 1. Розподіл пацієнтів за віком

лише в 10,0 % осіб перевищувала норму в 10 разів, а в решти в середньому становила (118,4 ± 24,8) і (155,8 ± 26,3) Од/л відповідно. Зміни в сечі (діурез, наявність еритроцитів, лейкоцитів, кількість білка) відзначено у всіх пацієнтів.

Діагноз лептоспірозу підтверджено лабораторно, здебільшого (93,3 %) за допомогою РАЛ із лептоспірами. Крім того, на ранніх стадіях захворювання, коли антитіла ще можуть не утворитися, використовували ПЛР крові для виявлення ДНК лептоспір (у 56,7 % випадків).

Усім пацієнтам одразу призначали антибіотики – цефалоспорини (цефіпім, цефазолін; цефотрим, цефтизидим); патогенетичну терапію (дезінтоксикаційні середники, глюкокортикоїди, сечогінні, антигеморагічні засоби).

Метод багатофакторного математичного аналізу дав змогу створити модель прогнозування КРНПЛ на основі спільного впливу низки епідеміологічних, клінічних і лабораторних показників, ідентифікованих у пацієнтів.

Для побудови математичної моделі прогнозування відібрано ймовірні чинники, що впливають на КРНПЛ. у групу незалежних предикторів включили якісні фактори ризику прогресування і встановили їх градацію із числових значень: стать, місцевість проживання, сезонність, наявність супутньої патології, початковий діагноз; скарги під час госпіталізації: гарячка, нудота, блювання, біль у литкових м'язах, головний біль, загальна слабкість, колір шкіри та сечі, серовар лептоспір; і кількісні: вік, тривалість симптомів до госпіталізації та призначення антибіотикотерапії, розміри печінки та селезінки, кількість лейкоцитів (окремо паличкоядерних), тромбоцитів, ШОЕ, рівень креатиніну та сечовини в крові; зміни в сечі – діурез, наявність еритроцитів, лейкоцитів, кількість білка.

За допомогою багатофакторного регресійного аналізу виділено 14 найбільш значущих факторів ризику, за якими можна провести прогностичний аналіз ймовірності КРНПЛ (табл. 1).

Наступним етапом було встановлення відносної важливості факторів у прогнозуванні КРНПЛ із визначенням коефіцієнтів регресії Beta, які відображають для кожного включеного в аналіз фактора відношення щодо шансів впливу на розвиток несприятливого перебігу лептоспірозу в обстежених пацієнтів (табл. 2).

Таблиця 1

Фактори ризику виникнення КРНПЛ, їх індексація

Фактори	Умовні позначення факторів у математичній моделі прогнозування	Факторні діапазони та назви їх можливих варіантів	Числові значення факторних діапазонів
1	2	3	4
Вік, роки	X1	18–25	1
		26–44	2
		45–60	3
		61–75	4
Тривалість симптомів до госпіталізації, дні	X2	до 3	1
		4–9	2
		10 і більше	3
Попередній діагноз	X3	лептоспіроз	0
		ГРЗ	1
		пневмонія	2
		гепатит	3
		нефрит	4
		інші хвороби	5
Блювання	X4	немає	0
		є	1
Болі в литкових м'язах	X5	немає	0
		є	1
Олігоанурія	X6	діурез достатній	0
		олігурія	1
		анурія	2
Розміри печінки	X7	не збільшена	0
		збільшена	1
Розміри селезінки	X8	не збільшена	0
		збільшена	1
Збудник	X9	L. icterohaemorrhagiae	1
		L. canicola	2
		L. grippotyphosa	3
		L. hebdomadis	4
		L. australis	5
		L. pomona	6

Продовження таблиці 1

1	2	3	4
Пора року	X10	літо	1
		осінь	2
		зима	3
		весна	4
Відсоток паличкоядерних лейкоцитів	X11	до 5	0
		6–10	1
		11–20	2
		понад 20	3
ШОЕ, мм/год	X12	норма	0
		до 30 мм/год	1
		понад 30 мм/год	2
Кількість еритроцитів у сечі в полі зору	X13	до 3	0
		понад 3	1
Наявність білка в сечі	X14	немає	0
		є	1

Таблиця 2

Результати отримання значущих факторів для прогнозування КРНПЛ під час проведення багатофакторного регресійного аналізу в програмі Statistica 10.0

N = 60	**Regression Summary for Dependent Variable: КРНПЛ (1 in 11) R= ,96124760 R?= ,92399694 Adjusted R?= ,89808681 F(15,44)=35,662 p<0,0000 Std.Error of estimate: ,26822**					
	b*	**Std. Err. of b***	**b**	**Std. Err. of b**	**t(44)**	**p-value**
Предиктори			**1,14430**	**0,306425**	**3,73435**	**0,000538**
X1	0,511273	0,075663	0,02960	0,004380	6,75726	0,000000
X2	–0,214423	0,066120	–0,02767	0,008534	–3,24292	0,002260
X3	0,246339	0,054609	0,11851	0,026272	4,51094	0,000048
X4	0,304314	0,065819	0,68033	0,147146	4,62349	0,000033
X5	–0,607257	0,079747	–1,03276	0,135625	–7,61483	0,000000
X6	–0,393687	0,061093	–0,35955	0,055796	–6,44407	0,000000
X7	0,863418	0,106223	0,83688	0,102958	8,12836	0,000000
X8	–0,386631	0,078429	–0,59904	0,121516	–4,92969	0,000012
X9	–0,317005	0,055383	–0,16370	0,028600	–5,72387	0,000001
X10	–0,282839	0,061589	–0,22758	0,049556	–4,59236	0,000037
X11	–0,117214	0,048207	–0,00714	0,002936	–2,43149	0,019177
X12	0,297664	0,053309	0,01139	0,002039	5,58375	0,000001
X13	0,271796	0,051352	0,02897	0,005473	5,29286	0,000004
X14	0,329269	0,058080	1,10412	0,194755	5,66925	0,000001

Примітки: b – коефіцієнт регресії, Std. Err. of b – стандартна похибка, p-value – значення p.

Фактори ризику, в яких рівень значущості p-value > 0,05, були виключені з аналізу. Рівень значущості у 184 факторів ризику становив $p < 0,05$, тому їх було включено в нашу математичну модель.

На основі отриманих результатів (табл. 2) побудовано математичну модель для визначення КРНПЛ (1):

$$КРНПЛ = 0,02960 \times X1 - 0,02767 \times X2 + 0,11851 \times X3 + 0,68033 \times X4 - 1,03276 \times X5 - 0,35955 \times X6 + 0,83688 \times X7 - 0,59904 \times X8 - 0,16370 \times X9 - 0,22758 \times (X10) - 0,00714 \times (X11) + 0,01139 \times (X12) + 0,02897 \times (X13) + 1,10412 \times (X14) + 1,14430, \quad (1)$$

де КРНПЛ – коефіцієнт ризику несприятливого перебігу лептоспірозу; X1–X14 – фактори ризику з коефіцієнтами регресії.

Для оцінювання якості регресійної моделі проаналізовано залишкові відхилення, зокрема отримано їх гістограму (рис. 2). Як видно з гістограми, залишкові відхилення розподілені симетрично й наближаються до кривої нормального розподілу. Отже, статистична гіпотеза про відповідність розподілу залишків нормальному закону не відхиляється.

З метою додаткового підтвердження залишкових відхилень нормальному закону розподілу було побудовано нормально-ймовірнісний графік (рис. 3). Аналізуючи його дані, зауважуємо відсутність систематичних відхилень від нормально-ймовірнісної прямої. Це дає підстави стверджувати, що залишкові відхилення розподілені за нормальним законом розподілу.

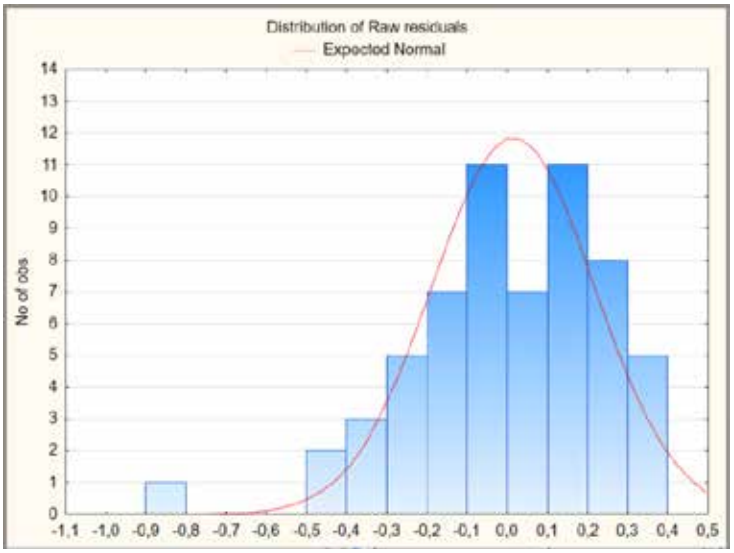

Рис. 2. Гістограма залишкових відхилень багатофакторної регресійної моделі прогнозування КРНПЛ

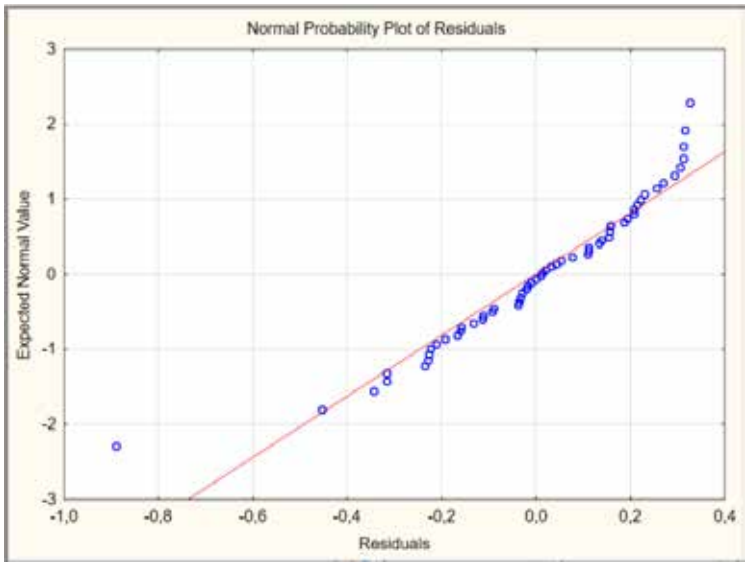

Рис. 3. Нормально-ймовірнісний графік залишкових відхилень багатофакторної регресійної моделі прогнозування КРНПЛ

Для оцінки прийняття моделі загалом провели аналіз ANOVA (табл. 3). Під час аналізу отриманих даних встановлено високий рівень прийняття моделі прогнозування КРНПЛ загалом, оскільки рівень значущості $p < 0,001$, а сама модель за використання середніх значень працюватиме краще за простий прогноз.

Таблиця 3

Результати аналізу ANOVA

Effect	Analysis of Variance; DV: КРНПЛ (1 in 111)				
	Sums of Squares	df	Mean Squares	F	p-value
Regress.	38,48447	15	2,565632	35,66161	0,000000
Residual	3,16553	44	0,071944		
Total	41,65000				

Для додаткового оцінювання якості математичної моделі КРНПЛ проаналізовано коефіцієнт детермінації Нейджелкерка (R^2), який показує, яка частина факторів врахована в прогнозуванні. Коефіцієнт детермінації змінюється від 0 до 1. Чим більше його значення наближається до 1, тим якісніша багатофакторна регресійна модель. у запропонованій математичній моделі КРНПЛ коефіцієнт детермінації становить $R^2 = 0,924$ (у програмі Statistica 10.0 $R^2 = 0,92399694$, табл. 2). Отже, 92,4 % факторів враховано в моделі прогнозування ризику розвитку тяжкого перебігу лептоспірозу.

Отже, серогрупа лептоспір, зокрема *L. Icterohaemorrhagiae*, частіше асоціювалася з тяжчими формами лептоспірозу [8; 11]. Ключовим фактором тяжкого перебігу хвороби був ще й час початку антибактерійної терапії, що збігається з даними інших науковців [10; 18; 19]. Іншим важливим предиктором став вік хворого. Відзначено чітку тенденцію до тяжчого перебігу захворювання зі збільшенням віку пацієнта. Інші дослідники описували вік як предиктор вищої смертності від цієї

інфекції [1; 13; 18]. Ще одним предиктором була чоловіча стать пацієнта, що, мабуть, зумовлено гендерно-специфічною професійною та побутовою ризикованою діяльністю [18]. З лабораторних параметрів на момент госпіталізації хворого мали прогностичне значення високі рівні креатиніну та білірубіну в крові, активність амінотрансфераз, кількість лейкоцитів у крові, у тому числі паличкоядерних форм, тромбоцитів і наявність еритроцитів і білка в сечі. Результати наших досліджень узгоджуються з даними зарубіжних науковців [11; 12; 18]. Особливу прогностичну цінність мав розвиток олігоанурії. Раннє визначення зазначених параметрів слугуватиме лікарям сигналом для інтенсивнішого лікування хворого.

Висновки

Діагностика лептоспірозу є складним завданням, оскільки існуючі діагностичні тести не завжди доступні, можуть давати хибні результати, що призводить до призначення неналежного лікування хворим і розвитку в них несприятливих наслідків.

Розроблені алгоритм і математична модель прогнозування КРНПЛ є високоінформативними і дають можливість вчасно оцінити ризик розвитку тяжкого перебігу лептоспірозу, своєчасно призначити адекватну терапію та запобігти летальному наслідку.

Перспективи подальших досліджень. Необхідні дослідження для подальшого пошуку надійних, можливо, імунологічних предикторів тяжкості перебігу лептоспірозу та розвитку несприятливих наслідків.

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STAGED SURGICAL TREATMENT OF GUNSHOT ABDOMINAL WOUNDS WITH DUODENAL INJURY

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STAGED SURGICAL TREATMENT OF GUNSHOT ABDOMINAL WOUNDS WITH DUODENAL INJURY

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Background. Combat-related duodenal injuries (DI) are among the most complex abdominal traumas, with high mortality, septic complications, and lasting dysfunction. The most difficult decisions occur at Role 2, where limited resources hinder definitive care. The lack of a standardized algorithm contributes to poor outcomes.

Objective. To develop and assess a surgical algorithm for DI adapted to the tiered system of military evacuation.

Materials and Methods. Thirty service members with DI were studied: 20 managed with the proposed algorithm (main group) and 10 without (comparison). Injury severity was graded by AAST. Outcomes included mortality, complications, feeding initiation, and hospital stay.

Results. Mortality was 10.0 % in the main group versus 80.0 % in the comparison ($p < 0.001$). Complications occurred in 85.0 % vs. 100 %. Enteral feeding started earlier (6.6 ± 0.4 vs. 8.6 ± 1.1 days, $p < 0.05$), and hospital stay was shorter (25.8 ± 4.2 vs. 42.9 ± 6.8 days, $p < 0.05$). The D2 segment was most often affected. Algorithm elements included FAST, laparo-centesis, and laparoscopy at Role 2; CT and endoscopy at Role 3; definitive repair and second-look surgery at Role 4.

Conclusions. The algorithm reduced mortality and complications and allowed flexible tactical adaptation. At Role 2, strict damage control, avoidance of major reconstruction, and preparation for evacuation are essential. These findings support implementing a unified treatment pathway for DPI across the military medical system, adjustable to resources and battlefield conditions.

Keywords: combat trauma, duodenal injury (DI), tactical surgery, medical evacuation.

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ЕТАПНЕ ХІРУРГІЧНЕ ЛІКУВАННЯ ВОГНЕПАЛЬНИХ ПОРАНЕНЬ ЖИВОТА З УШКОДЖЕННЯМ ДВАНАДЦЯТИПАЛОЇ КИШКИ

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Бойові ушкодження дванадцятипалої кишки належать до надскладних абдомінальних травм із високою летальністю та ризиком інфекційних ускладнень. Особливо критичним є вибір тактики на етапі Role 2 в умовах дефіциту ресурсів. у дослідженні проаналізовано 30 випадків, з яких 20 лікували за розробленим алгоритмом, а 10 – без нього. Застосування алгоритму дало можливість суттєво знизити летальність (10 % проти 80 %), скоротити госпіталізацію та прискорити відновлення ентерального харчування. Найчастіше уражався сегмент D2. Ключовими елементами стали FAST, лапароцентез і лапароскопія на II рівні, МСКТ та ендоскопія на III, реконструкція і second look на IV. Алгоритм підвищує ефективність допомоги, зменшує ускладнення та сприяє стандартизації хірургічної тактики при бойових пораненнях ДПК.

Ключові слова: бойова травма, дванадцятипала кишка, тактична хірургія, медична евакуація.

Introduction

In modern conditions of conducting combat operations, the provision of timely and effective surgical care to the wounded is a critical component of the military medical support system [1; 2]. Tactical medicine, which is developing at the intersection of military surgery, logistics, and emergency medicine, operates with the concept of staged medical evacuation, within which surgical interventions are integrated according to the severity of injury, distance from the combat zone, and availability of resources [1]. The first medical actions on the battlefield (Tactical Combat Casualty Care) are aimed at saving life with minimal means by temporary control of bleeding, ensuring airway patency, and rapid evacuation, without performing surgical manipulations. Starting from Role 2, which is represented by mobile surgical groups and stabilization points, the first surgical intervention is performed, known as damage control surgery, which aims to save life by stopping massive bleeding, combating shock, and preventing multiple organ failure [2; 3]. At the next level – Role 3 – the third level in case of DI is considered as a stabilization stage, where measures are carried out to stabilize the condition of the wounded and additional examination (using all necessary technical capabilities) with further evacuation to Role 4. If necessary, programmed relaparotomy (according to DCS tactics), control of bleeding, percutaneous transhepatic cholecystostomy under ultrasound guidance are performed [2; 4]. The final stage – Role 4 – involves providing a full spectrum of medical care in military medical centers on the territory of the state or beyond it, including reconstructive surgery and long-term recovery [2; 5]. Thus, the structure of providing surgical care in tactical medicine is based on the principles of staging, mobility, adaptability, and continuity, which makes it possible to ensure maximum survival of the

wounded in extremely difficult conditions of modern combat.

At the Role 2 stage – a mobile stabilization surgical unit – the choice of treatment tactics for combat DI is accompanied by a number of unresolved clinical and tactical issues that remain the subject of active discussion in the military surgical community [2; 3; 6]. The absence of a unified approach at this critical stage creates risks of variability in decision-making and directly affects patient survival and prognosis. In particular, there are still no clear criteria regarding the feasibility of primary reconstruction of the damaged duodenum in unstable patients. In cases of localized injuries that do not exceed 50 % of the circumference of the intestinal wall, primary suturing may be technically possible. However, under conditions of limited time, lack of full anesthesiological support, and limited resources, such tactics may lead to suture failure, peritonitis, and death [6]. In such situations, temporary solutions are more often chosen: packing, clip application, external drainage of the gallbladder, and transfer of definitive reconstruction to the next stage – Role 4.

A separate issue is the use of pyloric exclusion in combination with gastrojejunostomy, which is considered in injuries of D1–D2 segments, especially with combined pancreatic injury [7]. However, the implementation of this technique in Role 2 conditions is significantly limited both by the duration of the operation, which exceeds the critical threshold (60 minutes), and by the need for high surgical qualification. In addition, there are no consolidated indications for choosing this method in combat trauma.

No less debatable is the issue of resection of an intestinal segment in conditions of significant crushing or complete avulsion of a part of the duodenum [8; 9]. Although duodenojejunostomy and other types of reconstruction are considered standard for high-grade injuries (III–IV according to AAST), their implementation at Role 2 remains an exception rather than the rule [6]. In practice, the approach of biliary decompression (percutaneous transhepatic cholecystostomy), staged surgical interventions, and diagnostic laparoscopy (if equipment allows) predominates.

An even more complex situation arises in combined injuries of the duodenum, pancreas, and major vessels [10]. Such combinations are associated with an extremely high mortality risk; however, the algorithm of actions at Role 2 remains undefined.

The issue of criteria for safe evacuation of patients after primary intervention also remains unresolved. There is no unified opinion regarding the optimal timing of transport, hemodynamic stability limits, or laboratory parameters that could be used as universal criteria for evacuation decision-making [1; 2, 11].

The use of negative pressure therapy (VAC) in an open abdominal cavity also requires standardization [12]. Although VAC therapy may be effective in posterior DI, its use in combat conditions is limited by technical difficulties and lack of standardized protocols.

Thus, the absence of unified regulated approaches to the treatment of DI at Role 2 determines the urgent need to develop a standardized algorithm that would include clear indications for primary suturing, reconstruction, drainage, use of VAC systems, criteria for evacuation safety, and selection between temporary and definitive surgical strategies. Such an algorithm must be adapted to the realities of military medicine, resource limitations, and dynamic tactical conditions. Its implementation will improve survival, reduce complications, and form a unified surgical doctrine for DI in combat conditions.

Objective. To prove the effectiveness of the proposed algorithm of surgical care in DI at Role 2–4 levels of medical support compared to the existing surgical treatment tactics.

Materials and Methods

The results of treatment of 30 patients with combat DI were analyzed, including 20 patients (main group) treated according to the developed algorithm and 10 patients (comparison group) treated without using the proposed recommendations.

To determine the severity of DI, the classification of the American Association for the Surgery of Trauma (AAST, 2018) was used [13]. The duration of hospital stay, number of complications, and mortality were evaluated.

The mean age of patients in the main group was 38.3 ± 2.3 years, and in the comparison group – 36.5 ± 3.5 years ($p > 0.05$).

Based on the analysis of current approaches to the management of DI [2; 6–10], we developed a structured treatment algorithm (Fig. 1).

Diagnostic Measures

Role 2 (Level 2 of medical care):

– Assessment of the patient's general condition;
– Determination of blood group and Rh factor, laboratory testing;
– Evaluation of the characteristics, size, and localization of entry and exit wounds;
– Emergency ultrasound examination using the FAST protocol [14];
– Abdominal radiography in two projections (or computed tomography if available and the patient is stable);
– Laparocentesis using the "floating catheter" technique (or gauze-assisted abdominal revision);
– Diagnostic laparoscopy (if indicated and equipment is available).

Role 3 (Level 3 of medical care):

– Reassessment of the patient after evacuation;
– Laboratory investigations;
– Full abdominal ultrasound examination;
– Radiography of the abdomen and other anatomical regions (as indicated);
– Multislice computed tomography;
– Video endoscopic examinations as required;
– Diagnostic laparoscopy (if indicated).

Role 4 (Level 4 of medical care):

– Reassessment after evacuation to Role 4;
– Comprehensive laboratory evaluation;
– Full abdominal ultrasound examination;
– Radiography (as indicated);
– Multislice computed tomography;
– Full video endoscopic evaluation (fibrogastroduodenoscopy, ERCP);
– Diagnostic and dynamic (second-look) laparoscopy.

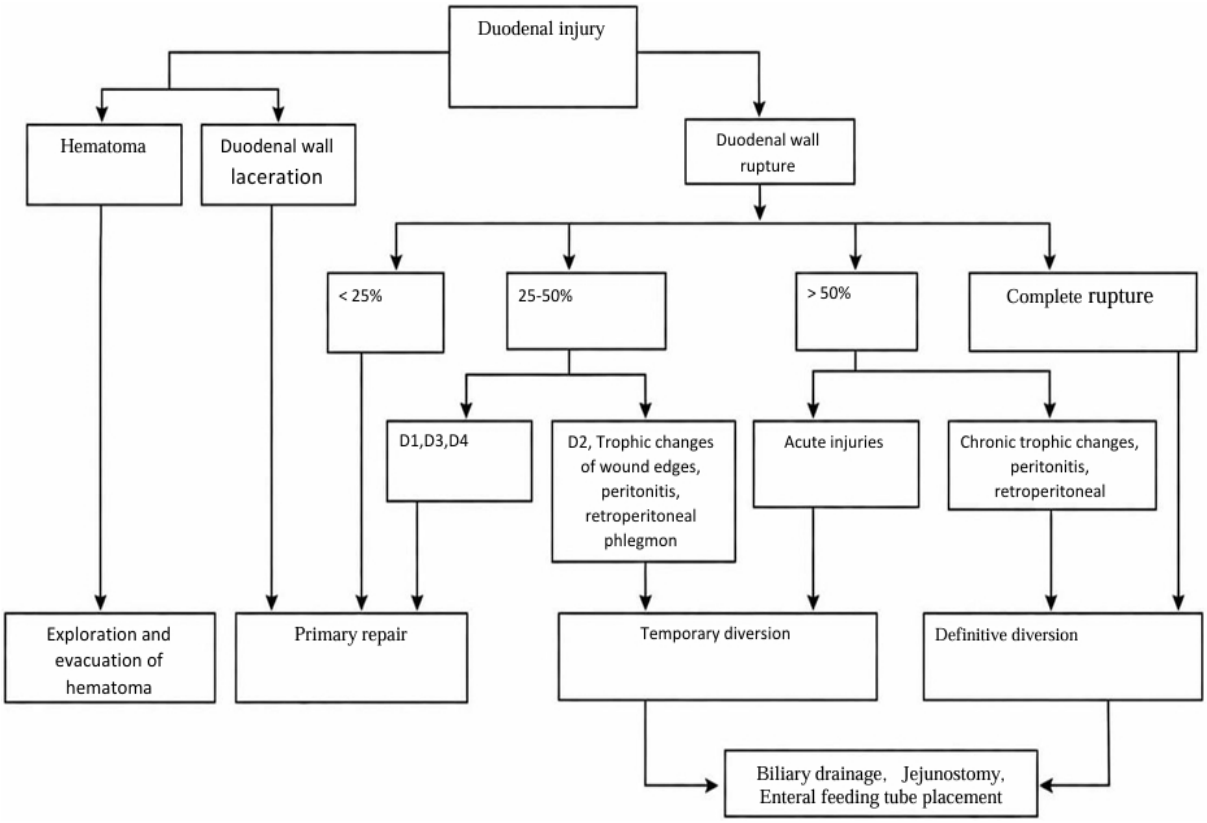

Fig. 1. Algorithm for DI management

The study was conducted in accordance with modern bioethical standards [15]. All participants or their authorized representatives provided informed consent. The study protocol No. 163 was approved by the Ethics Committee of the National Medical University named after O. O. Bohomolets (07.11.2022).

Statistical analysis was performed using frequency and variance analysis with Statistica 14.1.25 software (TIBCO, USA) [17].

Research results and their discussion

The second segment of the duodenum (D2) was most frequently affected: in 8 patients (40.0 %) of the main group and in 5 patients (50.0 %) of the comparison group. According to the AAST classification, in the main group there was 1 case of grade I injury, 9 cases (45.0 %) of grade II, and 10 cases (50.0 %) of grade III injury. In the comparison group, grade II injuries predominated (8 cases, 80.0 %), while grade I and III injuries occurred in one case each. No statistically significant difference between the groups was found ($p > 0.05$) (Table 1).

Table 1

Distribution of injuries according to the AAST classification

Grade	Main group (n = 20)	Comparison group (n = 10)
I	1(5.0 %)	1(10.0 %)
II	9(45.0 %)	8(80.0 %)
III	10(50.0 %)	1(10.0 %)
IV	–	–

In most cases, surgical intervention was performed within 24 hours after injury; however, in 7 patients (35.0 %) of the main group, surgery was delayed beyond this period. The primary surgical procedure was laparotomy with primary closure of the defect and duodenal decompression. The Strong procedure was performed in 8 cases (40.0 %) in the main group and in 6 cases (60.0 %) in the comparison group. Postoperative mortality was 10.0 % in the main group and reached 80.0 % in the comparison group ($\chi^2 = 11.72$; $p = 0.0006$).

Postoperative complications were observed in 85.0 % of patients in the main group (17 cases) and in 100 % of patients in the comparison group ($\chi^2 = 1.61$; $p = 0.20$), with sepsis being the most common complication (Table 2).

Table 2

Postoperative outcomes

Parameter	Main group	Comparison group	Statistics
Mortality	2(10.0 %)	8(80.0 %)	$\chi^2 = 11.72$; $p = 0.0006$
Complications	17(85.0 %)	10(100 %)	$\chi^2 = 1.61$; $p = 0.20$

Thoracic complications were observed in 5 patients (25.0 %) in the main group, while wound complications occurred in 7 patients (35.0 %). Fistula formation was recorded in 2 patients (10.0 %) in the main group and in all patients in the comparison group. One patient in the main group required reoperation. Bile leakage was observed in three patients, and disseminated intravascular coagulation (DIC syndrome) was diagnosed in one patient in the comparison group (Table 3).

Table 3

Structure of postoperative complications

Complication	Main group	Comparison group
Sepsis	17(85.0 %)	10(100 %)
Thoracic complications	5(25.0 %)	7(70 %)
Wound complications	7(35.0 %)	8(80 %)
Fistulas	2(10.0 %)	10(100 %)
Reoperation	1(5.0 %)	4(40 %)
Bile leakage	3	9(90 %)
DIC syndrome	–	1(10 %)

The mean time to initiation of enteral feeding was 6.6 ± 0.4 days in the main group and 8.6 ± 1.1 days in the comparison group ($p < 0.05$). The mean length of hospital stay was 25.8 ± 4.2 days in the main group and 42.9 ± 6.8 days in the comparison group ($p < 0.05$). Thus, implementation of the improved treatment algorithm significantly reduced mortality and improved functional outcomes in patients with DI (Table 4).

Table 4

Comparison of recovery parameters

Parameter	Main group	Comparison group	p
Time to enteral feeding (days)	6.6 ± 0.4	8.6 ± 1.1	< 0.05
Length of hospital stay (days)	25.8 ± 4.2	42.9 ± 6.8	< 0.05

The surgical management of combat-related abdominal trauma with DI at Role 2–4 levels of medical care in the main group was based on the following principles: adherence to the "golden hour" concept, application of damage control surgery (DCS), strict compliance with the staged approach to care, use of minimally invasive diagnostic and therapeutic methods (including ultrasound-guided interventions), adequate anesthesiological support, application of modern hemostatic and electrosurgical techniques, mobilization of the duodenum according to Kocher–Clermont and Cattell–Braasch (right medial visceral rotation), ultrasound-guided biliary drainage (when indicated), and a multidisciplinary approach to the development of the diagnostic and treatment algorithm.

Role 2 (Level 2 of medical care) At Role 2, the primary surgical interventions for DI included closure of defects. In cases of severe tissue destruction or complete rupture of a duodenal segment, temporary clipping of the wound edges was performed, with mandatory gastric decompression. Hemorrhage control was achieved by ligation, suturing, or electrocoagulation of bleeding vessels. When necessary, gauze packing of the abdominal cavity was performed using hemostatic materials or combined hemostatic techniques.

Role 3 (Level 3 of medical care) At Role 3, surgical interventions were primarily stabilizing in nature and included more detailed patient assessment using available diagnostic resources, including advanced imaging modalities. Within the framework of damage control surgery, programmed relaparotomy could be performed, along with control of residual bleeding and, when indicated, percutaneous transhepatic cholecystostomy under ultrasound guidance. After stabilization, patients were evacuated to Role 4 for definitive treatment.

Role 4 (Level 4 of medical care) At Role 4, the third phase of DCS was implemented, which in cases of severe injury could be divided into several surgical stages. Surgical procedures included duodenal diverticulization by suturing the pyloroduodenal junction, formation of an antecolic gastroenterostomy with a Braun enteroenterostomy (afferent loop length 40–50 cm). In cases of D1 segment injury with destruction of the pyloroduodenal junction, antrectomy was performed with formation of a gastroenterostomy on a long loop, also with Braun anastomosis. For severe injuries of the D2 segment (AAST grade III–IV), pancreatoduodenal resection or duodenectomy with external drainage of the common bile duct and pancreatic duct without anastomosis formation was indicated. Indications for total pancreatectomy included massive gunshot injuries of the duodenum (grade III–IV according to Moore classification), destructive pancreatic necrosis, or recurrent erosive hemorrhage. In injuries of the D3–D4 segments, the formation of a duodenojejunostomy is considered acceptable. In such cases, a perforated microirrigator may be introduced through the cystic duct into the afferent loop to provide local sanitation. In cases of duodenal suture failure, negative pressure therapy using the EndoVAC system proved to be effective. In the presence of purulent-inflammatory complications (subdiaphragmatic or subhepatic abscesses), ultrasound-guided puncture and drainage interventions within the framework of interventional ultrasonography are applied. Thus, the nature and extent of surgical interventions in combat-related abdominal trauma with duodenal injury are determined both by the level of medical care and by the patient's clinical condition, injury topography, intensity of combat activity in a given area, and evacuation capabilities. A certain overlap of surgical procedures may occur between Role 3 and Role 4 levels, particularly in situations where aeromedical evacuation is unavailable, and Role 3 facilities are compelled to assume part of the functions of higher-level specialized care.

At Role 2, the primary objective is to preserve vital functions through temporary damage control. In this context, damage control surgery (DCS) [9] involves the use of simple yet effective techniques, including primary repair of the intestinal defect (when feasible), temporary clipping of wound edges in cases of extensive damage, gastric decompression, abdominal packing in cases of hemorrhage, and ligation or coagulation of bleeding vessels. However, it is precisely at this stage that significant controversy exists regarding the extent of the primary surgical intervention.

In contrast to the main group, surgical management in the comparison group did not include systematic application of the damage control surgery concept, staged treatment according to levels of medical care, or a multidisciplinary decision-making algorithm. Minimally invasive and ultrasound-guided interventions were not utilized, including puncture-drainage techniques and percutaneous transhepatic cholecystostomy. Additionally, advanced surgical technologies such as active decompression techniques, negative pressure therapy (EndoVAC), programmed relaparotomy, and interventional ultrasonography were not

applied. In most cases, the surgical approach was limited to conventional laparotomy with primary repair of the injury, without clear differentiation of tactics based on the level of medical care. On the one hand, proponents of limited surgical intervention argue [17] that in unstable patients, under conditions of time constraints, limited instrumentation, or insufficient surgical expertise, any attempt at definitive reconstruction may lead to worsening hemorrhage, progression of shock, and fatal complications. On the other hand, some surgeons attempt to perform immediate definitive repair or even anastomosis, particularly in isolated injuries of AAST grade I–II. However, both literature data and analysis of clinical outcomes indicate [17] that such an approach is justified only in hemodynamically stable patients with limited injuries, when evacuation is either delayed or technically impossible.

Furthermore, there is ongoing debate regarding the appropriateness of using pyloric exclusion or biliary drainage at this stage [18]. These techniques may be beneficial in injuries involving the D1–D2 segments, particularly when combined with pancreatic injury; however, their implementation under Role 2 conditions requires sufficient surgical experience, operative time, and anesthesiological support, which are not always available. Thus, balancing the aggressiveness of surgical intervention with patient safety at this stage remains a key factor in clinical decision-making.

Following initial intervention at Role 2, patients should be evacuated as early as possible to Role 3 or Role 4 levels for further evaluation, repeat surgery (relaparotomy), and definitive anatomical reconstruction. Delayed definitive reconstruction allows stabilization of the metabolic state, restoration of hemodynamics, and reduction of the risk of suture failure and septic complications.

In general, the surgical management of combat-related DI should be based on the principle of survival and staged stabilization. The effectiveness of treatment depends not only on the choice of surgical technique but also on the coordination of a multidisciplinary team, including surgeons, anesthesiologists, intensive care specialists, traumatologists, and evacuation units. Such team interaction ensures an adaptive surgical strategy tailored to the dynamically changing clinical condition of the wounded patient and the operational situation in the combat zone.

Conclusions

1. The implementation of the developed surgical algorithm for combat-related DI, adapted to a multilevel medical support system, was associated with a significant improvement in treatment outcomes, including a reduction in postoperative mortality from 80.0 % to 10.0 %, shorter hospital stay, and earlier initiation of enteral nutrition.
2. Standardization of the staged surgical approach reduced the severity of the postoperative course and demonstrated a tendency toward a lower incidence of septic complications, including sepsis, fistula formation, and bile leakage, as well as a decreased need for reoperations.
3. The greatest clinical effectiveness of the proposed algorithm was observed in patients with AAST grade II–III DI, in whom its application resulted in significantly improved survival and functional outcomes.
4. The implementation of a unified algorithm for the management of DI within the military medical evacuation system is justified and appropriate, as it enhances the controllability of the treatment process, reduces variability in surgical decision-making, and improves overall clinical outcomes.

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PATHOMORPHOLOGICAL CHANGES OF THE RESPIRATORY TRACT IN COVID-19 BY AUTOPSY DATA IN THE ODESA REGION FOR 2020–2023

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PATHOMORPHOLOGICAL CHANGES OF THE RESPIRATORY TRACT IN COVID-19 BY AUTOPSY DATA IN THE ODESA REGION FOR 2020–2023

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Introduction. The spread of COVID-19 in Ukraine was documented on March 3, 2020. The first fatal case from coronavirus infection in Odesa region was recorded on April 23, 2020. A total of 1294 patients died from complications of the coronavirus disease in Odesa and Odesa region in 2020, 5560 patients died in 2021, and a total of 917 people died from coronavirus infection in 2022.

The aim of the study was to identify and study morphologic changes in the respiratory tract of patients who died from coronavirus infection in Odesa region.

Materials and methods. 50 cases of those who died between 2020 and 2023 with diagnosed COVID-19 (from the total number of those who died from complications of coronavirus disease in Odesa and the region) were randomly selected. Autopsy material was examined using routine morphologic methods.

Results and Discussion. Of the 7,785 people who died from complications of coronavirus disease: 3,922 cases were men (50.4 %), women – 3863(49.6 %). The largest group of the deceased that were people aged ≥ 71 years composed 3373 cases (43.3 % of the total number of those who died from complications of coronavirus disease). Of these, 1,691 were males (50.1 %) and 1,682 were females (49.8 %). Interstitial inflammatory infiltrate, cytopathic viral damage of alveolar epithelium, edema, hyaline membrane formation were found in the lung tissue of 47 deceased. The presence of multinucleated symplasts in the epithelium, desquamated atypical alveolocytes with large polymorphic nuclei, inclusions in the nuclei and cytoplasm, accumulations of erythrocytes, alveolar macrophages, marked edema, fibrin deposits were noted. Blood coagulation disorders occur due to damage to the endothelium of blood vessels, as well as liver cells, with the further development of thrombosis and hemorrhage. Hyperplasia of bronchiolar epithelium with areas of squamous cell metaplasia and dysplasia was also found.

Conclusions. The average age of the dead (men and women) was 64.5 ± 7.9 years. The revealed morphological changes in the respiratory tract are a consequence of both viral and leukocytic aggression. These changes underlie further progression of the disease and development of its complications.

Keywords: COVID-19, autopsy, SARS-CoV-2, pathomorphology, microscopic examination.

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ПАТОМОРФОЛОГІЧНІ ЗМІНИ РЕСПІРАТОРНОГО ТРАКТУ ЗА НАЯВНОСТІ COVID-19 ЗА ДАНИМИ АУТОПСІЙ В ОДЕСЬКІЙ ОБЛАСТІ ЗА 2020–2023 РОКИ

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Дослідження зосереджено на виявленні та інтерпретації морфологічних змін у респіраторному тракті пацієнтів, які померли від коронавірусної інфекції. Аутопсійний матеріал (із загальної кількості померлих від ускладнень коронавірусної хвороби в Одесі та області за 2020–2023 рр.) досліджували за допомогою рутинних морфологічних методів. Виявлені морфологічні зміни в респіраторному тракті є наслідками як вірусної, так і лейкоцитарної агресії та лежать в основі подальшого прогресування захворювання й розвитку його ускладнень.

Ключові слова: COVID-19, аутопсія, SARS-CoV-2, патоморфологія коронавірусної хвороби.

Introduction

On March 11, 2020, the WHO announced the beginning of the COVID-19 pandemic caused by the SARS-CoV-2 pathogen [1]. The first case of SARS-CoV-2 in the Odesa region was registered on March 25, 2020. The causative agent of the new COVID pandemic was SARS-CoV-2, a single-stranded RNA virus of the Coronaviridae family. The pathogenesis of COVID-19 is complex and still not fully understood [2; 3]. Despite previous data on the impact of viral infection on the entire body [4], it should be noted that society was not ready for the variable manifestation of SARS-CoV-2. At the same time, despite the rapid spread of the disease, which led to the recognition of the pandemic status worldwide, the virus itself and its manifestations were constantly changing, which led to the presence of differences in manifestations during the pandemic in different regions [5; 6].

Autopsy remains a research method that allows you to detect changes in organs and tissues throughout the body, and the results of autopsies of the first deaths from SARS-CoV-2 infection in Wuhan have long remained a reference point for the medical community around the world, but even in 2020, data were obtained that differed from the initial results [7; 8]. In particular, despite the large list of generally recognized changes in the lungs, numerous publications have differences in the description of morphological changes. This may be due, on the one hand, to regional characteristics, and, on the other hand, to changes in the virus itself during the pandemic and the corresponding change in the consequences of its presence in the body.

Based on the above, the **purpose** of this study was to identify and study morphological changes in the respiratory tract of patients who died from coronavirus infection in the Odesa region.

Materials and Methods

Among 7785 people who died from complications of coronavirus disease, 50 cases of people who died between 2020 and 2023 with diagnosed COVID-19 (from the total number of deaths from complications of coronavirus disease in Odesa and the region) were randomly selected. Their autopsies were performed at the Odesa Regional Bureau of Forensic Medical Examination. SARS-CoV-2 was confirmed by PCR either in vivo or postmortem. Autopsy material was fixed in 10 % neutral buffered formalin solution for at least 72 hours, with further standard histologic dehydration plus paraffinization, after that serial sections were prepared and stained with hematoxylin and eosin and picrofuchsin according to van Gieson. Macro- and microscopic changes in the respiratory tract were also evaluated [9]. The study was performed in accordance with the principles of the Helsinki Declaration of the World Medical Association "Ethical Principles of Medical Research Concerning Human Subjects" (2013), the procedure was done after approval from the Regional Ethical Review Board at Odesa National Medical University, protocol 11, 6th March, 2023.

Research results and their discussion

Of the 7,785 deceased patients (due to complications of coronavirus disease): 3,922 were men (50.4 %), women – 3,863(49.6 %). The largest group of the decease that were people aged ≥ 71 years totaled 3,373 cases (43.3 % of the total number of those who died from complications of coronavirus disease). Of these, 1,691 were males (50.1 %) and 1,682 were females (49.8 %). The average age of the dead (men and women) was 64.5 ± 7.9 years. According to medical history data, all the deceased had comorbid pathology (ischemic heart disease, atherosclerosis, hypertension, diabetes mellitus, obesity), multiple severe concomitant diseases, and various immunodeficiency states. During macro- and microscopic examination of the trachea and lungs of those who died from complications of COVID-19, we identified morphological features distinguishing COVID-19 from other acute respiratory viral infections. In the trachea we determined variably expressed hemorrhagic changes of the mucous membrane, weakly expressed in the proximal part and moderately or sharply manifested in the distal part and main bronchi, the mucous membrane was covered with mucus. There were also signs of blood circulation disturbance of microcirculatory vessels in submucous layer of trachea and bronchi in the form of various microangiopathies: stasis, thrombi, perivascular diapedesis hemorrhages and edema. The respiratory epithelium showed edema, dystrophy, foci of damage (Fig. 1), foci of desquamation (Fig. 2), enlarged nuclei were detected in bronchial epithelium cells (Fig. 3), basal cell hyperplasia of respiratory epithelium with formation of foci of squamous cell metaplasia, which leads to a sharp decrease in the barrier function of the epithelium.

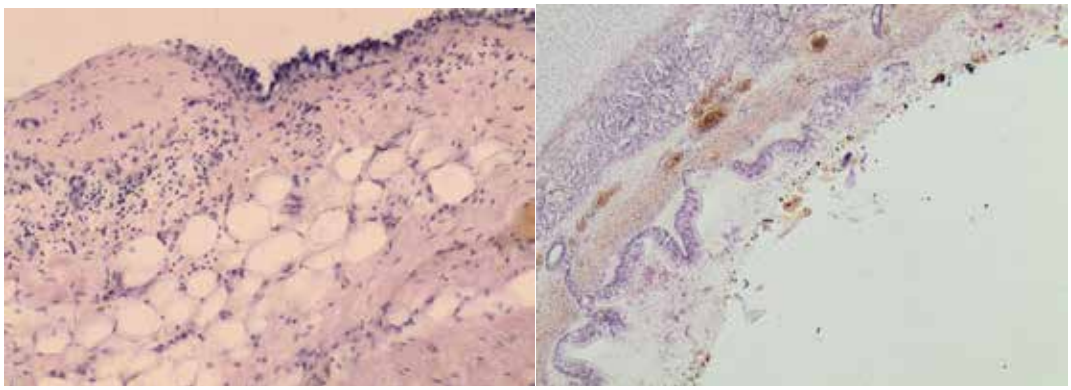

Fig. 1. Tracheal mucosa in COVID-19. Edema, epithelium is sloughed, focally necrotized, foci of epithelial proliferation with the presence of large epitheliocytes with hyperchromic nuclei, microcirculatory hemorrhage, erythrocyte sludge are determined. Inflammatory infiltration is weakly expressed. Hematoxylin and eosin staining, ×120

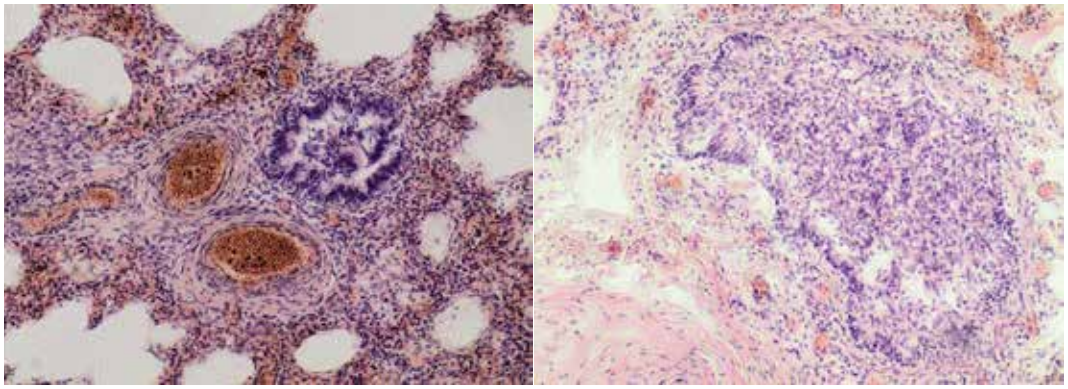

Fig. 2. Desquamation of bronchial epithelium, pronounced hyperemia. Hematoxylin and eosin staining, ×40

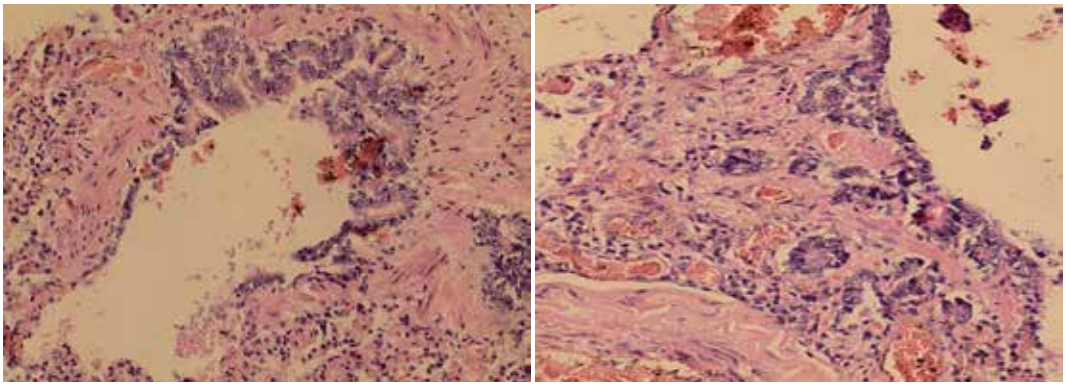

Fig. 3. Bronchial wall. Focal epithelium is absent, desquamated with foci of necrosis, enlarged epitheliocytes with hyperchromic nuclei (virus-associated changes) are determined. Hematoxylin and eosin staining, ×120

According to the results of our own observations we revealed the following morphological signs of coronavirus lung lesion: macroscopically the mass and size of the lungs were increased, the tissue was airless, unevenly compacted, on the section – dark pink, in some places red with a matte tint, in the posterior-lower sections with a whitish-gray tint, fleshy density to the touch. Dark bloody and frothy fluid flowed from the surface of lung sections when pressing. Pieces of lung tissue sank when immersed in formalin. In some cases subpleural foci of wedge-shaped, dark-red color, dense consistency were observed. The lumen of the pulmonary artery branches was obturated with crumbling masses of red color. Pleura was smooth, with injected vessels and hemorrhages – "lacquered lungs" (Fig. 4). Microscopically, at the beginning of the disease (exudative stage) diffuse alveolar lesions, "shock lungs" with accumulation of fibrinous exudate in the alveoli, acute alveolar distress syndrome, signs of viral hemorrhagic pneumonia, thrombosis of pulmonary artery branches, presence of hyaline membranes in the alveoli are detected.

Also microscopically, thickening of alveolar septa due to edema and hemorrhage, with signs of diffuse alveolar damage, acute bronchiolitis, pronounced edema and hemorrhagia in the interstitial tissue (Fig. 5), pulmonary artery thrombosis (Fig. 6), bronchospasm (Fig. 7), dystelectasis and atelectasis. Blood coagulation disorders occur due to damage to vascular endothelium as well as liver cells, with further development of thrombosis and hemorrhage. The development of vasculitis of small branches of the pulmonary artery is also characteristic of COVID-19 [17].

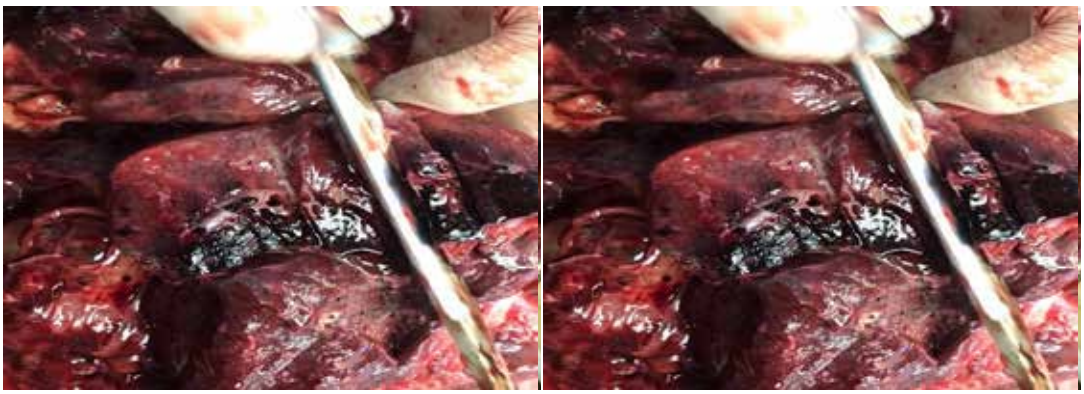

Fig. 4. "Lacquered lungs" of a deceased patient with verified COVID-19

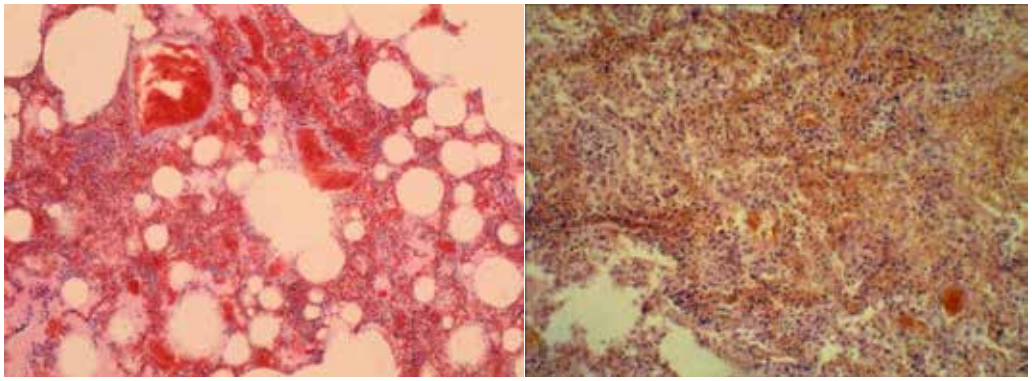

Fig. 5. Diffuse alveolar lesion. Hemorrhages in the walls of alveoli with desquamation of alveolar epithelium. Hematoxylin and eosin staining, ×100

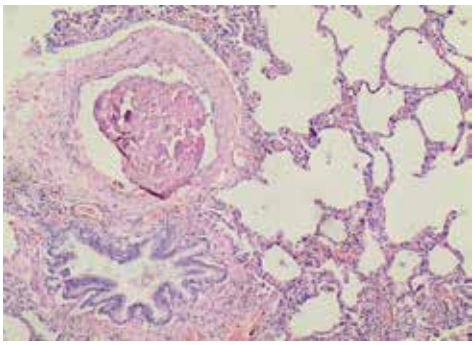

Fig. 6. Small bronchus spasm, epithelium is preserved, enlarged epitheliocytes with hyperchromic nuclei are focally determined. The lumen of the small branch of the pulmonary artery is obturated by a white thrombus with signs of organization. Hematoxylin and eosin staining, ×120

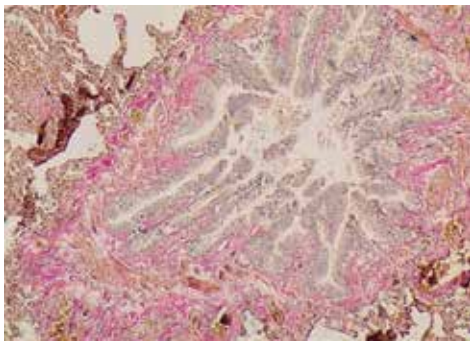

Fig. 7. Bronchial spasm. Epithelium is preserved, stasis of MCB vessels. Van Gieson staining, ×250

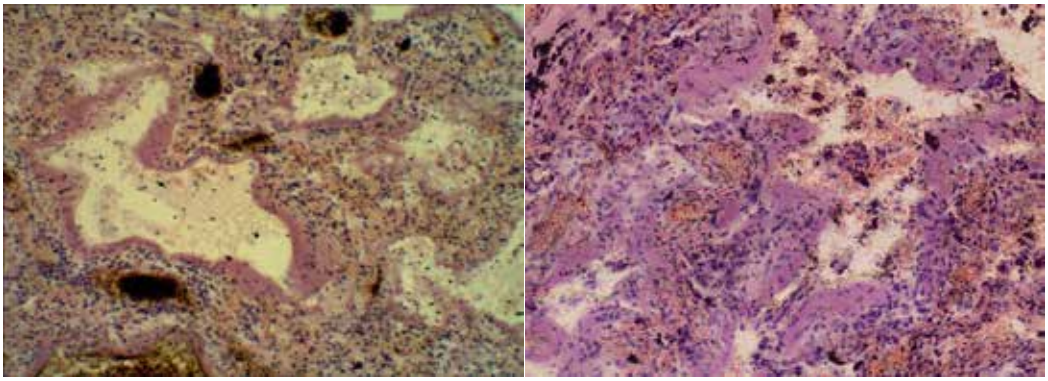

Fig. 8. Diffuse alveolar lesion, exudative phase. Multiple hemorrhages in the walls of alveoli with desquamation of alveolar epithelium, hyaline membranes. Thrombosis of microcirculatory vessels with perivascular inflammatory infiltrate. Hematoxylin and eosin staining ×100

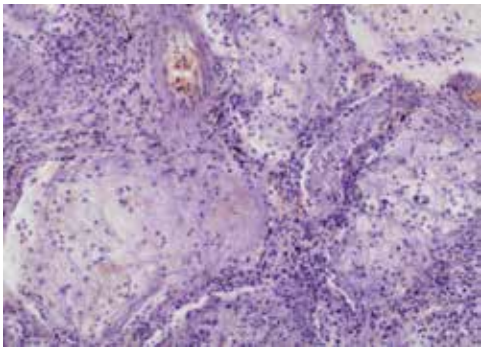

Fig. 9. Diffuse alveolar lesion. Fibrinous purulent exudate in the lumen of dilated alveoli. Hematoxylin and eosin staining, ×60

Interstitial inflammation differed in severity: from moderate in interstitial tissue to weak in vessel walls. The presence of multinucleated giant symplasts, desquamated alveolocytes with large polymorphic nuclei, granular cytoplasm, inclusions in nuclei and cytoplasm, as well as accumulations of erythrocytes, alveolar macrophages, edematous fluid, fibrin were observed in the lumen of dilated alveoli. The presence in most cases in alveoli and bronchioles of hyaline membranes (Fig. 8) lining their inner surface was also noted.

In 11 cases, virus-induced cytopathic changes in the respiratory tract and activation of bacterial and fungal flora caused the development of bilateral lobular pneumonia. Neutrophilic leukocytes and fibrin were present in large quantities in the lumen of the alveoli (Fig. 9). This morphologic picture is probably due to the immunosuppressive effect of the virus and the development of opportunistic bacterial and bacterial-fungal respiratory tract infections [17].

In the proliferative stage reparative processes of lung tissue develop with proliferation of fibroblasts and myofibroblasts, hyperplasia of type I pneumocytes, metaplastic changes in bronchial epithelium, focally with formation of adenomatous structures, dysplasia of squamous epithelium (Fig. 10), fibrosis (Fig. 11) and sclerosis of pulmonary interstitium, "carnification". Fragments of hyaline membranes may be preserved.

Among the factors leading to the changes we have described, it should be noted that in the pathogenesis of SARS-CoV-2, a very high affinity of its S-protein for the angiotensin-converting enzyme 2 (ACE-2) receptor has been identified. This protein is expressed at the receptor for ACE-2 in respiratory tract epithelia, alveolocytes, alveolar monocytes, vascular endothelium, gastrointestinal epithelia, kidney, myocardium, and some parts of the CNS. The direct action of the virus damages the endothelium of pulmonary vessels and other peripheral vessels, which induces hypercoagulability and an aggressive immune response. Due to this diffuse, massive aggression of SARS-CoV-2 towards the vascular endothelium, COVID-19 "masks" are very common in the form of exacerbation and aggravation of comorbid diseases: IHD, hypertension, diabetes mellitus, metabolic syndrome, immunodeficiency states [5; 10]. In case of the SARS-CoV-2 damage to lungs, type 1 and 2 alveolocytes and vascular endothelial cells are affected, which leads to impaired function of the aerohematic barrier and surfactant alveolar complex [11]. The main target cells for SARS-CoV-2 are alveolar epithelial cells, in the cytoplasm of which the virus replication occurs. After virions are assembled, they pass into cytoplasmic vacuoles, which migrate to the cell membrane and exit into the extracellular space via exocytosis. Expression of virus antigens on the cell surface before virions leave the cell does not occur, so antibody formation and interferon synthesis are stimulated relatively late. The formation of syncytium under the influence of the virus enables the latter to spread rapidly in tissues.

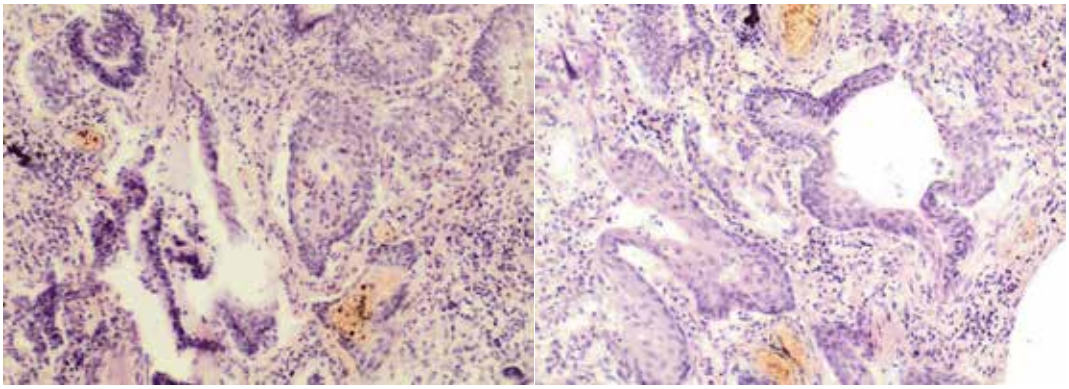

Fig. 10. Diffuse alveolar lesion, late stage. Squamous cell metaplasia of alveolar epithelium, fibrin and erythrocytes in the lumen of alveoli. Hematoxylin and eosin staining, ×120

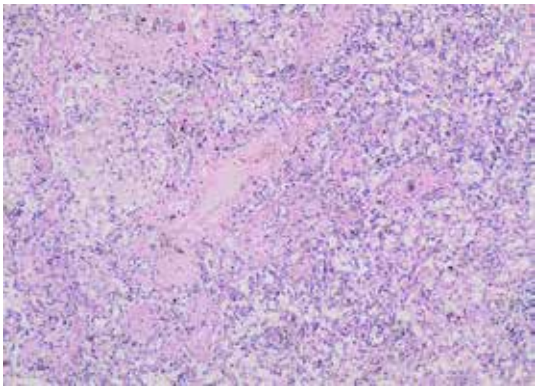

Fig. 11. Diffuse alveolar lesion, late stage. Diffuse fibrosis of the interalveolar septa. There is also focal edema and inflammatory infiltration of the interalveolar septa. Hematoxylin and eosin staining, ×40

Damaged epithelial cells produce cytokines [1] that attract leukocytes and activate neighboring endothelial cells, which stimulate infiltration which is inherent to the consequences of viral infection [12]. Also leukocytes induce production of reactive oxygen species, which in turn also damage the alveolar-capillary barrier, and activated macrophages cause apoptosis of epithelial cells [13]. Lung damage begins with diffuse alveolar damage, then against the background of cytokine storm there is tissue and vascular damage, development of inflammatory reaction and coagulopathy, destructive-productive thrombovasculitis of small arteries, development of acute alveolitis and viral-bacterial pneumonia with further fibrosis, focal adenomatosis and epithelial dysplasia [1; 7]. Viral and/or simultaneous bacterial infection, in addition to diffuse damage to alveocytes, leads to increased permeability of cell membranes, increased transport of fluid rich in albumin and fibrin into the interstitial lung tissue and alveolar lumen with the subsequent development of interstitial and alveolar edema. Along with this, changes in the elastic properties of surfactant are observed [14]. Destruction of surfactant leads to the development of alveolar collapse, a sharp disturbance of gas exchange leads to the development of acute respiratory distress syndrome. In addition to the activation of the inflammatory response, hypoxemia observed in patients with severe pneumonia and ARDS can potentiate the development of multiorgan failure, disseminated intravascular coagulation syndrome and in some cases lead to death [15]. Pathomorphologic changes in the lungs in COVID-19 are determined not only by the direct cytotoxic effect of SARS-CoV-2 on type II alveocytes, but also by the development of diffuse pulmonary intravascular coagulopathy. Changes in the lung tissue in COVID-19 are diffuse in nature, with the results of the CT examination showing the "ground-glass opacity" sign.

Our data could be used for explanation of severe epidemiologic consequences of SARS-CoV-2 pandemic events [16] with transformed inflammatory process in different organs and tissue [17; 18] and appearance of autoimmune processes.

The lungs bore the brunt of COVID-19 in autopsy studies, as has been described in previous studies [6; 19; 20]. A notable finding in our study was diffuse alveolar damage, which is commonly considered a histological hallmark of acute respiratory distress syndrome. It has three phases: an exudative phase that usually appears within 1–7 days, a proliferative phase that usually appears after 1–3 weeks, and a fibrotic phase that usually occurs after three weeks of illness [6]. In our data, we cannot state that the prevalence of proliferative diffuse alveolar damage was higher than that of exudative diffuse alveolar damage. The fibrotic phase was not observed frequently enough.

As in other studies, we found microscopic and macroscopic evidence of secondary respiratory infections in the form of bronchopneumonia and lung abscesses [6; 20]. Such infections among COVID-19 patients may be caused by prolonged hospitalization, prolonged mechanical ventilation, use of central venous catheters, immunosuppressive drugs such as steroids and tocilizumab, and potential gaps in routine infection prevention measures due to overburdened hospitals during this pandemic. An important feature of autopsy findings is evidence of thrombi and pulmonary embolism.

According to the currently accepted views on the pathogenetic mechanisms of SARS-CoV-2 lesions, in the lungs there is both a direct action of the virus on bronchial, alveolar epithelium and endothelium of small vessels, and damage associated with the action of "altered" macrophages, lymphocytes, neutrophils. The morphologic picture observed in the lungs generally corresponds to the action of the described pathogenetic mechanisms.

Conclusions

The results of the study showed that predominantly among those who died from complications of COVID-19 were people older than 71 years (43.3 %) with extensive comorbid pathology (IHD, diabetes mellitus, hypertension, malignant tumors, immunodeficiencies). Among those examined, bilateral bacterial pneumonia was diagnosed in 22 %. The predominant cause of death was severe respiratory failure, respiratory distress syndrome.

Autopsy macroscopically revealed: increase in the size of lungs, loss of airiness, presence of subpleural dark-red areas, smooth shiny pleura – "lacquered lungs".

Diffuse alveolar damage, edema and hemorrhages of interstitial tissue are determined microscopically. In the lumen of alveoli there is an accumulation of a large amount of fluid, fibrin and the presence of hyaline membranes along the walls of preserved alveoli. The presence of multinucleated symplasts, alveolocytes with polymorphic nuclei, neutrophils in the lumen of alveoli attracted attention. In vessels there was endothelium sloughing and the presence of endotheliocytes with polymorphic nuclei.

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CLINICAL PROFILE OF PATIENTS WITH PATHOLOGICAL ENDOMETRIAL CHANGES ASSOCIATED WITH METABOLIC FACTORS

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The aim of the study was to characterize the clinical profile of women with pathological endometrial changes associated with metabolic disorders, with an emphasis on disease course, comorbidities, and risk determinants.

Materials and methods. The study was conducted at the Multidisciplinary Medical Center of Odesa National Medical University and included 103 women who were examined between 2023 and 2025. Based on clinical and morphological findings, patients were divided into five groups: simple endometrial hyperplasia (n = 39), atypical endometrial hyperplasia (n = 9), endometrial cancer (n = 25), polycystic ovary syndrome (PCOS; n = 16), and a control group of healthy women (n = 14). Diagnosis was verified histologically using biopsy or surgical specimens. Cancer staging was performed according to the 2023 FIGO classification. All patients underwent comprehensive clinical, laboratory, and instrumental evaluation.

Results. Mean body weight and body mass index (BMI) in patients with hyperplasia and endometrial cancer corresponded to class I obesity and were significantly higher than in controls ($p < 0.05$). In the PCOS group, BMI values corresponded to overweight with marked variability. Obesity was prevalent in most women with endometrial pathology. Abnormal uterine bleeding was the leading symptom (69.2–92 %), while pain and urinary or bowel dysfunction were more typical of malignant disease. Cardiovascular and endocrine comorbidities predominated. Ultrasonography revealed progressive endometrial thickening, structural heterogeneity, and increased vascularization associated with disease severity.

Conclusions. Endometrial pathology is strongly associated with obesity and metabolic disorders. Ultrasonographic findings demonstrate high diagnostic value. Modifiable risk factors, particularly obesity, play a significant role in disease progression, highlighting the need for early detection and multidisciplinary management.

Keywords: endometrium, hyperplasia, abnormal uterine bleeding, obesity, carcinoma.

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КЛІНІЧНИЙ ПРОФІЛЬ ПАЦІЄНТОК ІЗ ПАТОЛОГІЧНИМИ ЗМІНАМИ ЕНДОМЕТРІЯ У ВЗАЄМОЗВ'ЯЗКУ З МЕТАБОЛІЧНИМИ ФАКТОРАМИ

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Мета дослідження полягала у визначенні клінічного профілю пацієнток із патологічними змінами ендометрія на тлі метаболічних порушень для встановлення супутньої патології та факторів ризику. Обстежено 103 пацієнтки, розподілені на групи залежно від морфологічного діагнозу. Встановлено, що середній ІМТ та маса тіла достовірно вищі у всіх патологічних групах порівняно з контролем, найвищі показники – у пацієнток із раком ендометрія. Провідний симптом – аномальна маткова кровотеча. Найчастіше супутніми станами були серцево-судинні й ендокринні захворювання. Ультразвукові зміни корелювали зі ступенем проліферації ендометрія. Отримані дані підтверджують найбільш часту клінічну асоціацію ожиріння та метаболічних порушень із наявністю патології ендометрія та підкреслюють необхідність мультидисциплінарного й персоналізованого підходу до ведення пацієнток групи ризику.

Ключові слова: ендометрій, гіперплазія, аномальна маткова кровотеча, ожиріння, карцинома.

Introduction

Endometrial pathology, including hyperplastic processes and endometrial cancer, occupies a leading position in the structure of gynecological morbidity and female mortality worldwide [1]. Over recent decades, a persistent upward trend in the incidence of these conditions has been observed, largely associated with the increasing prevalence of obesity, metabolic syndrome, and endocrine disorders [2]. According to international studies, a BMI ≥ 30 kg/m² is one of the most powerful independent risk factors for the development of both endometrial hyperplasia and endometrial cancer, exceeding even age over 45 years in prognostic significance [3]. The combination of obesity with insulin resistance, diabetes mellitus, and a hyperestrogenic state creates a pathogenetic basis for proliferative changes of the endometrium and their potential malignant transformation [4]. In this context, comprehensive clinical assessment of patients with endometrial pathology – taking into account metabolic status, comorbid conditions, and specific features of the clinical course – becomes particularly important, serving as a foundation for risk stratification and the personalization of therapeutic strategies.

The aim of the study. To determine the clinical profile of women with pathological endometrial changes associated with metabolic disorders, to identify the most significant clinical and somatic characteristics related to different forms of endometrial pathology.

Materials and Methods

The study was conducted at the Multidisciplinary Medical Center of Odesa National Medical University during 2023–2025. A total of 103 inpatient and outpatient female patients were examined. Based on the examination results, the patients were divided into the following groups:

• **Group Ia** – women with histologically confirmed endometrial hyperplasia without atypia (n = 39), according to the WHO 2014 classification;

• **Group Ib** – women with atypical endometrial hyperplasia / endometrial intraepithelial neoplasia (EIN) (n = 9), according to the WHO 2014 classification;

• **Group II** – patients with endometrial cancer (n = 25), according to the 2023 FIGO classification;

• **Group III (comparison group)** – women with polycystic ovary syndrome (PCOS), diagnosed according to the Rotterdam criteria (n = 16);

• **Group IV (control group)** – clinically healthy women without endometrial pathology (n = 14).

For all groups, morphological verification of the diagnosis was performed by histological examination of endometrial biopsy specimens and surgical samples obtained during pipelle biopsy, hysteroscopy, or hysterectomy. Cancer staging was carried out in accordance with the FIGO classification (2023).

All enrolled patients underwent a comprehensive clinical and anamnestic assessment according to the study protocol. Anthropometric evaluation included measurement of body weight (kg) and height (m), followed by calculation of BMI using the standard formula:

$$\text{BMI} = \text{body weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}.$$

Assessment of social status took into account age, level of education, marital status, and type of professional activity. Menstrual function was analyzed based on medical history data and included evaluation of age at menarche, regularity and duration of the menstrual cycle, volume of menstrual blood loss, as well as the presence and nature of menstrual disorders.

The examination protocol also included general clinical, laboratory, and instrumental investigations. Ultrasound examination was performed transabdominally and transvaginally during the first phase of the menstrual cycle (days 5–9) or on any day in postmenopausal women, in accordance with the objectives of the study.

The study was conducted in compliance with the principles of the Declaration of Helsinki of the World Medical Association, Ethical Principles for Medical Research Involving Human Subjects, approved by the Bioethics Committee (Protocol No. 18 dated December 6, 2023). Written informed consent was obtained from all participants prior to inclusion in the study.

Research results and their discussion

Analysis of age-related characteristics demonstrated that the mean age of patients in groups Ia, Ib, and IV was statistically comparable and was 47.6 years (95 % CI: 43.9–51.4), 47.0 years (95 % CI: 34.6–59.4), and 44.21 years (95 % CI: 35.0–53.4), respectively. In contrast, patients with endometrial cancer (group II) were significantly older, with a mean age of 60.1 years (95 % CI: 55.8–64.3), while women with polycystic ovary syndrome (PCOS, group III) were the youngest, with a mean age of 26.17 years (95 % CI: 19.6–32.8).

Anthropometric assessment revealed that the mean body weight in groups Ia, Ib, and II was 87.4 ± 11.6 kg, 89.1 ± 12.4 kg, and 85.6 ± 10.9 kg, respectively, which was significantly higher compared with the control group (72.3 ± 9.8 kg; $p < 0.05$). Mean height did not differ significantly between groups and ranged from 1.63 to 1.66 m.

The mean BMI values in groups Ia (31.8 ± 3.9 kg/m²), Ib (32.4 ± 4.1 kg/m²), and II (31.1 ± 3.7 kg/m²) corresponded to class I obesity and were significantly higher than in the control group (26.1 ± 3.2 kg/m²; $p < 0.05$). In women with PCOS, the mean BMI was 27.8 ± 4.6 kg/m², corresponding to the overweight category and characterized by pronounced interindividual variability.

Analysis of menstrual function showed that in group Ia, menarche at the age of 12–13 years was reported in 84.6 % of patients. A regular menstrual cycle was observed in 53.8 % of women, while 46.2 % had an irregular cycle. Menorrhagia was reported in 30.8 % of cases, dysmenorrhea in 43.6 %, and premenstrual syndrome (PMS) symptoms in 66.7 %.

In group Ib, menarche at 12–13 years occurred in 88.9 % of women. A regular menstrual cycle was maintained in 44.4 % of patients. Both menorrhagia and dysmenorrhea were reported in 44.4 % of cases, while PMS symptoms were present in 66.7 %.

In group II, menarche at 12–13 years was reported in 84.0 % of women. A regular menstrual cycle was observed in 64.0 % of patients; however, abnormal uterine bleeding predominated later in life. Menorrhagia was recorded in 24.0 % of cases, dysmenorrhea in 40.0 %, and PMS symptoms in 60.0 %.

In group III, a regular menstrual cycle was observed in only 37.5 % of patients, while 62.5 % had an irregular cycle. Menorrhagia was rare (6.3 %), whereas PMS symptoms were reported by 75.0 % of women.

In the control group (group IV), menarche at 12–13 years was observed in 78.6 % of women. A regular menstrual cycle was maintained in 85.7 % of patients; menorrhagia occurred in 7.1 %, and PMS symptoms were reported in 71.4 %.

Social status was assessed based on employment, marital status, educational level, and the presence of temporary or permanent absence from work.

In group Ia, most women were permanently employed. Employment sectors included services, trade, and the beauty industry (12 patients, 30.8 %), administrative and office work (10 patients, 25.6 %), healthcare and pharmaceutical fields (5 patients, 12.8 %), and education and science (4 patients, 10.3 %). Eight women (20.5 %) were temporarily unemployed or on leave. No pensioners were identified in this group. Higher education was reported in 27 patients (69.2 %), and 26 women (66.7 %) were married.

In group Ib, 7 patients (77.8 %) were employed, including 3 women (33.3 %) in the service sector, 2(22.2 %) in administrative and office positions, and 1(11.1 %) each in healthcare/pharmaceuticals and education/science. Two women (22.2 %) were temporarily unemployed; no pensioners were identified. Higher education was reported in 7 patients (77.8 %).

In group II, the proportion of women who were temporarily unemployed or retired was the highest (6 patients, 24.0 %). Among employed women, administrative and office work (6 patients, 24.0 %) and the service sector (7 patients, 28.0 %) predominated, while healthcare/pharmaceuticals and education/science employed 3 patients each (12.0 %). Pensioners accounted for 4 women (16.0 %) in this group. Higher education was reported in 16 patients (64.0 %), and 18 women (72.0 %) were married.

In group III, most patients were socially active; 2 women (12.5 %) were temporarily unemployed, and no pensioners were identified. Employment was most common in the service sector (6 patients, 37.5 %) and administrative and office work (4 patients, 25.0 %), while healthcare/pharmaceuticals and education/science employed 2 patients each (12.5 %). The majority of women had completed or incomplete higher education.

In group IV, 4 women (28.6 %) were temporarily unemployed or on leave, with no pensioners identified. Among employed participants, the service sector (5 women, 35.8 %) and administrative and office work (3 women, 21.4 %) predominated. Higher education was reported in 9 women (64.3 %).

The leading clinical symptom in patients with endometrial hyperplasia and endometrial cancer was abnormal uterine bleeding (AUB), which was observed in 69.2–92.0 % of cases. Pain syndrome and dysfunction of adjacent organs were more frequently reported in patients with malignant pathology. The distribution of clinical symptoms is presented in Table 1.

Analysis of comorbid conditions demonstrated a predominance of cardiovascular and endocrine disorders in groups with hyperplastic and malignant endometrial changes, with the highest prevalence observed among patients with endometrial cancer.

In groups Ia and II, cardiovascular diseases were identified in 14 patients (35.9 % and 56 %, respectively). In the control group, cardiovascular pathology was detected in 3 patients (21.4 %). No cardiovascular diseases were recorded in groups Ib and III.

Endocrine disorders included diabetes mellitus and thyroid dysfunction. In group Ia, diabetes mellitus was diagnosed in 2 women (5.1 %), while thyroid disorders were identified in 3 patients (7.7 %). In group II, diabetes mellitus was detected in 5 women (20 %), whereas thyroid dysfunction was observed in 1 case (4 %). In group Ib, 1 case of diabetes mellitus (11 %) was recorded. No additional endocrine disorders were registered among women with PCOS.

Gastrointestinal diseases and anemia were observed only sporadically, predominantly in patients with simple endometrial hyperplasia and endometrial cancer. The overall structure of comorbid conditions is presented in Figure 1.

Ultrasound examination revealed clear intergroup differences. Endometrial hyperplasia and endometrial cancer were characterized by increased M-echo thickness, structural heterogeneity of the endometrium, and altered

Table 1

The distribution of clinical symptoms

Symptoms	Ia	Ib	II	III
AUB	69.2 %	77.8 %	92 %	56.3 %
Pain syndrome	6 %	22 %	48 %	25 %
Dysfunction of adjacent organs	–	7 %	28 %	6.3 %
Watery discharge	–	9 %	20 %	12.5 %

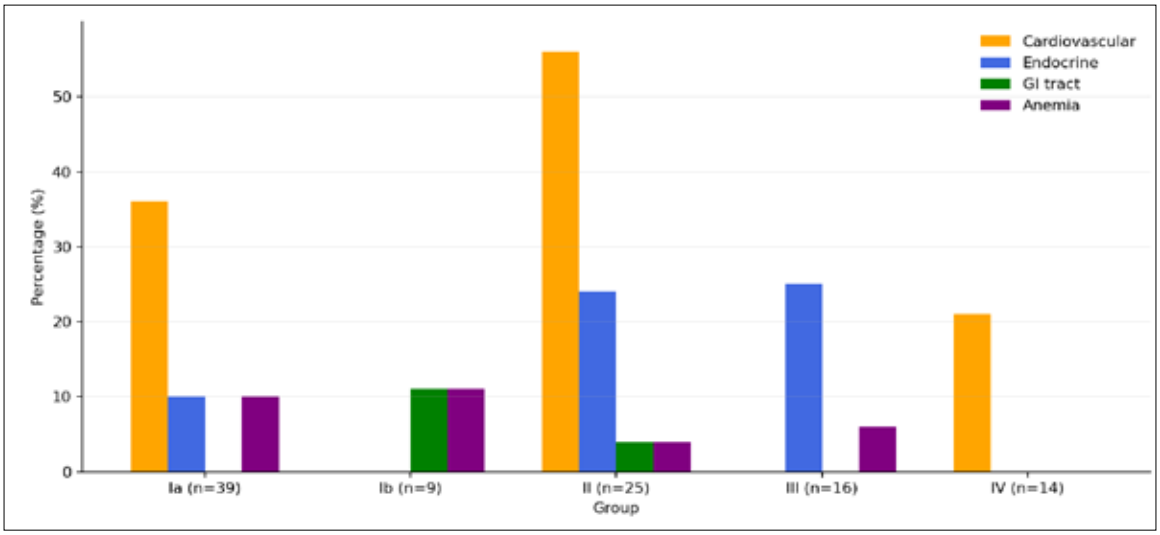

Fig. 1. Structure of comorbid conditions

vascularization, which correlated with the degree of proliferative activity. In women with PCOS, ovarian changes predominated with a relatively preserved endometrium, whereas in the control group the echographic pattern corresponded to the age-related norm.

A comparative characterization of the echographic features of the study groups is presented in Table 2.

The obtained results are consistent with current concepts of the pathogenesis of hyperplastic and malignant endometrial diseases as outlined in the ESGO, ESMO, and NCCN guidelines [5; 6; 7], which consider endometrial cancer a hormonally and metabolically associated disease, particularly in women with obesity and components of metabolic syndrome. According to the ESGO/ESTRO/ESP recommendations (2021–2023), excess body weight, insulin resistance, and diabetes mellitus are defined as key modifiable risk factors for the development of both endometrial hyperplasia and endometrial cancer. In our study, the mean BMI values in the hyperplasia and endometrial cancer groups corresponded to class I obesity, supporting the concept of a chronic hyperestrogenic environment driven by peripheral aromatization of androgens in adipose tissue as a central pathogenetic mechanism.

The NCCN guidelines (version 2024–2025) emphasize that in patients with endometrial pathology, obesity and diabetes mellitus not only increase disease risk but also worsen prognosis, affecting disease course, complication rates, and overall survival. The high prevalence of cardiovascular and endocrine comorbidity identified in our study, particularly in the endometrial cancer group, is fully consistent with these statements and highlights the need for mandatory cardiometabolic assessment of such patients already at the stage of primary diagnosis.

Importantly, the ESMO Clinical Practice Guidelines (2022–2024) consider abnormal uterine bleeding a key early clinical marker of endometrial pathology regardless of age, especially in women with obesity. In our study, abnormal uterine bleeding was the dominant symptom in most patients with hyperplasia and in more than 90 % of patients with endometrial cancer, supporting the appropriateness of a more aggressive diagnostic strategy in this category of women, including early hysteroscopy and morphological verification.

The ultrasound characteristics identified in our study (increased M-echo thickness, structural heterogeneity of the endometrium, and increased vascularization) are consistent with ESGO and NCCN recommendations, which underline the role of transvaginal ultrasound as the first-line risk stratification tool. At the same time, the guidelines stress that echographic features should not be considered in isolation and must be interpreted in conjunction with clinical and metabolic characteristics, which fully aligns with the concept of our study.

Particular attention should be paid to the group of patients with PCOS. According to ESMO and NCCN, PCOS is regarded as a condition associated with an increased risk of endometrial hyperplasia due to chronic anovulation and hyperestrogenism without adequate progesterone protection. Our findings demonstrating a predominance of ovarian changes with a relatively preserved endometrium in young patients with PCOS support the need for active surveillance in this group, with a focus on prevention of endometrial pathology.

Current ESGO/ESMO/NCCN recommendations also emphasize the transition from purely morphological to integrated clinicomolecular risk stratification. Although the present study primarily focused on clinical and metabolic profiles, the results confirm that these factors should serve as the foundation for subsequent molecular classification (POLE, MMRd, p53-abn, NSMP) and for selecting individualized treatment strategies.

Thus, the study findings not only agree with current international guidelines but also underscore their practical relevance in real-world clinical practice. A comprehensive assessment of clinical, metabolic, and echographic patient profiles enables optimization of early diagnosis, risk stratification, and personalized management of women

Table 2

Comparative characteristics of echographic features of the study groups

Feature	Ia	Ib	II	III	IV
Mean endometrial thickness (M-echo, mm)	12.9	12.1	11.6	9.8 ± 0.3	8.2 ± 1.1
Endometrial structure	Heterogeneous, microcystic changes (70 %)	Heterogeneous, increased echogenicity (100 %)	Heterogeneous, increased echogenicity (72 %)	Homogeneous	Homogeneous
Endometrial vascularization	Increased in 30 %	Increased in 50 %	Increased in 40 %	Reduced	Normal
Right ovary size (mm)	27 × 16 ± 14	26 × 15 ± 13	21 × 12 ± 11	35 × 26 ± 24	31 × 19 ± 17
Right ovary volume (cm^3)	3.2 ± 0.8	3.0 ± 0.8	1.6 ± 0.9	11.7 ± 3.2	4.8 ± 0.9
Left ovary size (mm)	26 × 15 ± 13	25 × 14 ± 12	23 × 13 ± 12	34 × 25 ± 23	30 × 18 ± 16
Left ovary volume (cm^3)	3.0 ± 0.7	2.7 ± 0.7	1.8 ± 1.0	11.0 ± 1.9	4.9 ± 0.8
Follicles	Dominant (55 %)	Single (37 %)	Absent	Multiple (24, 2–9 mm)	Normal
Additional findings	Fibroids (14,8 %), hydrosalpynx (5 %)	Subserous fibroids (33 %)	Hydrosalpinx (20 %)	Thickened capsule (100 %)	No pathology

with endometrial pathology, fully consistent with the modern paradigm of gynecologic oncology.

Conclusions

1. The clinical profile of patients with endometrial pathology is characterized by a high prevalence of obesity and cardiovascular and endocrine comorbidities.

2. Abnormal uterine bleeding is the leading clinical manifestation of hyperplastic and malignant endometrial changes.

3. Ultrasound features have high diagnostic value and correlate with the severity of the pathological process.

4. Modifiable risk factors, particularly obesity and metabolic disorders, play a key role in the progression of endometrial pathology.

5. Integration of clinical, morphological, metabolic, and instrumental data forms the basis of a personalized approach to the prevention, diagnosis, and treatment of endometrial diseases.

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VISUALIZATION OF COMBAT INJURIES: TEMPORAL STRUCTURE AND DEMOGRAPHIC DETERMINANTS

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VISUALIZATION OF COMBAT INJURIES: TEMPORAL STRUCTURE AND DEMOGRAPHIC DETERMINANTS
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Background. Modern warfare with widespread use of body armour has shifted the spectrum of combat injuries. The study aims to describe the pattern of combat-related injuries from computed tomography (CT) imaging during the full-scale invasion of Ukraine and to assess the predictive value of age alone employing machine learning methods.

Materials and methods. Opportunistic retrospective cohort study of 606 consecutively evacuated adult males who underwent CT at a second-level medical centre from April 2022 to September 2025. Multiclass automated machine learning (H2O AutoML) was trained using age as the sole predictor of CT-diagnosed injury category.

Results and discussion. No acute pathology was found in 50.3 % of scans. The most common findings were metallic foreign bodies in soft tissues (25.5 %) and extremity fractures. Penetrating torso and severe traumatic brain injuries were rare (< 0.3 %). The age patterns strongly influenced injury pattern: soft-tissue shrapnel wounds predominated in patients < 40 years, whereas fractures and degenerative changes prevailed in older combatants. Over four years, the proportion of chronic and combined injuries increased 2–3-fold. The best-performing generalised linear model achieved R^2 = 0.9996, but log-loss remained high (5.04) in middle-aged groups, confirming limited predictive power of age alone.

Conclusion. CT remains a gold standard in stratifying combat injuries. Machine-learning models using demographic variables are promising as clinical decision-support tools in resource-constrained wartime settings.

Keywords: computed tomography; combat trauma; machine learning; Ukraine war.

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ВІЗУАЛІЗАЦІЯ БОЙОВИХ УШКОДЖЕНЬ: ТЕМПОРАЛЬНА СТРУКТУРА ТА ДЕМОГРАФІЧНІ ДЕТЕРМІНАНТИ
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Ретроспективне дослідження комп'ютерної томографії 606 поранених військових за 04.2022 – 09.2025: 50,3 % пацієнтів без гострої патології. Домінували металеві сторонні тіла в м'яких тканинах (25,5 %) та переломи кінцівок; тяжкі торакальні / черепно-мозкова травма – < 0,3 % через ефект бронезахисту. Визначено віковий профіль: < 40 років – уламкові контузії м'яких тканин; > 40 років – переломи, гемартрози, дегенеративні зміни опорно-рухового апарату. Лінійна модель лише за віком досягла R^2 = 0,9996, але log-loss 5,04 вказує на потребу додаткових предикторів. Комп'ютерна томографія залишається золотим стандартом стратифікації бойових ушкоджень. Машинне навчання на демографічних даних має потенціал як інструмент підтримки рішень в умовах війни.

Ключові слова: комп'ютерна томографія; бойова травма; машинне навчання; війна в Україні.

Introduction

Combat injuries differ from civilian trauma in being predominantly penetrating or blast-related, caused by fragmentation and firearms [1]. Protective equipment such as body armor and helmets mitigates risk to specific anatomical zones. The affected population primarily consists of young, healthy men, which influences their initial clinical status and rehabilitation potential.

Conflicts in Ukraine, Gaza, Iraq, and Afghanistan have refined imaging protocols and improved management of military and civilian patients [2; 3]. Computed tomography (CT) is the standard initial diagnostic modality for severe injuries, guiding clinical decisions through rapid assessment of injury extent and location [5–7]. In modern warfare with explosives and high-velocity weapons, CT enables precise injury evaluation and prognostic prediction [8].

Diagnostic complexity has driven integration of CT findings with quantitative analysis. Although machine learning (ML) predicts outcomes in traumatic brain injury, wartime application in the Ukrainian healthcare system demands infrastructural adaptation, external validation, and consideration of combat-specific injury patterns [9–11]. This study addresses the lack of regional analyses combining

CT data with combat injury demographics, including age, aligning with global ML trends for outcome prediction.

The aim of this research was to analyze the structure of combat injuries using CT data among veterans wounded during the full-scale invasion and to evaluate the role of demographic factors in predicting injury typology employing machine learning methods.

Materials and Methods

In an opportunistic, retrospective, observational, descriptive study, a cohort of patients with combat-related injuries was assembled, who were admitted to a second-level medical center during the first four years of the full-scale invasion (April 2022–September 2025). Adult male patients (> 18 years) evacuated from the combat zone and had undergone CT for clinical indications were included; civilian patients were excluded. Data were obtained from electronic medical records by targeted search by age, date of examination, status, CT type, main radiological findings, and surgical outcomes. All records were anonymized and processed in accordance with the Declaration of Helsinki and applicable national legislation; the study was approved by the Ethics Committee of Odesa National Medical University (protocol No. 2, Feb 3, 2025).

In ~95 % of cases, brain CT was performed for suspected traumatic brain injury (TBI); chest CT was done only in the presence of external signs of injury or a specific request, whereas routine chest assessment was done by radiography. Imaging was performed using a NeuViz 64In multi-slice CT scanner (Neusoft Medical Systems Co., Ltd., China) with regular phantom calibration; quality control ensured image homogeneity, noise level, geometric accuracy, and Hounsfield unit consistency, thereby supporting reproducibility of results.

To quantify the effect of age on injury type, a multi-class H2O AutoML model [12] was developed, with age as the only predictor and diagnosis category as the outcome. For each patient, the model generated a set of relative probability scores for membership in each class; predictions were based on a linear combination of age with learned weights and normalization of outputs to a probability distribution. Automatic class balancing was applied to address class imbalance, and hyperparameter optimization was handled by the AutoML framework. To improve robustness, k-fold (k = 5) cross-validation was used; each fold produced a separate probability distribution, which was averaged by the final ensemble model to reduce random variation and increase prediction stability. Model performance was assessed using log loss, mean per-class error (MPCE), root mean square error (RMSE), and R^2 [13]. After training, a final prediction table containing the most probable diagnosis and the full probability spectrum for all diagnostic categories were generated. Computations were performed in R (ver. 4.3.2), and descriptive statistics are presented as means and SD.

Research results and their discussion

Over 36 months, CT was performed in 606 patients (mean age 37 ± 2 years): year 1 – 163(26.9 %); year 2 – 204(33.7 %); year 3 – 190(31.4 %); year 4 – 49(8.0 %). Primary mechanisms were mine-explosive injuries (59.9 %) and falls (40.1 %). Over half (50.3 %) showed no acute pathology, reflecting predominant use of CT to confirm or rule out clinically significant conditions [5–7].

The largest group of structural abnormalities comprised respiratory pathology (pleural and mediastinal changes), predominantly chronic inflammatory processes (sinusitis, pneumofibrosis), whereas specific infections such as tuberculosis were less common; isolated cases of emphysema, hydrothorax, or metastases (< 0.2 %) reflected age-related or somatic comorbidity. ENT pathology (ear, paranasal sinuses, orbit) was mostly chronic (sinusitis, mastoiditis > 4 %), with isolated polyps and developmental anomalies demonstrating CT diagnostic sensitivity. Musculoskeletal pathology (≈ 5 %) primarily involved degenerative-dystrophic spinal changes (osteochondrosis, spondyloarthrosis) consistent with the age and occupational profile of the combatant cohort, whereas isolated vascular lesions (haemangioma, aseptic necrosis), CNS findings (cysts, hygromas), and abdominal organ abnormalities (hepatosis, hydronephrosis) were incidental and clinically insignificant. Rare systemic diseases (sarcoidosis, metastases, < 0.3 %) carried prognostic weight warranting follow-up. Overall, non-combat pathology consisted of chronic inflammatory and degenerative processes affecting the respiratory system and musculoskeletal apparatus, with nearly a quarter of scans showing no CT evidence of pathology – confirming the rationale for CT use in early detection of subclinical changes.

The structure of combat injuries comprised soft-tissue injuries and isolated limb fractures (Fig. 1A), with a minor proportion of intracranial or thoracic injuries.

This injury pattern is typical of modern combat, where body armour and helmets substantially reduce lethality but increase the proportion of musculoskeletal injuries (Fig. 2, 3). It aligns with epidemiological trends in trauma patterns during military conflicts of the past decades [14].

Over 25 % cases involved metal-density foreign bodies in soft tissues, reflecting the predominance of contusion and fragmentation injuries (Fig. 1B, 4).

Soft-tissue defects, including wounds with loss of covering structures, were identified in 5.5 % patients (Fig. 5), consistent with the frequency of open injuries associated with blast mechanisms [2–3].

Mild traumatic brain injuries without visible CT abnormalities (concussion and subclinical disturbances) accounted for 3.3 %. Among fractures, lower-limb injuries (tibia, femur) predominated, whereas upper-limb fractures were less frequent; this pattern might reflect more effective torso armour and the characteristics of blast loading, although formal correlation analysis was beyond the scope of this study.

Thoracic injuries (haemothorax, hydropneumothorax, lung contusion) were rare (≤ 0.3 %), supporting the effectiveness of individual body armour. Isolated changes of the middle ear, nose, and paranasal sinuses related to blast acoustic trauma were also uncommon (< 0.2 %).

Lower-limb amputation states (0.7 %) and isolated upper-limb amputations reflected severe combined injuries and required staged reconstructive management. Postoperative changes (after laparotomy, splenectomy, vertebroplasty), including follow-up examinations, were recorded in fewer than 0.3 % of cases.

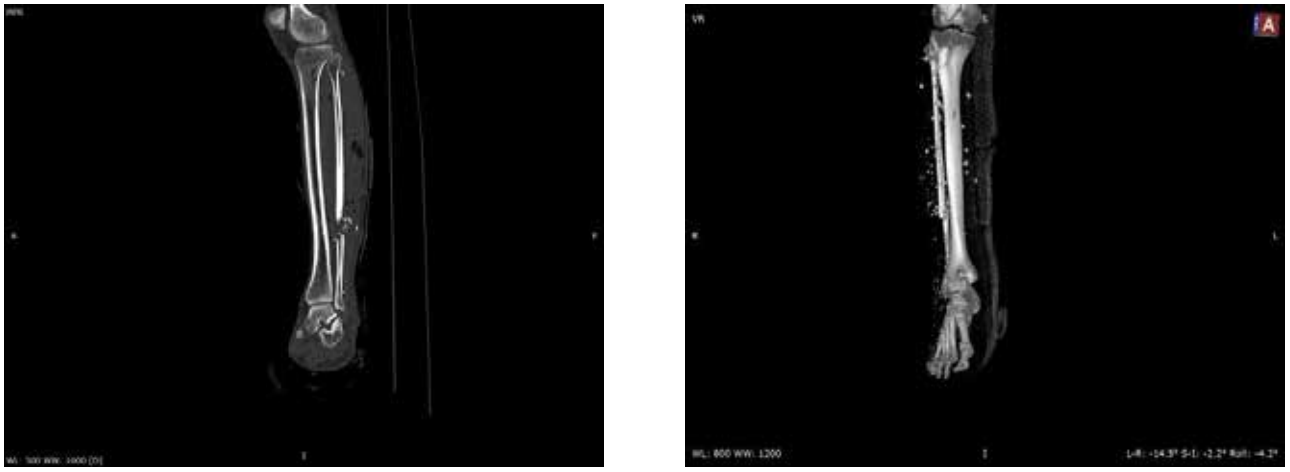

Fig. 1. Patient K., 28. Fracture of the fibula with multiple fragments; cast applied. A. MSCT image of the right lower leg (computed reconstruction). B. MSCT. Subtractive 3D reconstruction

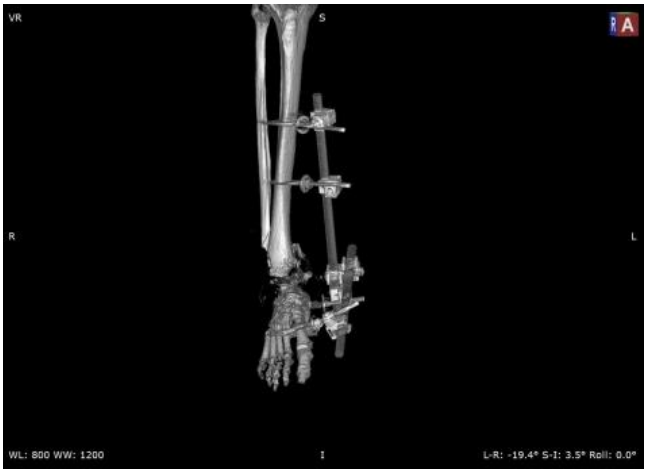

Fig. 2. Patient L., 35. MSCT. Subtractive 3D reconstruction of the right lower limb. Distal metaphyseal fractures. External fixation apparatus

Fig. 3. Patient M., 27. Metal plate system osteosynthesis (MOS) of the orbital floor and anterior wall of the maxillary sinus with metal plates: A. 3D reconstruction of the CT skull bone sequence. B. MSCT, axial projection

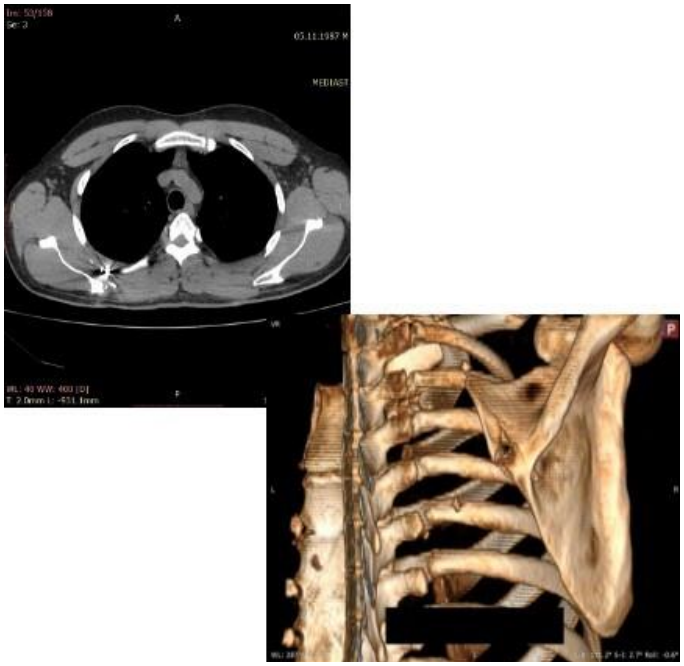

Fig. 4. Patient N., 35. Gunshot fracture of the right scapula: A. MSCT, axial chest projection. B. Subtractive 3D reconstruction

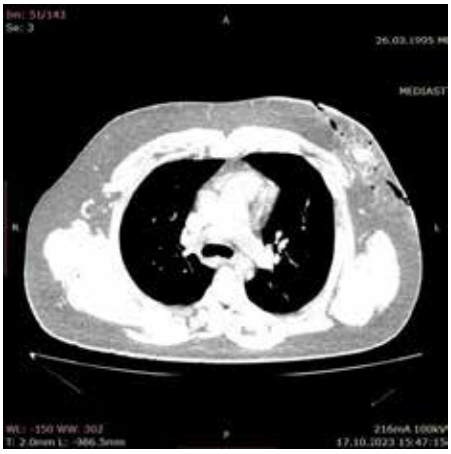

Fig. 5. Patient O., 28. MSCT chest, axial projection. Penetrating wound of soft tissues of the left anterior chest wall

The low proportion of metal-density foreign bodies in bone, together with a relative increase in haemarthroses and degenerative or post-traumatic changes, suggests a chronic component of cumulative trauma (Fig. 6).

Degenerative-dystrophic processes (spondylosis, arthrosis, retrolisthesis) were predominantly recorded in patients older than 35 years and accounted for a minor proportion of the total sample (< 1 %).

Role of age in injury frequency and severity

Analysis of clinical data from 2022–2025 revealed distinct age-stratified patterns of combat injuries (Fig. 7).

In younger groups (< 40 years), superficial injuries were more common, including infiltrates and metal-density foreign bodies in soft tissues, whereas in older age categories fractures and secondary degenerative changes were observed more frequently.

For the 25–39 years age range, maximum density of soft-tissue injuries, tibia fractures, and knee joint injuries was noted. The increased frequency of loading-type injuries – tibia fractures, haemarthroses, and soft-tissue haematomas – is consistent with previous observations in combat personnel of this age [14].

In middle-aged patients (40–59 years), the injury profile shifted towards chronic and combined processes: osteochondrosis, scapula, clavicle, and pelvic bone fractures were more frequent, along with metatuberculous lung changes as secondary post-traumatic or reactive manifestations. This spectrum reflects the cumulative effect of repeated mechanical loading with degenerative tissue remodelling; some cases involved polytrauma combining fractures, soft-tissue injuries, haematomas, intra-articular haemorrhages, and vertebral compression deformities. Such clinical heterogeneity produced the greatest variability in this age group, complicating differentiation and prognostication, driven by high physical activity, prolonged overloading, and secondary degenerative processes against a background of microtrauma and post-stress musculoskeletal changes [10; 12; 14].

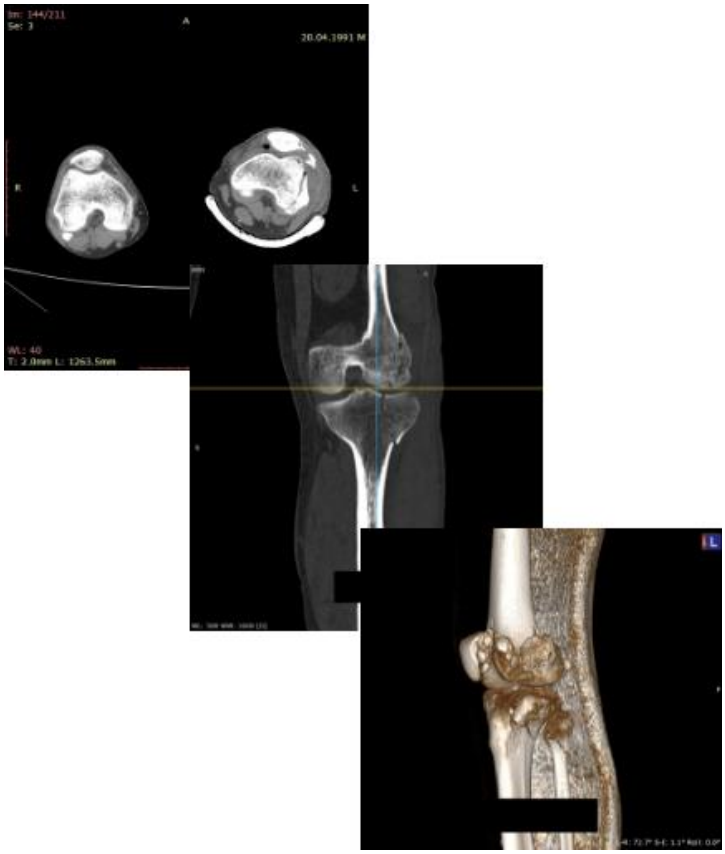

Fig. 6. Patient P., 31. Intra-articular comminuted fracture of the left knee joint involving the lateral condyles of the femur, tibia, and patella. Pneumohemarthrosis. MSCT of the left knee joint: A. Axial projection of both joints. B. Vertical reconstruction of the left joint (posterior). C. Subtractive 3D reconstruction of the left knee joint

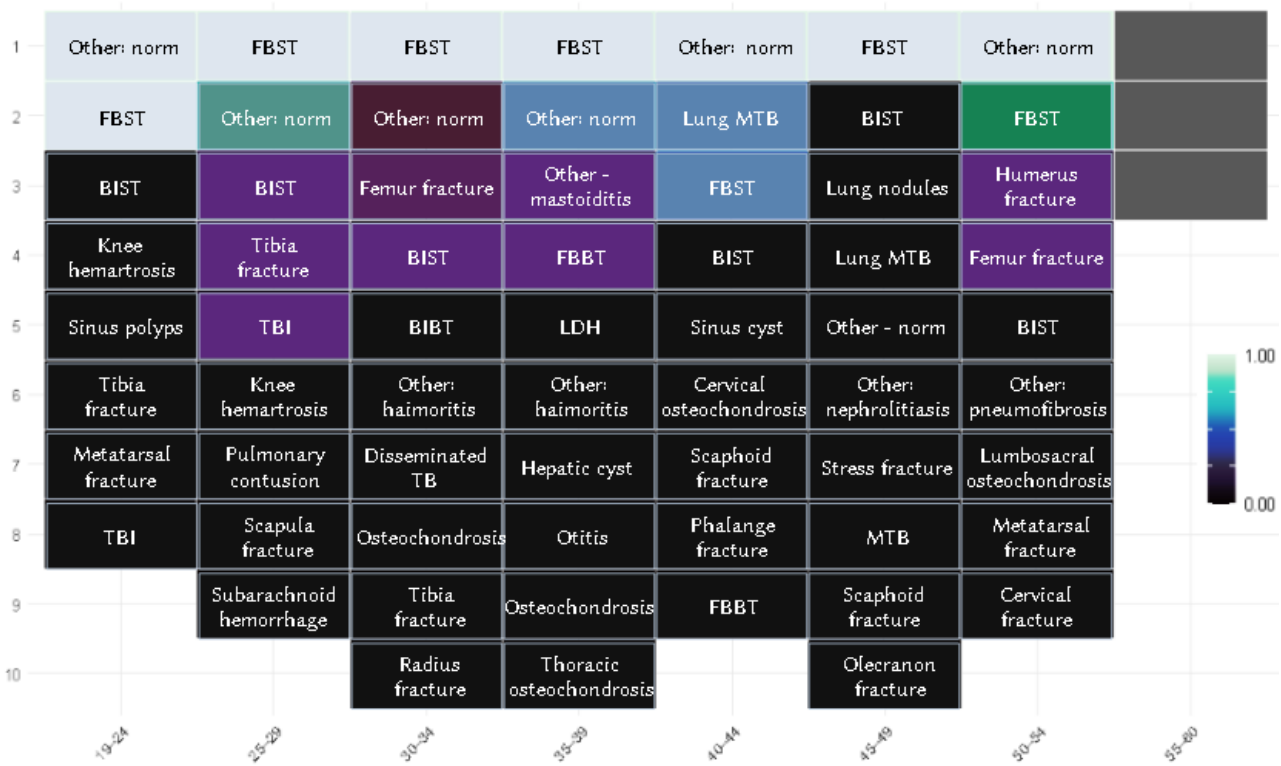

Fig. 7. Distribution of the most common diagnoses by age stratification (19–60 years). Axes: x – age groups; y – normalised ranking of diagnoses by prevalence. BIBT – blast injury of bone tissue; BIST – blast injury of soft tissue; FBBT – foreign bodies in bone tissue; FBST – foreign bodies in soft tissue; LDH – lumbar disc herniation; MTB – mycobacterium tuberculosis; TB – tuberculosis; TBI – traumatic brain injury

In older age groups (> 40 years), a decrease in incidence was noted alongside an increase in mean injury severity. Fractures of the radius, humerus, and femur predominated, reflecting age-related local reductions in bone mineral density and heightened risk of low-energy fractures.

A model of age impact

A multi-class generalized linear model (GLM) showed strong performance: log loss = 5.04, MPCE = 0.308, RMSE = 0.99, R^2 = 0.9996. The high R^2 value (with cautious interpretation) indicates model stability, whereas elevated log loss in middle-aged groups reflects increased data entropy due to class imbalance and the limited predictive power of age as the sole predictor [15; 16].

Comparison of model predictions with empirical data confirmed that age alone is an insufficient predictor: classification accuracy declined in the 30–59 years groups due to greater diversity of clinical scenarios. Normalized per-class accuracy varied substantially owing to uneven observation distribution [17], whereas younger and older cohorts showed more homogeneous classification patterns. Probabilities greater than 0.7 were presently considered as high model confidence, 0.3–0.7 as a zone of clinical uncertainty, and less than 0.1 as improbable outcomes.

Perfect classification accuracy (1.00) was achieved for soft-tissue defects, epidural haematoma, lung contusion, metatuberculous changes, and osteochondrosis, whereas lower values (0.02–0.17) were characteristic of metal-density foreign bodies in soft tissues, tibia fractures, and femur fractures – conditions with over-representation or complex morphology.

The full spectrum of predicted probabilities reflects model confidence and enables ranking of pathologies by reliability, rendering the approach suitable for initial prognostication of lesion localization in CT diagnostics. Combinations of high-probability comorbidities (eg, pelvic fractures with internal haemorrhage) could support automated generation of markers in clinical information systems, aligning with contemporary approaches to interpretable machine learning in clinical practice [6; 10; 11; 18–20].

Temporal evolution

Over 36 months, the temporal injury profile shifted from predominantly acute soft-tissue injuries early in the period to degenerative-dystrophic pathologies in 2024–2025. Soft-tissue injuries (metal-density foreign bodies) showed decreasing frequency – from ~ 27 % in 2022 to 18–20 % in 2025 – reflecting reduced isolated acute pathology amid stabilized combat loading and improved primary care. Traumatic brain injuries remained stable throughout (~ 45–52 % annually), underscoring the persistent nature of severe combined injuries (Fig. 8) and limited prevention opportunities in combat conditions [8].

A temporal shift was also noted in the morphological spectrum toward recurrent and combined injuries. Osteochondrosis, haemarthrosis, and bone fractures increased 2–3-fold compared with the initial period:

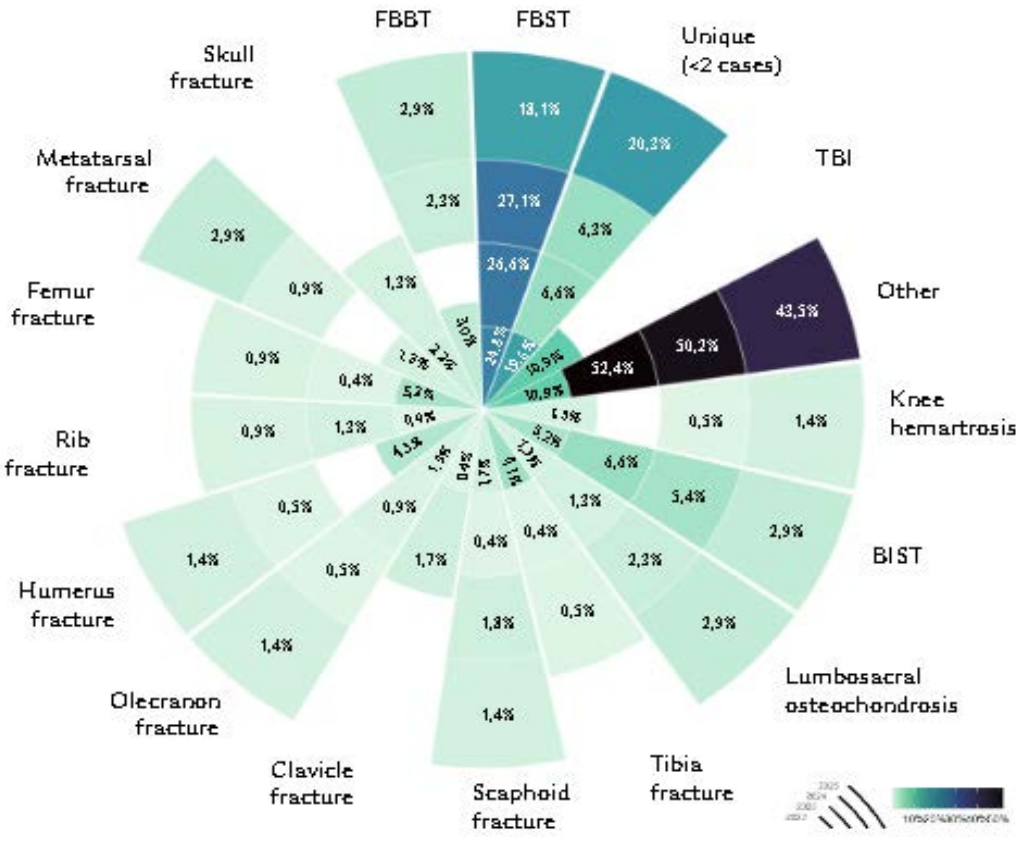

Fig. 8. Distribution of diagnoses, 2022–2025. BIST – blast injury in soft tissue; FBBT – foreign bodies in bone tissue; FBST – foreign bodies in soft tissue

their combined prevalence rose from 1–3 % in 2022 to over 6–8 % in 2025, with haemarthrosis of the knee joint showing peak frequency. The rise in degenerative-dystrophic processes relates to accumulation of post-traumatic sequelae, musculoskeletal overloading, and ageing of the patient cohort.

Rare nosologies, nearly absent at the start of observation, began to be recorded from 2024 onwards at moderate frequency, including metatuberculous changes, soft-tissue defects, and unique combined injuries. Overall, the traumatological profile evolved from acute to chronic and polytraumatic patterns, with implications for clinical prognostication, rehabilitation strategy development, and inpatient resource planning [20]. This study captured only a subset of wounded patients, as patient distribution depended on evacuation availability, receiving facility capacity, and need for specialized care.

Conclusions

1. Computed tomography enables rapid severity stratification of injuries and remains the cornerstone diagnostic tool at second-level hospital admission.
2. Statistical analysis revealed age-related differences in injury types: younger patients more frequently showed multiple fragmentation injuries, whereas older patients exhibited combined trauma dominated by cranio-cerebral components and degenerative-dystrophic pathology.
3. The multi-class machine learning model demonstrates potential for injury type prediction from demographic data, supporting its use as a clinical decision support tool.
4. These findings validate the rationale for implementing regional CT data analysis systems using machine learning methods to enhance diagnostic accuracy and outcome prediction for combat injuries.

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КОМПЛАЄНТНІСТЬ ДІТЕЙ ІЗ ГЕМОБЛАСТОЗАМИ ТА ОЖИРІННЯМ У ПЕРІОДІ ПІДТРИМУВАЛЬНОЇ ТЕРАПІЇ: АНАЛІЗ БАР'ЄРІВ ПРИХИЛЬНОСТІ

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КОМПЛАЄНТНІСТЬ ДІТЕЙ ІЗ ГЕМОБЛАСТОЗАМИ ТА ОЖИРІННЯМ у ПЕРІОДІ ПІДТРИМУВАЛЬНОЇ ТЕРАПІЇ: АНАЛІЗ БАР'ЄРІВ ПРИХИЛЬНОСТІ

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Актуальність. Прихильність до лікування є ключовим чинником ефективності терапії педіатричних гемобластозів, особливо під час підтримувального лікування.

Мета дослідження. Визначити рівень комплаєнтності до підтримувальної терапії у дітей з гемобластозами на формування терапевтичної прихильності.

Матеріали та методи. Обстежено 166 дітей віком 8–18 років із гемобластозами, ожиріння виявлено у 66(39,7 %). Комплаєнтність оцінювали за клінічним і поведінковим підходами. Статистичний аналіз включав OR, 95 % ДІ, точний тест Фішера.

Результати. Прийнятну комплаєнтність встановлено у 84,9 % дітей. Факторами ризику були стомлення від лікування, низький соціально-економічний статус, підлітковий вік та ожиріння (OR = 3,23).

Висновки. Комплаєнтність має мультифакторний характер, а ожиріння може бути незалежним предиктором її зниження.

Ключові слова: діти, гемобластози, ожиріння, комплаєнтність, підтримувальна терапія.

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COMPLIANCE OF CHILDREN WITH HEMOBLASTOSIS DURING MAINTENANCE THERAPY: AN ANALYSIS OF BARRIERS TO ADHERENCE

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Background. Treatment adherence is a key factor in the effectiveness of therapy in pediatric hemoblastoses, especially during maintenance therapy.

Objective. To determine the level of compliance with maintenance therapy in children with hemoblastoses and to assess the factors influencing the formation of therapeutic adherence.

Materials and methods. A total of 166 children aged 8–18 years with hemoblastoses were examined; obesity was detected in 66(39.7 %). Compliance was assessed using clinical and behavioral approaches. Statistical analysis included OR, 95 % CI, and Fisher's exact test.

Results. Acceptable compliance was established in 84.9 % of children. Risk factors included treatment fatigue, low socioeconomic status, adolescence, and obesity (OR = 3.23).

Conclusions. Compliance has a multifactorial nature, and obesity can be considered an independent predictor of its decrease.

Keywords: children, hemoblastoses, obesity, compliance, maintenance therapy.

Вступ

Гемобластози залишаються однією з провідних причин онкологічної захворюваності в дитячому віці та становлять значну частку злоякісних новоутворень у педіатричній популяції [4; 13]. Завдяки впровадженню сучасних протоколів лікування, інтенсифікації хіміотерапії та розвитку підтримувальної терапії рівень виживаності дітей із лейкемією значно зріс і в окремих групах перевищує 85–90 % [3; 13].

Разом із тим ефективність лікування значною мірою залежить не лише від біологічних особливостей пухлини й адекватності терапевтичних протоколів, але й від рівня комплаєнтності пацієнтів до лікування [5; 7]. Недостатня прихильність до терапії, особливо під час тривалого етапу підтримувального лікування, може призводити до зниження інтенсивності терапії, підвищення ризику рецидиву та погіршення прогнозу захворювання [8; 14; 15].

Проблема комплаєнтності в дитячій онкогематології має мультифакторний характер. Ожиріння розглядається як один із значущих факторів, що впливають на перебіг онкологічних захворювань у дитячому віці та асоціюється з погіршенням довгострокових результатів лікування [10]. Дослідження свідчать, що на рівень прихильності до лікування можуть впливати психологічні, поведінкові, соціально-економічні та сімейні фактори [5; 7; 11]. Особливе значення має підлітковий вік, який асоціюється зі зниженням контролю з боку батьків і зростанням самостійності пацієнтів [1; 6].

Окрему увагу останнім часом приділяють проблемі ожиріння у дітей, які перенесли онкологічні захворювання. За даними досліджень, поширеність ожиріння серед цієї категорії пацієнтів є значно вищою, ніж у загальній популяції, і може досягати 15–56 % [2]. Ожиріння може негативно впливати як на фізичний стан дитини, так і на її психоемоційний статус, що потенційно знижує прихильність до лікування [9].

Водночас взаємозв'язок між метаболічними порушеннями, психоемоційним станом і терапевтичною прихильністю у дітей з гемобластозами залишається недостатньо дослідженим, що обумовлює необхідність комплексного вивчення факторів ризику некомплаєнтності.

У зв'язку із цим вивчення факторів, які впливають на комплаєнтність під час підтримувальної терапії у дітей із гемобластозами, є важливим для оптимізації лікувальної тактики та покращення довгострокових результатів терапії.

Мета дослідження – визначити рівень комплаєнтності до підтримувальної терапії у дітей з гемобластозами й оцінити вплив медичних, когнітивно-емоційних і соціально-демографічних факторів, зокрема ожиріння, на формування терапевтичної прихильності.

Матеріали та методи дослідження

Дослідження проведено відповідно до принципів Гельсінської декларації та правил належної клінічної практики. Протокол дослідження схвалено локальним етичним комітетом КНП «Одеська обласна дитяча клінічна лікарня» ООР (протокол № 32 від 10.02.2022). Від батьків дітей було отримано письмову інформовану згоду.

Критерії включення: діти віком 8–18 років з підтвердженим діагнозом гемобластозу, які проходили підтримувальну терапію після завершення інтенсивних етапів лікування та мали дані для оцінки комплаєнтності та бар'єрів прихильності.

Критерії виключення: відсутність ключових даних щодо комплаєнтності / бар'єрів; тяжкі супутні стани, що унеможливлювали оцінку показників.

До дослідження залучено 166 дітей (96 хлопчиків та 70 дівчаток). Структура захворювань включала: гострий лімфобластний лейкоз – 86(53 %), гострий мієлобластний лейкоз – 16(10 %), неходжкінські лімфоми – 18(11 %), лімфогранулематоз – 31(19 %), гістіоцитоз – 8(5 %), хронічна мієлоїдна лейкемія – 4(2 %). Ожиріння діагностовано у 66 дітей (39,7 %) за критеріями ВООЗ: ІМТ ≥ 95-го перцентиля для віку та статі.

Оцінка комплаєнтності проводилася із застосуванням трьох підходів. Клінічний підхід передбачав оцінку відповідності фактично отриманих доз хіміотерапії призначеному протоколу лікування. Поведінковий підхід оцінював ступінь відповідності поведінки пацієнта медичним рекомендаціям (регулярність приймання лікарських засобів, дотримання графіка візитів до лікаря). Доказовий (статистичний) підхід передбачав визначення порогу прийнятної комплаєнтності на основі її зв'язку з клінічними наслідками.

Категоріальні змінні наведено як n (%) з довірчим інтервалом 95 % (95 % ДІ). Для порівняння груп використано точний тест Фішера. Для оцінки асоціацій розраховували відношення шансів (OR) з довірчим інтервалом 95 % (95 % ДІ). Статистично значущими вважали відмінності, якщо $p < 0,05$. Аналіз статистичних даних проводили із застосуванням пакета статистичних програм SPSS (версія 26.0, IBM Corp., США).

Результати дослідження та їх обговорення

Під час інтерпретації результатів враховували, що в науковій літературі відсутній універсальний поріг комплаєнтності для всіх типів гемобластозів. у гострий період лікування прийнятним вважається рівень комплаєнтності 95–100 % (оптимальним є повне дотримання терапевтичного протоколу). Для найпоширенішого дитячого гемобластозу – гострого лімфобластного лейкозу – доказово встановлено, що рівень комплаєнтності під час підтримувальної терапії ≥ 95 % асоціюється зі зниженням ризику рецидиву [4].

У проведеному дослідженні рівень комплаєнтності під час індукційної та консолідаційної терапії був наближеним до оптимального (> 95 %) і становив 97,2 % (95 % ДІ 93,8–99,1). Натомість на етапі підтримувальної терапії комплаєнтність знижувалася до 84,9 %. Отримані результати свідчать, що підтримувальна терапія є критичним етапом лікування, під час якого ризик зниження терапевтичної прихильності є найбільш високим. Ці дані узгоджуються з результатами сучасних міжнародних досліджень, які показують, що саме на етапі підтримувальної терапії прихильність до лікування знижується до 70–90 % [15].

З метою визначення факторів, пов'язаних зі зниженням комплаєнтності, було проаналізовано потенційні бар'єри лікування, які умовно поділено на когнітивно-емоційні, медичні та соціально-демографічні. Результати аналізу когнітивно-емоційних факторів наведено в табл. 1.

Як видно з таблиці 1, статистично значущий зв'язок із некомплаєнтністю встановлено для «конкретного типу мислення» ($p < 0,001$), індивідуальних психологічних особливостей пацієнта ($p = 0,003$), наявності ожиріння ($p < 0,01$) та стигматизації або булінгу дітей з ожирінням ($p = 0,001$). Натомість негативне сприйняття хвороби або поганого прогнозу не продемонструвало статистично значущої асоціації з рівнем комплаєнтності.

Аналіз потенційних медичних факторів наведено в табл. 2.

Серед медичних чинників статистично значущий вплив на некомплаєнтність мали побічні ефекти лікування ($p = 0,029$), тривала терапія та «стомлення від лікування» ($p < 0,001$). Інші фактори, зокрема нерозуміння медичних інструкцій або недостатня комунікація з медичним персоналом, не показали статистично значущого зв'язку з комплаєнтністю.

Результати аналізу соціально-демографічних факторів наведені в табл. 3. Аналіз показав, що підлітковий вік ($p < 0,001$), низький соціально-економічний статус сім'ї ($p < 0,001$) та наявність братів і сестер у сім'ї ($p = 0,012$) були асоційовані зі зниженням комплаєнтності. Стать пацієнта й освітній рівень батьків не продемонстрували статистично значущого впливу на рівень терапевтичної прихильності.

Таблиця 1

Потенційні когнітивно-емоційні бар'єри комплаєнтності до терапії дітей із гемобластозами

Бар'єр	Прийнятна комплаєнтність			Неприйнятна комплаєнтність			Тест Фішера, p
	n	%	(95 % ДІ)	n	%	(95 % ДІ)	
«Конкретне мислення»	9	6,4	3,4–11,7	16	64,0	44,5–79,8	< 0,001
Поганий прогноз	20	14,2	9,4–20,9	5	20,0	8,9–39,1	0,542
Індивідуальні особливості пацієнта	6	4,3	2,0–9,0	6	24,0	11,5–43,4	0,003
Негативне сприйняття хвороби та лікування	29	20,6	14,7–28,0	8	32,0	17,2–51,6	0,204
Ожиріння	50	35,5	27,6–44,1	16	64,0	42,5–81,5	< 0,01
Стигматизація та булінг дітей з ожирінням	7	5,0	2,4–9,9	7	28,0	14,3–47,6	0,001

Таблиця 2

Потенційні медичні бар'єри комплаєнтності до терапії дітей із гемобластозами

Бар'єр	Прийнятна комплаєнтність			Неприйнятна комплаєнтність			p (Фішера)
	n	%	95 % ДІ	n	%	95 % ДІ	
Нерозуміння медичних інструкцій	10	7,1	3,9–12,6	4	16,0	6,4–34,7	0,231
Погана комунікація з медперсоналом	7	5,0	2,4–9,9	3	12,0	4,2–30,0	0,176
Побічні ефекти лікування	8	5,7	2,9–10,8	5	20,0	8,9–39,1	0,029
Тривала терапія, «стомлення» від лікування	4	2,8	1,1–7,1	9	36,0	20,2–55,5	< 0,001

Таблиця 3

Потенційні соціально-демографічні бар'єри комплаєнтності до терапії дітей із гемобластозом

Бар'єр	Прийнятна комплаєнтність			Неприйнятна комплаєнтність			p (Фішера)
	n	%	(95 % ДІ)	n	%	(95 % ДІ)	
Низький освітній рівень	19	13,5	8,8–20,1	5	20,0	8,9–39,1	0,367
Підлітковий вік	10	7,1	3,9–12,6	12	48,0	30,0–66,5	< 0,001
Стать (чоловіча)	76	53,9	45,7–61,9	12	48,0	30,0–66,5	0,666
Погані соціально-економічні умови	11	7,8	4,4–13,4	13	52,0	33,5–70,0	< 0,001
Наявність сиблінгів	45	31,9	24,8–40,0	15	60,0	40,7–76,6	0,012

Для кількісної оцінки сили асоціацій між окремими факторами та некомплаєнтністю було розраховано відношення шансів (odds ratio, OR) з довірчими інтервалами 95 %. З усіх проаналізованих факторів до фінальної моделі відношення шансів було включено чотири найбільш клінічно значущі предиктори, які продемонстрували статистично достовірну асоціацію з некомплаєнтністю та мали найбільшу силу зв'язку. До них належали стомлення від лікування, низький соціально-економічний статус, підлітковий вік та ожиріння. Вибір цих факторів зумовлений їх клінічною релевантністю та здатністю відображати різні компоненти біопсихосоціальної моделі формування терапевтичної прихильності (табл. 4). На рис. 1 представлено некориговані відношення шансів (OR) для основних факторів, які продемонстрували статистично значущу асоціацію з некомплаєнтністю.

Таблиця 4

Фактори ризику некомплаєнтності до підтримувальної терапії

Фактор	OR	P
Стомлення від лікування	19,3	< 0,001
Низький соціально-економічний статус	12,8	< 0,001
Підлітковий вік	12,1	< 0,001
Ожиріння	3,23	< 0,01

Отримані результати підтверджують, що терапевтична прихильність (комплаєнтність) до лікування у дітей із гемобластозами є складним багатофакторним феноменом, який формується під впливом клінічних, психологічних та соціально-економічних чинників [5; 7; 11]. Психоемоційні порушення та труднощі адаптації є важливими чинниками, що можуть знижувати прихильність до лікування у дітей з онкологічними захворюваннями [12]. Це узгоджується із сучасною біопсихосоціальною моделлю формування комплаєнтності в педіатричній онкогематології.

У нашому дослідженні встановлено, що рівень терапевтичної прихильності до терапії був високим на етапах інтенсивного лікування, проте знижувався під час підтримувальної терапії. Подібна закономірність описана в численних міжнародних дослідженнях. Однак систематичний огляд Zeng XL et al. (2023) показав, що рівень комплаєнтності у дітей із гострим лімфобластним лейкозом під час підтримувальної терапії коливається в межах 70–90 %, тоді як оптимальний рівень прихильності повинен перевищувати 95 % [15].

У проведеному дослідженні також встановлено, що окремі випадки неповного виконання протоколу лікування були зафіксовані у 15 пацієнтів (9,0 %; 95 % ДІ 4,7–13,4), що може розглядатися як потенційний фактор зниження терапевтичної прихильності.

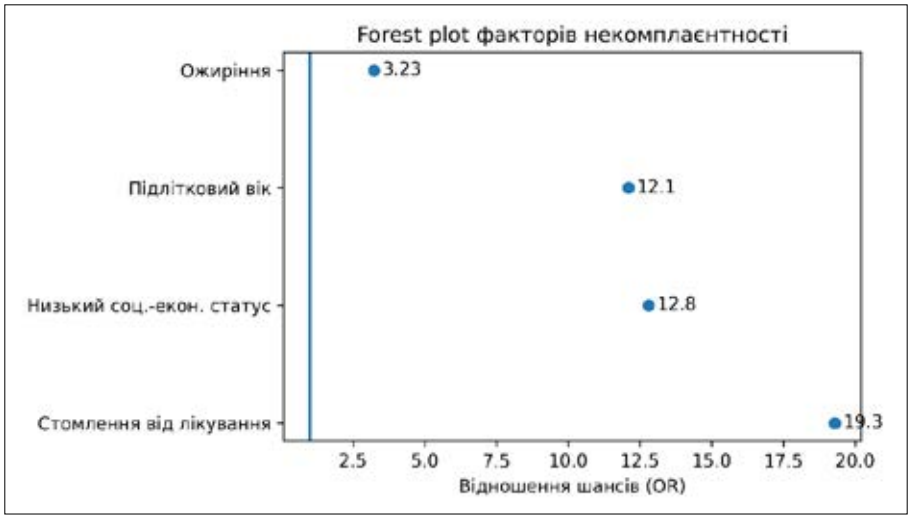

Рис. 1. Forest plot факторів некомплаєнтності до підтримувальної терапії у дітей з гемобластозами

*Примітка. Точки відображають відношення шансів (OR). Вертикальна лінія відповідає OR = 1.

Найсильнішим фактором у нашому дослідженні є «стомлення від лікування», що виникає за тривалого терапевтичного процесу (OR = 19,3; 95 % ДІ: 8,1–45,9; p < 0,001). Цей результат підтверджує, що тривале лікування, необхідність регулярного приймання лікарських засобів, часті госпіталізації та наявність побічних ефектів терапії можуть призводити до поступового зниження мотивації пацієнтів та їх родин до дотримання терапевтичного режиму, що підкреслює необхідність психологічної підтримки й освітніх програм для пацієнтів. Цей феномен розглядається в сучасних дослідженнях як один із ключових поведінкових факторів зниження терапевтичної прихильності у дітей з онкогематологічними захворюваннями [8].

Також встановлено, що низький соціально-економічний статус (OR = 12,8; 95 % ДІ: 5,4–30,1; p < 0,01) та підлітковий вік (OR = 12,1; 95 % ДІ: 4,9–28,7; p < 0,01) асоціюються зі значним підвищенням ризику порушення терапевтичного режиму. Подібні результати були отримані в дослідженнях щодо соціальних і сімейних детермінант прихильності до лікування в дитячій онкології [6]. Це пояснюється як віковими психологічними особливостями, так і поступовим зменшенням контролю з боку батьків.

Важливим результатом нашого дослідження є встановлення зв'язку між ожирінням і зниженням комплаєнтності. Отримані дані дають змогу розглядати ожиріння як незалежний предиктор зниження комплаєнтності під час підтримувальної терапії (OR = 3,23; 95 % ДІ: 1,4–7,2; p ≤ 0,01). Про клінічне значення ожиріння в контексті гемобластозів у дітей також свідчить зв'язок між стигматизацією / булінгом дітей з ожирінням і зниженням комплаєнтності (p < 0,001). За даними сучасних досліджень, поширеність ожиріння серед дітей, які пережили гемобластози, значно перевищує показники загальної популяції та може становити 15–56 % [2]. Отримані результати дають можливість розглядати ожиріння не лише як метаболічний стан, але і як потенційний психосоціальний фактор ризику порушення терапевтичної прихильності у дітей із гемобластозами та підкреслюють важливу роль психоемоційних факторів у формуванні некомплаєнтності. Виявлено, що когнітивні особливості мислення й індивідуальні психологічні характеристики пацієнта можуть суттєво впливати на дотримання терапевтичного режиму. Оцінка психоемоційних порушень дає змогу виявляти інтерналізовані розлади (тривогу, депресію) на ранніх етапах і своєчасно скоригувати супровід. Підтверджено, що психологічні характеристики пацієнта та сімейного середовища є важливими детермінантами терапевтичної прихильності в дитячій онкогематології [7; 11].

Перевагою цього дослідження є відносно велика вибірка пацієнтів із різними типами гемобластозів, завдяки чому вдалося комплексно оцінити медичні, психоемоційні й соціально-демографічні фактори формування терапевтичної прихильності.

Отримані дані мають важливе клінічне значення, оскільки дають можливість ідентифікувати ключові фактори ризику зниження терапевтичної прихильності та можуть бути використані для розробки індивідуалізованих програм психологічної і соціальної підтримки дітей із гемобластозами.

Таким чином, результати дослідження свідчать, що некомплаєнтність у дітей із гемобластозами формується в межах біопсихосоціальної моделі, де клінічні, психологічні та соціально-економічні фактори взаємодіють між собою. Це підкреслює необхідність мультидисциплінарного підходу до ведення таких пацієнтів, який має передбачати не лише оптимізацію медикаментозної терапії, але й психологічну підтримку, соціальну допомогу й індивідуалізовані стратегії підвищення комплаєнтності.

Висновки

1. Рівень комплаєнтності у дітей із гемобластозами є високим на етапах інтенсивної терапії, однак знижується під час підтримувальної терапії.

2. Некомплаєнтність формується під впливом комплексу когнітивно-емоційних, медичних і соціально-демографічних факторів, що підтверджує

мультифакторний характер терапевтичної прихильності в дитячій онкогематології.

3. Найбільш значущими предикторами зниження комплаєнтності є підлітковий вік, низький соціально-економічний статус, стомлення від лікування та наявність ожиріння.

4. Ожиріння може розглядатися як незалежний предиктор зниження терапевтичної прихильності у дітей із гемобластозами.

5. Отримані результати підкреслюють необхідність мультидисциплінарного підходу до ведення таких пацієнтів із залученням психологічної та соціальної підтримки.

Перспективи подальших досліджень

Незважаючи на переконливі докази значущості оцінки психоемоційного статусу та ЯЖ, у науковій літературі відзначається недостатність стандартизованих підходів до скринінгу психоемоційних порушень у дітей з онкогематологічними захворюваннями. Більшість досліджень зосереджені на гострій лімфобластній лейкемії, тоді як інші гемобластози (гострі мієлоїдні лейкемії, неходжкінські лімфоми) залишаються менш вивченими. Перспективним напрямом є розробка персоналізованих втручань, що враховують не лише нозологію, але й вік дитини, етап лікування та сімейний контекст.

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THE IMPACT OF ELEVATED HOMOCYSTEINE LEVELS ON THE DEVELOPMENT OF STRESS-ASSOCIATED ANXIETY AND DEPRESSIVE DISORDERS

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Methods. A prospective observational study included 131 adults (mean age 43.35 ± 16.37 years; 54.2 % women). Anxiety and depression were assessed using the GAD-7 and PHQ-9 scales. Homocysteine levels were quantified by LC-MS. Group comparisons and odds ratios (OR, 95 % CI) were calculated; $p < 0.05$ was considered statistically significant.

Results. Elevated homocysteine levels (≥ 10 μmol/L) were detected in 50.4 % of participants, while concentrations > 15 μmol/L were observed in 11.5 %. Homocysteine levels were approximately two-fold higher in individuals with clinically significant symptoms compared with those with subclinical manifestations (anxiety: 13.98 ± 4.50 vs 6.88 ± 2.08; depression: 13.92 ± 4.43 vs 6.87 ± 2.05; $p < 0.001$). Homocysteine ≥ 10 μmol/L was strongly associated with clinically significant anxiety (OR = 157.5; 95 % CI 33.4–741.6; $p < 0.001$) and depression (OR = 320.0; 95 % CI 40.0–2557.8; $p < 0.001$).

Conclusions. Hyperhomocysteinemia was common among individuals exposed to prolonged war-related stress and closely associated with the severity of anxiety and depression. Elevated homocysteine levels were identified in 50.4 % of the examined participants with ADDs, indicating a high prevalence of disturbances in one-carbon metabolism. A dose-dependent relationship between homocysteine concentration and ADDs severity was observed. Increased homocysteine levels were associated with a higher probability of clinically significant anxiety (58 %) and depressive disorders (64 %). These findings support the pathogenetic role of hyperhomocysteinemia in stress-associated ADDs and justify the use of homocysteine as a biomarker of risk, severity, and prognosis of anxiety-phobic and affective disorders.

Keywords: homocysteine, stress-associated disorders, anxiety depression, methylation, one-carbon metabolism.

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ВПЛИВ ПІДВИЩЕНОГО РІВНЯ ГОМОЦИСТЕЇНУ НА РОЗВИТОК СТРЕС-АСОЦІЙОВАНИХ ТРИВОЖНИХ ТА ДЕПРЕСИВНИХ РОЗЛАДІВ

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У дослідженні виявлено високу поширеність порушень одновуглецевого метаболізму серед осіб, які тривалий час перебували в умовах воєнного психотравмувального стресу. Підвищений рівень гомоцистеїну (≥ 10 мкмоль/л) виявлено у 50,4 % обстежених, що свідчить про метаболічну вразливість до тривожно-депресивних розладів (ТДР). Встановлено дозозалежний зв'язок між концентрацією гомоцистеїну та вираженістю ТДР. у пацієнтів із клінічно значущими симптомами тривоги та депресії його рівень становив близько 14 мкмоль/л, що майже вдвічі перевищувало показники осіб із субклінічними проявами (6,9 мкмоль/л). Підвищений гомоцистеїн був пов'язаний зі зростанням ризику клінічно значущої тривоги та депресії, підтверджуючи його патогенетичну роль і доцільність використання як біомаркера ризику та тяжкості ТДР.

Ключові слова: гомоцистеїн, стрес-асоційовані розлади, тривожно-депресивні розлади, метилювання, одно-вуглецевий метаболізм.

Introduction

Anxiety-depressive disorders (ADDs) are among the most common mental disorders today and constitute one of the leading medical and social problems worldwide [1]. In Ukraine, the urgency of this problem has become particularly acute due to the full-scale war, which is accompanied by the prolonged impact of extreme stressors, including direct threats to life, the loss of loved ones, forced displacement, socioeconomic instability, and psychological uncertainty [2]. According to international epidemiological studies, in populations exposed to armed conflict, the prevalence of anxiety and depressive disorders increases by 2–3 times compared to peacetime conditions, and their course is often characterized by chronicity and reduced response to standard therapy [3].

Homocysteine is a sulfur-containing amino acid formed during methionine metabolism and is a key component of one-carbon metabolism [4]. Its remethylation to methionine occurs with the participation of the enzyme methylenetetrahydrofolate reductase (MTHFR) and depends on an adequate supply of folic acid and vitamin B_{12} [5]. Impaired remethylation, as well as common MTHFR genetic polymorphisms, are associated with elevated homocysteine levels [6]. Homocysteine accumulation is considered a potentially neurotoxic factor and is associated with the development of a range of neurological and psychiatric disorders, including depression, anxiety, schizophrenia, cognitive impairments, and neurodegenerative diseases [7].

In addition, homocysteine can disrupt the biosynthesis of neurotransmitters. In the 5-methyltetrahydrofolate cycle, S-adenosylmethionine (SAM) – which is a methyl group donor and a precursor for the synthesis of serotonin, melatonin, norepinephrine, and dopamine – is demethylated to S-adenosylhomocysteine (SAH), and further to homocysteine, which is normally converted back to SAM [8].

Research findings also confirm the link between homocysteine and depression. It has been shown that low folate levels are a predictor of poor response to antidepressant therapy, as well as an increased risk of depression relapse [9]. The use of folic acid and/or vitamin B_{12} in patients with elevated homocysteine levels, compared to a placebo in healthy elderly individuals, resulted in a statistically significant reduction in serum homocysteine concentrations [10], but was not accompanied by an improvement in cognitive function [11] or a reduction in depressive symptoms [9].

At the same time, in clinical studies involving patients with depression, the use of folic acid and/or vitamin B_{12}, including as adjunctive therapy to antidepressants, has been associated in several studies with a reduction in the severity of depressive symptoms [12; 13]. A more pronounced reduction in symptoms was observed in patients with depression who had MTHFR gene polymorphisms [14]. In one study, the addition of folates and/or vitamin B_{12} to antidepressant therapy after remission was associated with a reduced risk of depression recurrence [15].

Despite the availability of a significant amount of data indicating a link between hyperhomocysteinemia and depression, research findings in this area remain inconsistent [16; 17]. Such variability in results may be due to differences in dietary habits, use of vitamin supplements, folate levels, as well as genetic, socioeconomic, and family factors that can modify homocysteine concentration and mental status.

Therefore, studying homocysteine levels in patients with ADDs under conditions of psychoemotional distress caused by the war in Ukraine is of particular relevance. Assessing homocysteine levels not only deepens our understanding of the biological mechanisms underlying stress-related disorders but also helps identify biochemical markers of ADDs severity and the risk of relapse. In addition, measuring homocysteine levels may have important prognostic significance regarding sensitivity to antidepressant therapy for ADDs, opening up prospects for a personalized approach to treatment.

Aim of the study. To determine the role of elevated homocysteine levels in the development of stress-associated ADDs and to assess the severity of these disorders in patients experiencing prolonged war-related psychological trauma.

Materials and Methods

This prospective observational study was conducted at the Saint Damian Healer Clinic in Kyiv and the Department of Psychiatry, Psychotherapy, Addiction Medicine, and Medical Psychology at Donetsk National Medical University (DNMU).

The study was conducted in accordance with the principles of bioethics and in compliance with the provisions of the Declaration of Helsinki ("Ethical Principles for Medical Research Involving Human Subjects"), as well as the UNESCO Universal Declaration on Bioethics and Human Rights. Prior to the start of the study, approval was obtained from the DNMU Ethics Committee (Protocol No. 3 dated March 5, 2025). All participants provided written informed consent to participate in the study.

The study included 131 patients who were residents of Ukraine, of whom 71(54.2 %) were women and 60(45.8 %) were men. The mean age of the participants was 43.35 ± 16.37 years, the median was 44 years, with an age range from 18 to 75 years, indicating adequate age representativeness of the sample.

In cases where subclinical symptoms were identified that did not meet the diagnostic criteria for anxiety-phobic and affective disorders according to the International Classification of Diseases, 10th Revision (ICD-10), psychoemotional distress was coded using code Z73.3 (stress, not classified elsewhere). This group included 75 individuals, accounting for 56.4 % of the total number of examinees.

Clinically significant anxiety disorders meeting the diagnostic criteria for mental disorders according to ICD-10 were identified in 56(43.6 %) of the examined individuals. Generalized anxiety disorder (F41.1) was identified in 13 patients (22.8 %), mixed anxiety-depressive disorder (F41.2) in 19 patients (37.3 %), adjustment disorder with anxiety-depressive symptoms (F43.2) in 17 patients (29.8 %), a moderate depressive episode (F32.1) in 5 individuals (10.5 %), and dysthymia (F34.1) in 2 patients (3.5 %).

The study employed a comprehensive approach that included clinical-psychopathological, psychometric, and biochemical-molecular methods, as well as statistical analysis of the obtained data.

Anxiety and depression symptoms were identified using screening psychometric instruments, specifically the Generalized Anxiety Disorder Scale (GAD-7) [18] and the Patient Health Questionnaire (PHQ-9) [19].

The GAD-7 scale was used to quantitatively assess the severity of anxiety symptoms. Each of the 7 items was rated on a 4-point scale with a total score ranging from 0 to 21. A total GAD-7 score of ≥ 10 points was considered a criterion for clinically significant anxiety.

The PHQ-9 mental health questionnaire was used to assess depression. Each of the 9 items was rated on a similar 4-point scale (0–3 points), with a total score ranging from 0 to 27. A total PHQ-9 score of ≥ 10 points was defined as the threshold criterion for clinically significant depressive symptoms.

In the presence of clinically significant indicators of anxiety and depression, the results of the psychometric assessment were used as an auxiliary tool to confirm the nosological classification of mental disorders in combination with a clinical-psychopathological examination method. To confirm anxiety-phobic and affective disorders, the Structured Clinical Interview for DSM-5 Disorders (SCID-5) was used to establish a mental diagnosis in accordance with ICD-10 criteria.

Within the scope of this study, a comprehensive assessment of biochemical markers of one-carbon metabolism was conducted, reflecting the functional state of homocysteine methylation and remethylation processes. The analysis included the determination of several interrelated groups of indicators that characterize the metabolic and epigenetic mechanisms involved in the regulation of neurobiological processes.

Biological samples were collected via blood draw, followed by plasma analysis at accredited laboratory (Genova Diagnostics, USA). Methylation metabolite concentrations were determined using liquid chromatography-mass spectrometry (LC-MS). To assess the efficiency of methylation, homocysteine levels were measured, as homocysteine is considered a key biomarker of one-carbon metabolism disorders and a potential factor in the development of stress-associated ADDs.

Mathematical and statistical analysis was performed using Microsoft Excel 2019 software. Quantitative mathematical changes are presented as the mean (M) and standard deviation (SD). Linear regression analysis was used to analyze independent variables associated with homocysteine levels and indicators of anxiety and depression. To assess the risk of clinically significant anxiety and depression depending on homocysteine levels, odds ratios (OR) were calculated with a 95 % confidence interval (95 % CI). Quantitative indicators were compared between two independent groups using the nonparametric Mann–Whitney U test. A p-value of <0.05 was considered statistically significant.

Research results and their discussion

To comprehensively assess the state of one-carbon metabolism, an analysis of the distribution of serum homocysteine levels was performed. Table 1 presents the main descriptive statistics reflecting the distribution of homocysteine concentrations, the frequency of elevated levels, the prevalence of clinically significant hyperhomocysteinemia among the study participants, as well as the mean homocysteine level in patients with subclinical and clinical anxiety-depressive symptoms.

Table 1

Descriptive characteristics of homocysteine levels among the study participants (n = 131)

Indicator	Value
Mean homocysteine level, μmol/L (M ± SD)	9.89 ± 4.79
Median, μmol/L	10.0
Interquartile range (IQR), μmol/L	7.0–12.0
Minimum value, μmol/L	2.0
Maximum value, μmol/L	39.0
Patients with homocysteine levels < 10 μmol/L, n (%)	65(49.6 %)
Patients with homocysteine levels > 10 μmol/L, n (%)	66(50.4 %)
Patients with homocysteine levels > 15 μmol/L, n (%)	15(11.5 %)
Homocysteine in patients with clinical anxiety, μmol/L (M ± SD)	13.98 ± 4.50
Homocysteine in patients with subclinical anxiety, μmol/L (M ± SD)	6.88 ± 2.08
Homocysteine in patients with clinical depression, μmol/L (M ± SD)	13.92 ± 4.43
Homocysteine in patients with subclinical depression, μmol/L (M ± SD)	6.87 ± 2.05

Note: 0–5 μmol/L – low homocysteine level, 5–10 μmol/L – normal homocysteine level, 10–15 μmol/L – elevated homocysteine level, > 15 μmol/L – clinically significant hyperhomocysteinemia.

Analysis of homocysteine levels in the study sample revealed significant interindividual variability in this biochemical marker, reflecting the heterogeneity of one-carbon metabolism disorders. The mean homocysteine level was 9.89 ± 4.79 μmol/L. The observed range of values (from 2.0 to 39.0 μmol/L) indicates not only the presence of individuals with normal levels but also a significant proportion of patients with marked hyperhomocysteinemia.

In half of the examined patients (50.4 %), homocysteine levels exceeded the threshold value of 10 μmol/L, which is considered a clinically significant marker of methylation disorders and increased neurometabolic risk. In 15 patients (11.5 %), homocysteine concentration was greater than 15 μmol/L, corresponding to moderate and severe hyperhomocysteinemia and associated with neurotoxic, pro-inflammatory, and epigenetic abnormalities.

A comparative analysis of homocysteine levels according to the severity of anxiety symptoms revealed significant differences between the clinical groups. In patients with clinically significant anxiety, the mean homocysteine level was 13.98 ± 4.50 μmol/L, which was more than twice the corresponding value in the group with subclinical anxiety symptoms (6.88 ± 2.08 μmol/L, $p < 0.001$). The data obtained indicate a clear association between elevated homocysteine levels and more severe anxiety symptoms.

A similar pattern was observed regarding depressive symptoms. In patients with clinically significant depression, the mean homocysteine level was 13.92 ± 4.43 μmol/L, whereas in the group with subclinical depression it was nearly half as low – 6.87 ± 2.05 μmol/L ($p < 0.001$). The observed differences indicate a potential pathogenic role of hyperhomocysteinemia in the development of clinically significant ADDs.

The Spearman correlation analysis did not reveal any statistically significant associations between homocysteine levels and the age of the study participants ($\rho = -0.03$; $p = 0.71$), nor between homocysteine levels and gender ($\rho = 0.04$; $p = 0.62$). These results indicate that major demographic factors do not influence the variability of homocysteine concentration in the study sample. This suggests that elevated homocysteine levels in patients with ADDs are primarily driven by neurobiological mechanisms, specifically the effects of chronic psychoemotional distress and traumatic experiences, as well as disturbances in metabolic-epigenetic regulation associated with methylation processes.

To quantitatively assess the severity of anxiety symptoms in the study sample, a screening assessment was conducted using the GAD-7 scale. The results obtained allowed us to stratify patients by severity and characterize the distribution of clinically significant and subclinical anxiety in individuals who experienced prolonged distress under martial law. The analysis of the frequency distribution of GAD-7 scores is presented in Table 2.

A significant prevalence of anxiety of varying severity was observed in the study population. The lowest level of anxiety was recorded in only 24(18.3 %) patients. The largest group consisted of patients with mild anxiety, comprising 50 individuals (38.2 %).

Overall, in 57 patients (43.5 %), the level of anxiety reached a moderate or severe degree, indicating a high prevalence of clinically significant anxiety symptoms among individuals living under conditions of prolonged chronic stress.

The mean anxiety level on the GAD-7 scale among all study participants was 8.60±4.04 points, corresponding predominantly to mild-to-moderate anxiety.

Table 2

Anxiety structure among study participants according to the GAD-7 scale

Anxiety Level	Scores	N	%
Minimum	0–4	24	18.3
Mild	5–9	50	38.2
Moderate	10–14	46	35.1
Severe	≥ 15	11	8.4
Total		131	100

The odds ratio analysis demonstrated a very strong association between elevated homocysteine levels and the likelihood of developing clinically significant anxiety symptoms. In particular, in patients with homocysteine levels ≥ 10 μmol/L, the probability of clinically significant anxiety (GAD-7 ≥ 10 points) was significantly higher compared to those with homocysteine levels < 10 μmol/L (OR = 157.5; 95 % CI: 33.4–741.6; $p < 0.001$).

Linear regression analysis demonstrated a clear positive correlation between homocysteine levels and the severity of anxiety as assessed by the GAD-7 scale (Figure 1).

Elevated serum homocysteine levels were associated with an increase in the total score on the GAD-7 scale, indicating a gradual worsening of anxiety symptoms as metabolic disturbances progressed. The obtained coefficient of determination ($R^2 = 0.584$) indicated that more than half (58 %) of the variability in anxiety scores on the GAD-7 scale was statistically explained by homocysteine levels and suggested a significant contribution of one-carbon metabolism disorders.

Our findings are consistent with some scientific studies in which hyperhomocysteinemia is considered a biomarker of anxiety disorders. In particular, a link between elevated homocysteine and generalized anxiety and panic disorders has been reported [4].

The identified association between elevated homocysteine levels and the severity of anxiety symptoms can be explained by disruptions in key neurobiological mechanisms involved in stress adaptation. Hyperhomocysteinemia is accompanied by a decrease in

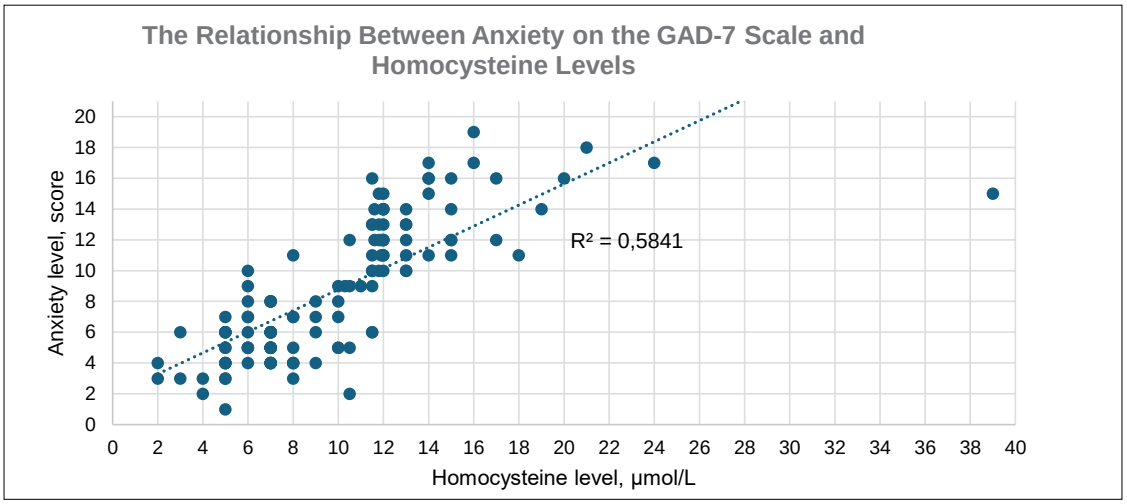

Fig. 1. Relationship between anxiety on the GAD-7 scale and homocysteine levels

cellular methylation capacity, leading to disruption of the epigenetic regulation of gene expression responsible for neuroplasticity, neurotransmission, and regulation of the hypothalamic-pituitary-adrenal (HPA) axis.

Under conditions of hyperhomocysteinemia, negative feedback mechanisms are disrupted, leading to persistent dysregulation of the cortisol response. This is accompanied by a decrease in the sensitivity of glucocorticoid receptors (FKBP5), disruption of the circadian rhythm of cortisol secretion, and a reduction in the body's adaptive reserve due to decreased expression of oxytocin receptor (OXTR) genes. This leads to hyperactivation of the amygdala, which plays a leading role in the formation of fear and anxiety, as well as to a reduction in the regulatory function of the prefrontal cortex.

Elevated homocysteine levels are accompanied by reduced expression of serotonin transporter (SLC6A) and serotonin type 1A receptor (HTR1A) genes, which significantly disrupts serotonergic neurotransmission and negatively affects the regulation of mood and behavior. At the same time, relative hyperactivation of the noradrenergic system is observed, which clinically manifests as increased vigilance, internal tension, and somato-vegetative symptoms of anxiety. Additionally, the balance between excitatory and inhibitory neurotransmitters is disrupted, particularly between glutamate and γ-aminobutyric acid (GABA), which contributes to the development of a state of neuronal hyperexcitability.

Hyperfunction of NMDA receptors leads to the activation of oxidative stress and mitochondrial dysfunction cascades, which damage neurons in the hippocampus and prefrontal cortex – structures involved in the regulation of mood, cognitive functions, and the emotional response to stress.

Our data are of particular scientific value in the context of war-related psychoemotional distress, as they are consistent with the findings of previous studies. In particular, the study by Lushchak O. et al. (2023) showed that patients with post-traumatic stress disorder (PTSD) have elevated homocysteine levels, and the duration of the disorder may serve as a predictor of the degree of its increase. The results obtained indicate the cumulative effect of chronic psychotraumatic stress on disturbances in one-carbon metabolism and methylation processes, which is of fundamental importance for understanding the biological mechanisms underlying the development of stress-associated disorders [20].

To assess the prevalence and severity of depressive symptoms in the study cohort, a screening survey was conducted using the PHQ-9 questionnaire. The results were stratified according to the generally accepted cutoff scores of the scale, which allowed for a quantitative characterization of the distribution of depression by severity level (Table 3).

Table 3

Structure of depression among study participants based on the PHQ-9 mental health questionnaire

Level of depression	Scores	n	%
Minimum	0–4	41	31.3
Mild	5–9	34	26.0
Moderate	10–14	18	13.7
Moderately severe	15–19	35	26.7
Severe	≥ 20	3	2.3
Total		131	100

Analysis of the PHQ-9 questionnaire data demonstrated significant heterogeneity in the clinical manifestations of depressive symptoms among the study participants. In 41 patients (31.3 %), the scores corresponded to the minimal level of depression, indicating the absence of or clinically insignificant manifestations. At the same time, 34 individuals (26.0 %) were found to have mild depressive symptoms. Overall, 75(57.3 %) patients exhibited subclinical manifestations of depression that did not meet the diagnostic criteria for affective disorders according to the ICD-10.

Clinically significant depressive symptoms (PHQ-9 ≥ 10 points) were observed in 56 patients, accounting for 42.7 % of those examined. Specifically, in 18 individuals (13.7 %), symptoms corresponded to a moderate level of depression; in 35 patients (26.7 %), to a moderate-to-severe level; and in 3 individuals (2.3 %), a severe level of depression was recorded. This distribution indicates a significant prevalence of affective disorders among the study population and a high level of wartime psychoemotional distress.

The mean depression score on the PHQ-9 scale among all participants was 9.10 ± 5.86 points, which corresponds to the boundary between mild and moderate depression. The interquartile range of 4–15 points indicates an asymmetric distribution of scores with a shift toward higher values, reflecting the presence of a significant proportion of patients with clinically significant depressive symptoms.

It is worth noting that an extremely high odds ratio for the development of clinically significant depression (PHQ-9 ≥ 10 points) was found in patients with elevated homocysteine levels (OR = 320.0; 95 % CI: 40.0–2557.8; $p < 0.001$), indicating a strong association between hyperhomocysteinemia and the development of depressive disorders.

Figure 2 shows the relationship between the severity of depression on the PHQ-9 scale and serum homocysteine levels in patients who experienced prolonged psychoemotional stress under martial law conditions.

Analysis of the results demonstrates a clear positive linear relationship between homocysteine levels and the severity of depression. As serum homocysteine concentrations increase, there is a consistent rise in PHQ-9 scores.

The coefficient of determination ($R^2 = 0.6372$) indicates that approximately 64 % of cases of depression depend on homocysteine levels. It is worth mentioning that at homocysteine concentrations < 10 μmol/L, low and moderate PHQ-9 scores predominate, whereas at levels ≥ 10 μmol/L, there is a significant increase in the proportion of patients with clinically significant depression. Individual cases with very high homocysteine levels (≥ 20 μmol/L) are accompanied by moderately severe and severe depressive symptoms, further emphasizing the dose-dependent effect.

The results obtained are consistent with current understanding of the key role of hyperhomocysteinemia in the pathogenesis of depressive disorders as a biochemical

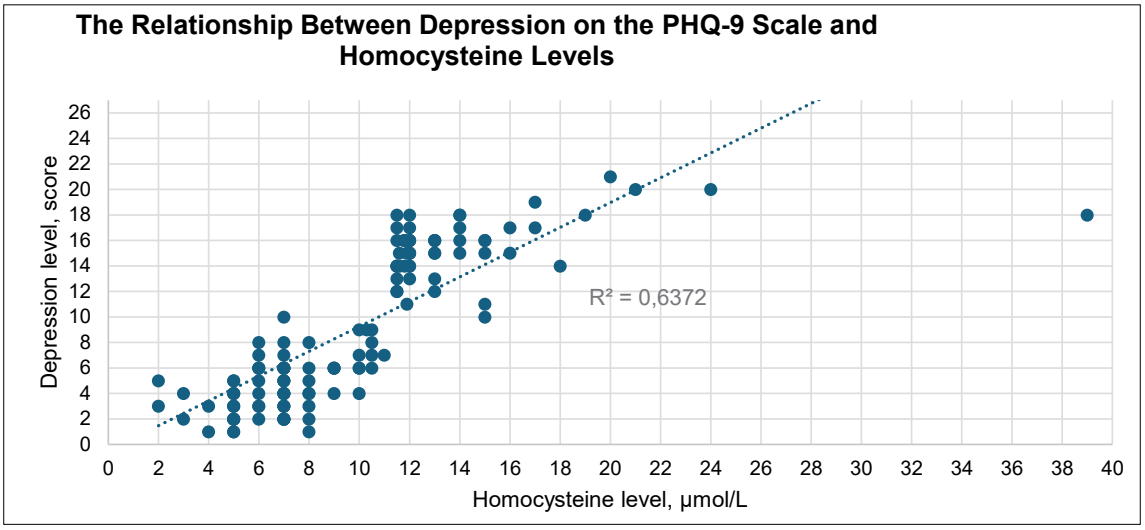

Fig. 2. Relationship between depression severity on the PHQ-9 scale and homocysteine levels

marker and a major pathogenic factor [6]. Elevated homocysteine levels reflect significant disturbances in one-carbon metabolism, leading to dysfunction in methylation processes, neuroplasticity, and neurotransmitter regulation.

Hyperhomocysteinemia leads to a shift in the balance of the methionine cycle toward the accumulation of SAH, which is a potent endogenous inhibitor of methyltransferases. This results in a functional decrease in the methylation index even at normal or subnormal SAM levels. Consequently, the methylation of DNA, RNA, proteins, and phospholipids is inhibited, which has direct epigenetic consequences.

Disruption of DNA methylation leads to dysregulation of gene expression responsible for neuroplasticity, neurogenesis, neurotransmitter regulation, and stress response, particularly genes encoding neurotrophic factors (BDNF), dopamine and serotonin receptors (COMT, DRD1, DRD2, DRD3, DRD4, HTR1A, SLC6A4), as well as enzymes involved in neurotransmitter metabolism (CACNA1C, ANK3, GSK3B, CHRNA3/CHRNA5, CNR1) and stress response genes (FKBP5, OXTR).

Elevated homocysteine levels are considered not only a marker of one-carbon metabolism disorders but also an active pro-inflammatory marker capable of initiating and sustaining a cascade of immuno-inflammatory reactions. Homocysteine stimulates the expression of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), at both peripheral and central levels. Elevated concentrations of these cytokines lead to the activation of microglia, the brain's primary immune cells, which is a key step in the development of neuroinflammation.

Chronic neuroinflammation and reduced expression of BDNF and its associated signaling pathways contribute to dendritic atrophy, decreased synaptic plasticity, and functional disintegration of the limbic-prefrontal networks of the brain, which are characteristic neurobiological markers of depression.

In addition to epigenetic mechanisms, homocysteine possesses direct neurotoxic properties; its excess can activate NMDA receptors, leading to increased calcium influx into neurons, the activation of oxidative stress cascades, and the development of mitochondrial dysfunction. Additionally, hyperhomocysteinemia is associated with depletion of the transsulfuration pathway and reduced levels of glutathione, the primary intracellular antioxidant. Glutathione deficiency exacerbates oxidative and nitrosative (NO) stress, further contributes to microglial activation, and worsens the state of chronic neuroinflammation.

In situations of prolonged psychoemotional and traumatic stress caused by war, these metabolic disturbances take on particular clinical significance. Prolonged activation of the HPA axis leads to persistent hypercortisolism, which further inhibits methylation, disrupts homocysteine remethylation and neuroplasticity, exacerbates neuroinflammation and oxidative stress, and causes mitochondrial and neurotransmitter dysfunction. Thus, a vicious cycle forms in which chronic stress, hyperhomocysteinemia, and depressive symptoms potentiate one another.

Conclusions

1. A high prevalence of one-carbon metabolism disorders was observed among patients who had lived under prolonged conditions of war-related stress. Elevated homocysteine levels (≥ 10 μmol/L) were recorded in half of the study participants (50.4 %), indicating significant metabolic vulnerability.

2. Homocysteine levels are closely associated with the severity of anxiety and depression. In patients with clinically significant anxiety, the mean homocysteine concentration was 13.98 ± 4.50 μmol/L, which was nearly twice as high compared to patients with subclinical anxiety (6.88 ± 2.08 μmol/L). In patients with clinically significant depression, homocysteine levels reached 13.92 ± 4.43 μmol/L, whereas in the group with subclinical depression, they were 6.87 ± 2.05 μmol/L. These differences indicate a clear dose-dependent relationship between hyperhomocysteinemia and the severity of affective disorders and confirm its potential pathogenetic role in the development of stress-associated mood disorders.

3. Extremely high odds ratios for the development of clinically significant anxiety and depression were found in

the presence of elevated homocysteine levels (OR = 157.5; 95 % CI: 33.4–741.6; $p < 0.001$) for anxiety and depression (OR = 320.0; 95 % CI: 40.0–2557.8; $p < 0.001$), indicating the key role of hyperhomocysteinemia as a biomarker of ADDs.

4. The results of linear regression analysis indicate that elevated homocysteine levels are associated with a significant increase in the likelihood of clinically significant anxiety (58 %) and depressive symptoms (64 %) and confirm the role of homocysteine as a biomarker of risk and severity of ADDs.

5. The obtained results confirm the pathogenetic role of hyperhomocysteinemia in the development of stress-associated ADDs through disruptions in methylation processes, epigenetic regulation, neuroplasticity, oxidative, mitochondrial, and neurotransmitter dysfunction, and the activation of neuroinflammatory processes.

6. Under conditions of prolonged war-related traumatic stress, hyperhomocysteinemia can be considered not only as a biochemical marker but also as a key factor forming a pathological cycle between dysregulation of the HPA axis, metabolic disturbances, neuroplasticity, and affective symptoms.

7. Determining homocysteine levels in patients with stress-related disorders is of significant clinical importance for risk stratification, assessing the severity of ADDs, and potentially predicting response to treatment with antidepressants.

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CHARACTERISTICS OF DERMAL BLOOD CIRCULATION AND SKIN MICROBIOCENOSIS IN PATIENTS WITH LICHEN PLANUS AND RATIONALE FOR OPTIMIZED THERAPY OF THIS DERMATOSIS

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CHARACTERISTICS OF DERMAL BLOOD CIRCULATION AND SKIN MICROBIOCENOSIS IN PATIENTS WITH LICHEN PLANUS AND RATIONALE FOR OPTIMIZED THERAPY OF THIS DERMATOSIS

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Introduction. The unclear etiology, complex pathogenetic mechanisms of lichen planus (LP) emphasize the necessity for further investigation into specific triggering factors – in particular, disturbances in dermal microcirculation and skin microbiocenosis – which play a significant role in the manifestation of this dermatosis and may contribute to the optimization of therapeutic strategies.

The aim of the study was to assess the functional state of dermal microcirculation and skin microbiocenosis in patients with different clinical forms of lichen planus.

Materials and methods. The study included 91 patients with LP (59 women and 32 men), aged 21–65 years. The typical form of LP was diagnosed in 69 patients (75.8 %), the hypertrophic form in 12(13.2 %), and the pigmentary form in 10(11.0 %). The functional state of dermal microcirculation was assessed using laser Doppler flowmetry. Bacteriological (culture-based) analysis of the skin microbiota was also performed, sampling from both lesional and unaffected skin, with enumeration and identification of microbial colonies.

Results. Patients with typical, hypertrophic, and pigmentary forms of LP exhibited a stagnant-stasis type of circulation in affected areas and a spastic type in visually unaffected areas. Microbiological analysis of LP lesions revealed polymicrobial colonization, while unaffected skin areas predominantly showed colonization by two microbial species. These findings underscore the significance of dermal microcirculation disorders and altered skin microbiocenosis in the pathogenesis of LP.

Conclusions. Optimization of therapy in patients with LP – particularly through targeted correction of dermal microcirculation impairments and individualized antibiotic therapy aimed at restoring the normal skin microbiota – can enhance the effectiveness of treatment.

Keywords: lichen planus, dermal microcirculation, skin microbiocenosis.

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В. І. Степаненко, К. А. Манвелова

ХАРАКТЕРИСТИКА СТАНУ ДЕРМАЛЬНОГО КРОВООБІГУ І МІКРОБІОЦЕНОЗУ ШКІРИ У ХВОРИХ НА ЧЕРВОНИЙ ПЛЕСКАТИЙ ЛИШАЙ ТА ОБГРУНТУВАННЯ ОПТИМІЗАЦІЇ ТЕРАПІЇ ЦЬОГО ДЕРМАТОЗУ

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У статті представлено результати досліджень стану дермального кровообігу та результати бактеріологічного дослідження мікрофлори шкіри у хворих на червоний плескатий лишай (ЧПЛ). Встановлено, що у хворих на типову, гіпертрофічну і пігментну форми цього дерматозу реєструвався застійно-стазичний тип кровообігу в ділянках ураження шкіри та спастичний тип – у ділянках візуально незміненої шкіри. Мікробіологічними дослідженнями в ділянках ураження шкіри хворих на ЧПЛ виявлено наявність поліінфікування, що було представлено асоціацією трьох і більше різних мікробних агентів, зокрема *S. aureus* + *S. pyogenes* + *S. epidermidis* + «інші мікроорганізми», а в ділянках візуально незміненої шкіри – біінфікування. Аналіз проведених досліджень вказує на значення порушень дермального кровообігу й мікробіоценозу шкіри в патогенезі ЧПЛ та потребує оптимізації терапевтичної корекції, що сприятиме підвищенню ефективності лікування хворих на цей дерматоз.

Ключові слова: хворі на червоний плескатий лишай, дермальний кровообіг, мікробіоценоз шкіри, обґрунтування оптимізації терапії.

Introduction

Lichen planus (LP) belongs to the group of common skin diseases, as its proportion in the structure of dermatoses was 1–2 %. The need for further study of LP was driven by unclear etiology, complex pathogenic mechanisms, and variable clinical outcomes, including treatment-resistant forms of this dermatosis [1–4].

This dermatosis was characterized by a variety of clinical manifestations, which creates additional difficulties in making a diagnosis. In addition to typical forms, there were atypical clinical manifestations of LP. Combinations of several variants of the course were often encountered, for example – atrophic and annular. On visible mucous membranes, erosive-ulcerative and exudative-hyperemic forms were quite often identified [17]. On smooth skin, annular, linear foci of lesions were possible, as well as

pigmented macules. Atrophic changes with hyperkeratotic overlays, verrucous proliferations or herpetiformly arranged were observed [5]. At present, this dermatosis with localization of rash elements on the oral mucosa was considered as a potentially precancerous condition with the possibility of development of epithelioma [6].

Among the trigger factors of LP manifestation, the following were distinguished: neurogenic, immune, infectious, toxic-allergic, metabolic, etc. [7–13]. To date, insufficient attention was paid to the study of the significance of dermal blood circulation in the development of this pathological process. It was established that in the dermis of skin lesion foci of patients with LP, the vessels of the papillary layer were dilated, and the walls of arterioles were moderately sclerosed. In addition, perivascular band-like infiltrates were observed, which contain fibroblasts, polynuclears, mast cells, lymphoid elements. Arterioles located in the reticular layer often have a narrowed diameter, and their walls were infiltrated predominantly by lymphocytes [14–16].

It has also been proven that in LP, microcirculatory disorders occur, which consist in changes in the structure and barrier function of microvessels. The presence of spasms of the arterial link, signs of venous hyperemia and venous stasis have been established, which lead to changes in the trophism of the skin and mucous membrane and a decrease in their resistance, which contributes to the complicated course of this dermatosis [1; 14–16].

A more detailed study regarding the possible influence on the development of LP also requires an assessment of the significance of microorganisms that were located in the skin foci of the pathological process, since the course of this dermatosis was accompanied by structural restructuring of the skin microbiocenosis, which was manifested by a decrease in the number of symbionts and an increase in the proportion of opportunistic microorganisms [18]. The presence in patients with LP of qualitative and quantitative changes in the microflora of the oral mucosa leads to the development of dysbiosis of varying severity, and *Candida albicans* contributes to a more severe course of the dermatosis [19; 20].

Thus, the above data indicate the presence of a number of insufficiently studied mechanisms of development of LP. In particular, in patients with this dermatosis, approaches to assessing the state of skin vascularization were unstructured, there was no analysis of microbial colonization in the lesion foci, and criteria for assessing the severity of corresponding changes have not been traced. The relationship between the corresponding factors of dermatosis development remains poorly understood. This indicates the expediency of further study of the pathogenetic links of LP development and the search for additional therapeutic means to optimize the complex treatment of patients with this dermatosis.

Aim of the study. Determination of disorders of the functional state of dermal blood circulation and skin microbiocenosis in patients with different clinical forms of LP and pathogenetic rationale for optimizing complex therapy of this dermatosis.

Materials and Methods

The studies were carried out in compliance with the provisions and principles of the Helsinki Declaration of the World Medical Association "Ethical principles for medical research involving human subjects" (conclusions of the bioethics commission of Bogomolets National Medical University, Protocol No. 187 dated 23.09.2024). The study included 91 patients with LP who, during the period 2024–2025, underwent examination and treatment at the clinical bases of the Department of Dermatology and Venereology with a course in cosmetology of Bogomolets National Medical University: the dermatovenerological department of St. Michael's Clinical Hospital of Kyiv and the Municipal Non-Profit Enterprise "Dermatovenereology in Kyiv". All patients provided written consent for the processing of personal data. The age of the examined patients ranged 21–65 years; according to sex, there were 59 women and 32 men. The duration of LP disease ranged from 1 week to 5 years. In each case, the diagnosis was made on the basis of clinical examination of the patient, taking into account patient complaints, anamnesis data, the nature of the clinical picture of the dermatosis, the extent of the pathological process on the skin, and the presence of complications. All patients also underwent general clinical examination and, if necessary, consultation with related specialists. The determination of the state of the microcirculatory bed of the skin was carried out in 91 patients with LP using laser Doppler flowmetry (LDF) on the device "Vingmed SD-100" (company "Medata", Sweden). The state of dermal blood circulation was determined, in particular, generalizing indicators: microcirculation index (MI), standard deviation of the microcirculation index (SD), coefficient of variation (CV); amplitude spectrum: amplitude of slow oscillations (ALF), amplitude of pulse oscillations (ACF), amplitude of fast oscillations (AHF); components of the mechanisms of modulation of dermal tissue blood flow: the first component of the active mechanism of modulation of tissue blood flow (1CAMTBF = ALF/MI), the second component of the active mechanism of modulation of tissue blood flow (2CAMTBF = SD/ALF), the first component of the passive mechanism of modulation of tissue blood flow (1CPMTBF = ACF/SD), the second component of the passive mechanism of modulation of tissue blood flow (2CPMTBF = AHF/SD); index parameters: intravascular resistance (IR), coefficient of microcirculation efficiency (CME) in areas of lesional skin (area α) and unaffected skin (area β).

Microbiological analysis of the skin microflora from areas α and β was also performed in 91 patients with LP using the contact agar plate method, followed by morphological identification of the microorganisms.

The control group consisted of 30 practically healthy individuals, matched by age and sex.

Statistical processing of the research results was carried out using generally accepted parametric and nonparametric methods of statistical analysis in medical and biological studies on a personal computer using the programs Statistica 6.0 ("Statsoft", USA) and Microsoft Excel. The values of the arithmetic mean (μ), standard deviation (σ), and the error of the mean (m) were determined. The level of significance of differences (p) was calculated using Student's t-test (t). In the case of non-uniform distribution of features, significance was determined using the

nonparametric Mann–Whitney test. To determine the degree of relationship between two indicators, the correlation coefficient (r) was calculated. Positive values of r indicated a direct relationship of indicators, negative values indicated an inverse relationship between them (r equal to up to 0.30 indicated a weak degree of relationship, from 0.31 to 0.50 – a moderate degree of relationship, from 0.51 to 0.70 – a significant degree, and from 0.71 to 1.00 – a high degree of relationship between the studied indicators).

Research results and their discussion

91 patients with LP were examined. Among the probable causes of dermatosis occurrence, the dominant positions were occupied by neuro-psychic factors, bacterial and viral infections, which were noted, respectively, in 31(34.1 %) and 19(20.8 %) patients. Notably, 16(17.6 %) patients could not identify the probable cause of dermatosis development.

Concomitant pathology was detected in 42(46.2 %) patients and was represented by diseases of the gastrointestinal tract (in 13–14.3 %), pathology of peripheral circulation (in 4–4.4 %), and the nervous system (in 3–3.3 %). In 7(11.9 %) women, gynecological diseases were diagnosed. Among other diseases suffered before the onset of LP, the leading positions were occupied by acute respiratory viral infections, which were observed in 88(96.7 %) patients.

Disseminated LP was diagnosed in all observed patients. In 69(75.8 %) patients, a typical form of dermatosis was identified, in 12(13.2 %) – hypertrophic, and in 11(11.0 %) – pigmented. In 58(63.7 %) patients, a progressive stage of the pathological process was verified, and in 33(36.3 %) – a stationary stage. Lesions of the oral mucosa were noted in 18(19.8 %) examined patients with LP.

So, in the examined patients, different clinical forms and stages of LP were diagnosed. The conducted analysis of skin clinical manifestations of LP proves the expediency of studying individual mechanisms of its development, in particular, the states of dermal blood circulation and skin microbiocenosis.

In the study of dermal blood circulation, it was established that in patients with LP, regardless of the clinical form of the dermatosis, suppression of the values of generalizing indicators was observed both in the areas α and β (at a distance of not less than 1–3 cm from the areas of LP rash lesions). At the same time, a decrease in the indicators of the amplitude spectrum of the microcirculatory bed of the skin, in particular MI, reflects insufficiency of tissue perfusion, SD – deterioration of the functioning of the mechanisms of modulation of the microcirculatory bed of the skin, and CV – suppression of vasomotor activity of microvessels. The results of the corresponding studies were presented in Table 1.

Data revealed that in the examined patients, regardless of the clinical form of the pathological process, multidirectional changes in the values of ALF occur in areas α and β. In particular, if in lesional area α its suppression was recorded: in the typical form of the dermatosis to 1.12 ± 0.04 perfusion units (PU), in the hypertrophic form – to 1.17 ± 0.03 PU, and in the pigmented form to 1.14 ± 0.05 PU (in individuals of the control group – 1.28 ± 0.05 PU; $p < 0.05$), then in unaffected area β, on the contrary, an increase was noted, respectively, to 1.46 ± 0.6 PU, 1.52 ± 0.08 PU and 1.43 ± 0.04 PU ($p < 0.05$). The values of the amplitude of fast oscillations (AHF) and the amplitude of pulse oscillations (ACF) decreased, regardless of the clinical forms of the disease ($p < 0.05$), both in areas α and β.

It was established that in the examined patients with LP, regardless of the clinical form of the pathological process, physiological values of the first component of the active mechanism of modulation of tissue blood flow (1CAMTBF) and the second component of the active mechanism of modulation of tissue blood flow (2CAMTBF) were registered in area α, in contrast to area β, where an increase in the level of 1CAMTBF was noted, which was associated with a decrease in the levels of 2CAMTBF. The activity of both 1CAMTBF and 2CAMTBF was recorded in a suppressed state ($p < 0.03$) in both areas of examination. As for intravascular resistance (IR), its physiological content was stated in lesional area α and an increase in unaffected area β. The increase in the levels of CME in both areas of the study deserves attention. These processes were independent of the clinical form of the dermatosis.

Since ALF reflects the endothelial activity of capillaries, precapillary sphincters and juxtacapillary ("shunting") blood flow, AHF – blood stasis in venules, ACF – vasodilation processes in the microcirculatory bed of the skin, 1CAMTBF and 2CAMTBF – respectively myogenic and neurogenic potentials, 1CPMTBF – cardiac, and 2CPMTBF – respiratory rhythms of fluctuations. IR reflects rheological properties, and CME makes it possible to volumetrically assess the ratio of active and

Table 1

Generalizing indicators of the state of the microcirculatory bed of the skin depending on the clinical form of lichen planus

Groups of examined patients	LDF examination areas	MI (M ± m), Perfusion Units	SD (M ± m), Perfusion Units	CV (M ± m), Perfusion Units
Patients with typical form of LP (n = 69)	α	4.05 ± 0.13*	0.61 ± 0.03*	15.21 ± 0.17*
	β	3.98 ± 0.15*	0.57 ± 0.04*	14.98 ± 0.16*
Patients with hypertrophic form of LP (n = 12)	α	4.12 ± 0.09*	0.63 ± 0.04*	15.35 ± 0.15*
	β	4.16 ± 0.13*	0.56 ± 0.05*	15.04 ± 0.15*
Patients with pigmented form of LP (n = 10)	α	3.98 ± 0.08*	0.59 ± 0.06*	15.07 ± 0.18*
	β	4.24 ± 0.17*	0.55 ± 0.06*	15.02 ± 0.14*
Control group (n = 30)	Unaffected skin	4.98 ± 0.15	0.79 ± 0.06	16.41 ± 0.14

Note: * – significant difference from the values of the corresponding indicator in individuals of the control group ($p < 0.05$).

passive modulation of blood flow, the obtained results demonstrate that, regardless of the clinical form of the dermatosis, in area α – a stagnant-stasis type, and in area β – a spastic type of blood flow was recorded.

Observations showed that in the examined patients with LP, regardless of the clinical stage of the pathological process, a decrease in the values of generalizing indicators was recorded both in areas α and β. This indicates insufficiency of tissue perfusion, functioning of the mechanisms of dermal blood circulation and vasomotor activity of microvessels. It was established that in patients with LP, regardless of the clinical stage of the dermatosis, multidirectional changes in ALF values were noted both in areas α and β. In particular, if in the progressive stage of the disease, its decrease to 1.09 ± 0.07 PU was stated (in the control group – 1.28 ± 0.05 PU; $p < 0.05$), then in the stationary stage, on the contrary, an increase to 1.40 ± 0.02 PU ($p < 0.05$). In area β, regardless of the clinical course of the dermatosis, an increase in ALF values was observed, respectively, to 1.53 ± 0.10 PU ($p < 0.05$) and 1.45 ± 0.04 PU ($p < 0.05$). The values of AHF and ACF were read, regardless of the clinical stage of the disease, in both areas of the study.

The dependence of the levels of 1CAMTBF and 2CAMTBF on the clinical stage of the dermatosis was recorded in patients with LP. Thus, if both indicators retained control values in the progressive course of the disease in area α, respectively, 0.24 ± 0.02 % (in individuals of the control group – 0.26 ± 0.03 %; $p > 0.05$) and 0.65 ± 0.05 % (in individuals of the control group – 0.68 ± 0.04 %; $p > 0.05$), then in area β 1CAMTBF increased to 0.38 ± 0.04 % ($p < 0.05$), and 2CAMTBF decreased to 0.040 ± 0.03 % ($p < 0.05$). In patients with the stationary stage of the dermatosis, the levels of 1CAMTBF in both areas of examination increased ($p < 0.05$), and 2CAMTBF decreased ($p < 0.05$). The activity of both 1CPMTBF and 2CPMTBF ($p < 0.05$) was recorded in a suppressed state, regardless of the course of the dermatosis.

It was stated that in patients with the progressive stage of LP, the preservation of control values of IR in area α – 3.72 ± 0.15 % (in individuals of the control group – 3.68 ± 0.09 % ($p > 0.05$)) and their increase in area β – 4.08 ± 0.17 % ($p < 0.05$) occur. In patients with the stationary stage of the dermatosis, an increase in the levels of the indicator in both areas was observed, respectively, to 3.97 ± 0.10 % ($p < 0.05$) and 4.02 ± 0.08 % ($p < 0.05$). An increase in CME values was recorded regardless of the stage of the pathological process and the area of study.

Thus, the obtained results of the values of generalizing indicators (MI, SD, CV), amplitude spectrum (ALF, AHF, ACF), components of the mechanisms of modulation of dermal tissue blood flow (1CAMTBF, 2CAMTBF, 1CPMTBF and 2CPMTBF), index parameters (IR and CME) of the microcirculatory bed of the skin make it possible to verify in patients with typical, hypertrophic and pigmented forms of LP, with the progressive stage of the dermatosis, a stagnant-stasis type of blood flow – in area α and a spastic type – in area β. In patients with the stationary stage of the pathological process, in areas both α and β, a spastic type of hemodynamics was identified. In individuals of the control group, a normotonic type of blood flow was observed. The obtained results of the corresponding studies require consideration in the development of optimized treatment management for patients with LP.

We also conducted a study of the state of the skin microbiocenosis in the examined patients with LP. Before the study, topical corticosteroids, local antiseptics and antifungal agents, as well as systemic antibiotics, were not used for three days.

According to the results of the conducted studies in individuals of the control group and in the examined patients with LP, a taxonomic composition of microorganisms was identified, which consisted mainly of *S. pyogenes, S. epidermidis, S. saprophyticus, S. aureus, E. coli* and "other species". Since representatives of the genera *Micrococcus*, *Bacillus*, *Sarcina*, *Acinetobacter* and other genera were very rarely encountered; therefore, they were grouped "other species". It was shown that in individuals of the control group the following were isolated: *S. aureus* – in 2(6.7 %) individuals, *E. coli* – in 2(6.7 %), *S. epidermidis* – in 3(10.0 %), *S. pyogenes* – in 4(13.3 %), *S. saprophyticus* – in 11(36.6 %), "other species" – in 8(26.7 %). It should be noted that among them, in 2(6.7 %) an association of *S. aureus* and *S. saprophyticus* was isolated, in 2(6.7 %) – *E. coli* and *S. saprophyticus*, and in 2(6.7 %) – *S. pyogenes* and "other species". Thus, the examined individuals of the control group demonstrated a monomicrobial skin colonization pattern.

A completely different picture was observed in patients with LP. In particular, in patients with the typical form of the dermatosis, the following associations were isolated from area α: *S. aureus*, *S. pyogenes* and *S. epidermidis* – in 25(36.2 %) individuals, *S. aureus*, "other species" and *S. saprophyticus* – in 15(21.7 %), *S. aureus, S. pyogenes, E. coli and S. epidermidis* – in 24(34.8 %), *E. coli* and *S. saprophyticus* – in 2(2.9 %). And only in 3(4 %) individuals *S. epidermidis* was isolated as a monomicrobial agent. Thus, patients with the typical form of LP were characterized by polymicrobial colonization of area α. The spectrum of the microbial landscape narrowed during microbiological examination of area β. The following combinations were recorded: *S. aureus* and *S. epidermidis* – in 26(37.7 %) individuals, *S. pyogenes* and *S. saprophyticus* – in 24(34.8 %), "other species" and *S. saprophyticus* – in 13(18.8 %) individuals. And only in 4(5.8 %) individuals *S. epidermidis* was isolated, and in 2(2.9 %) – *E. coli* as the only representatives of the skin microflora. Thus, patients with the typical form of LP were characterized by dual-species colonization of area β. It should be noted the excessive increase in the detected microorganisms in both areas of examination in this category of patients ($p < 0.05$).

In patients with the hypertrophic form of LP in area α, the following associations were registered: *S. aureus* and *S. saprophyticus* – in 3(25.0 %) individuals, "other species" and *S. saprophyticus* – in 3(25.0 %), *S. pyogenes* and *S. saprophyticus* – in 3(25.0 %), *S. epidermidis* and *E. coli* – in 3(25 %). Similar results were obtained for area β. Thus, in this category of patients, dual-species colonization of both areas α and β was noted. Also, in these patients, an increased number of isolated microorganisms ($p < 0.05$) was observed in both areas of the study.

It was shown that in patients with the pigmented form of LP in area α, the following combinations were recorded:

S. aureus and *S. saprophyticus* – in 2(20.0 %) individuals, "other species" and *S. saprophyticus* – in 3(30.0 %), *S. pyogenes* and *S. saprophyticus* – in 3(30.0 %), *S. epidermidis* and *E. coli* – in 2(20.0 %). Similar results were also obtained in area β. In this group of patients, dual-species colonization was observed both in areas α and β. Also, an excessive number of detected microorganisms ($p < 0.05$) was noted in these patients in both areas of examination.

In patients with the progressive stage of LP in area α, the following associations appear: *S. aureus*, *S. pyogenes* and *S. epidermidis* – in 22(37.9 %) individuals, *S. aureus*, "other species" and *S. saprophyticus* – in 15(25.8 %), *S. aureus*, *E. coli* and *S. saprophyticus* – in 6(10.4 %). And only in 3(5.2 %) individuals *S. epidermidis* was isolated as a single-species colonization. Thus, patients with the progressive stage of LP were characterized by polymicrobial colonization of area α. In area β, during microbiological examination, a narrowing of the spectrum of the microbial landscape of the skin was recorded. In particular, the following combinations were identified: *S. aureus* and *S. epidermidis* – in 19(32.8 %) individuals, *S. pyogenes* and *S. saprophyticus* – in 18(31.0 %), "other species" and *S. saprophyticus* – in 15(25.9 %), *S. epidermidis* and *E. coli* – in 6(10.3 %). In patients with the progressive stage of LP, dual-species colonization of area β was observed. Also, in these patients, an increased number of detected microorganisms was distinguished in both areas of examination.

It was established that in patients with the stationary stage of LP in area α, the following combinations were registered: *S. aureus* and *S. saprophyticus* – in 11(33.3 %) individuals, "other species" and *S. saprophyticus* – in 9(27.3 %), *S. pyogenes* and *S. saprophyticus* – in 7(21.2 %), *S. epidermidis* and *E. coli* – in 6(18.2 %). Comparable results were obtained in area β. The patients with the stationary stage of LP were characterized by dual-species colonization of both areas α and β. Attention was also required by the increased number of detected microorganisms in both areas of the study.

The control group showed a polymicrobial skin microbiocenosis composed of several bacterial species, including *S. aureus*, *S. pyogenes*, *S. epidermidis*, *S. saprophyticus*, and *E. Coli, "other species", which were isolated as* monomicrobial pathogens. A different picture was diagnosed in patients with LP; in particular, in patients with the typical form of the dermatosis in areas α, polymicrobial colonization occurs, which consists of associations of three or more of these microbial agents. Area β was characterized by a narrowing of the spectrum of microbial combinations to two components, that is, the development of dual-species colonization. Similar results were also obtained in patients with the progressive stage of the disease. A more problematic type of infection was identified in patients with hypertrophic and pigmented forms and the stationary stage of LP in both areas of the study. In addition, in the examined patients with LP, an increase in the microbial colonization of detected microorganisms was noted, which does not depend on the form of the dermatosis, the stage of the pathological process and the areas of skin examination.

The analysis of the studies conducted by us in patients with LP with different clinical forms of this dermatosis (typical, hypertrophic, pigmented) indicates the presence of a moderate degree of relationship between the state of dermal vascularization and skin microbiocenosis, which ranges from $r_1 = +0.32$ to $r_4 = +0.41$. A similar degree of relationship between the state of dermal blood circulation and skin microbiocenosis was also found in patients with progressive and stationary stages of the course of this dermatosis, which ranges from $r_7 = +0.31$ to $r_{10} = +0.44$.

Thus, the identified features of the skin microbiocenosis and dermal blood circulation in patients with LP indicate their important role in the pathogenesis of this dermatosis, which requires consideration in the development of optimized treatment management.

Conclusions

According to the analysis of the results of studies of the functional state of the dermal microcirculatory bed, in particular the microcirculation index (MI), standard deviation of the microcirculation index (SD), coefficient of variation (CV); amplitude spectrum: amplitude of slow oscillations (ALF), amplitude of pulse oscillations (ACF), amplitude of fast oscillations (AHF); components of the mechanisms of modulation of dermal tissue blood flow: the first component of the active mechanism of modulation of tissue blood flow (1CAMTBF = ALF/MI), the second component of the active mechanism of modulation of tissue blood flow (2CAMTBF = SD/ALF), the first component of the passive mechanism of modulation of tissue blood flow (1CPMTBF = ACF/SD), the second component of the passive mechanism of modulation of tissue blood flow (2CPMTBF = AHF/SD); index parameters: intravascular resistance (IR), coefficient of microcirculation efficiency (CME) in patients with typical, hypertrophic and pigmented forms of LP with the progressive stage of the dermatosis, a stagnant-stasis type of blood flow in the areas of the pathological process and a spastic type of blood flow in the areas of unaffected skin were verified. In patients with the corresponding clinical forms of LP with the stationary stage of the pathological process, a spastic type of hemodynamics was registered both in the areas of the pathological process and in the areas of unaffected skin.

The presence of changes in the skin microbiocenosis in patients with lichen planus was established. In particular, in patients with the typical form of the dermatosis with progressive and stationary stages of the course, polymicrobial colonization in the areas of skin lesions was diagnosed, which was represented by an association of three or more different microbial agents, and in the areas of unaffected skin, a narrowing of the spectrum of combinations of microorganisms to two components (dual-species colonization) was observed. A dual-species colonization of the skin was also detected in both lesional and unaffected areas in patients with hypertrophic and pigmented forms of LP with progressive and stationary stages of the course. In addition, in the examined patients with lichen planus, excessive bacterial load of the detected microorganisms was diagnosed, regardless of the clinical form of the dermatosis, the stage of the pathological process and the areas of skin examination.

Our findings indicate that in patients with different clinical forms of LP (typical, hypertrophic, pigmented), with

different stages of the course (progressive, stationary), a moderate degree of association between disturbances of the state of dermal blood circulation and skin microbiocenosis was observed.

Prospects for further research. Future research will focus on developing an improved, pathogenetically substantiated complex therapy for LP, aimed at individualized therapeutic correction of individual trigger factors significant in the manifestation of the dermatosis, in particular disorders of dermal blood circulation and skin microbiocenosis, which will contribute to increasing the effectiveness of treatment.

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CLINICAL AND DIAGNOSTIC ASPECTS OF THE TREATMENT OF PATIENTS WITH MIRIZZI SYNDROME

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CLINICAL AND DIAGNOSTIC ASPECTS OF THE TREATMENT OF PATIENTS WITH MIRIZZI SYNDROME
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Introduction. Mirizzi syndrome (MS) is a rare but clinically significant complication of gallstone disease that complicates diagnosis and increases the risk of iatrogenic bile-duct injury.

Aim. Improving treatment for patients with MS by retrospectively analyzing diagnostic approaches and surgical outcomes in patients treated in 2014–2024.

Materials and methods. We reviewed 1189 records of patients with gallstone cholecystitis; MS was identified in 72 cases (6.05 %). Patients were classified by Csendes (1989): type I 58(80.55 %), type II 11(15.27 %), type III 2(2.77 %), type IV 1(1.38 %). Ultrasound was mandatory for all patients; MRCP (31; 43.05 %), MSCT (6; 8.33 %) and ERCP (1; 1.38 %) were used for diagnostic clarification and operative planning.

Results and Discussion. Ultrasound enabled initial suspicion (dilated cystic duct with a stone in 48; 66.66 %) but was insufficient for accurate typing. ERCP was complicated by post-procedural pancreatitis in one case. Type I MS was managed with laparoscopic cholecystectomy, whereas types II–IV required open reconstructive biliary procedures. Postoperative complications occurred in 28 patients (38.88 %); no deaths were recorded.

Conclusions. MS management should be type-guided. Routine ultrasound should be complemented – particularly by MRCP – to improve preoperative classification and support safer, individualized surgery.

Keywords: Mirizzi syndrome, laparoscopy, cholecystectomy, diagnostics, complications.

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КЛІНІКО-ДІАГНОСТИЧНІ АСПЕКТИ ЛІКУВАННЯ ПАЦІЄНТІВ ІЗ СИНДРОМОМ МІРІЗЗІ
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Вступ. Синдром Міріззі – рідкісне ускладнення ЖКХ, що ускладнює діагностику та підвищує ризик ушкодження жовчних проток.

Мета – оцінити діагностику й результати хірургії за наявності СМ (2014–2024). Матеріали та методи: проведено ретроспективний аналіз 1189 випадків ЖКХ; СМ виявлено у 72(6.05 %), типування за Csendes.

Результати та обговорення. УЗД – базовий метод; для уточнення використовували МРХПГ 43,05 %, МСКТ 8,33 %, ЕРХПГ 1,38 %. у разі I типу переважала ЛХЕ, у разі II–IV – відкриті реконструктивні втручання. Ускладнення – 38,88 %, летальності не було.

Висновки. Тактика має залежати від типу; УЗД слід доповнювати насамперед МРХПГ для безпечного планування операції.

Ключові слова: синдром Міріззі, лапароскопія, холецистектомія, жовчнокам'яна хвороба.

Introduction

Mirizzi syndrome (MS) is a rare yet complex complication of gallstone disease (GSD), characterized by compression of the common bile duct or common hepatic duct by a gallstone impacted in the gallbladder neck or cystic duct. Prolonged chronic inflammation may lead to the formation of cholecystocholedochal fistulas and severe structural damage to the bile ducts, complicating both diagnosis and surgical treatment.

The reported incidence of MS varies widely – from 0.25 % to 6 % [1–4] among all patients with GSD. Despite its relative rarity, this condition is clinically significant due to the diagnostic complexity and the substantial risk of iatrogenic injury to the biliary tree during surgical procedures. To this day, Mirizzi syndrome remains a challenge for surgeons worldwide, particularly in emergency and urgent settings [1; 5–9].

The primary method of the initial diagnosis of Mirizzi syndrome (MS) is ultrasound (US), which has high sensitivity for detecting concrements, but relatively low specificity with regard to the syndrome itself. Modern imaging methods, such as magnetic resonance cholangiopancreatography (MRCP), multislice computed tomography (MSCT), and endoscopic retrograde

cholangiopancreatography (ERCP), make it possible to improve the accuracy of diagnosis; however, during ERCP complications may arise, such as pancreatitis, bleeding, perforation, and cholangitis; also, these methods are not always available in urgent care settings [4–7; 10]. Despite all the proposed methods of preoperative examination, MS may be diagnosed only during surgical intervention, which significantly increases the risks of iatrogenic injuries of the common bile duct (choledochus), especially in the presence of an infiltrate in the area of the gallbladder neck [4–11].

The treatment of Mirizzi syndrome depends on the type of pathology and may vary from laparoscopic cholecystectomy in type I (A. Csendes classification (1989)) to complex open surgical interventions with reconstructive manipulations on the bile ducts in more complex types of the syndrome. That is why the determination of a clear algorithm for diagnosis and for choosing the optimal type of surgical intervention is a relevant task of modern abdominal surgery.

The aim of this work is a retrospective analysis of the results of diagnosis and surgical treatment of patients with Mirizzi syndrome for the period from 2014 to 2024, which will make it possible to determine the main trends, the features of treatment, and to formulate recommendations regarding the improvement of approaches to this complex surgical problem.

Materials and Methods

A retrospective analysis was conducted of 1189 medical records of patients with gallstone cholecystitis who were treated at the "ORCMC" of the Department of Surgery of Odesa National Medical University during the period from 2014 to 2024. Among the total number of examined patients, Mirizzi syndrome (MS) was diagnosed in 72 cases, which amounted to 6.05 %. Of these, there were 51 women (70.84 %) and 21 men (29.16 %). The patients' ages ranged from 25 to 92 years.

All patients with Mirizzi syndrome were classified according to the A. Csendes classification (1989), which includes four types of the syndrome. The distribution of cases was as follows: MS type I – 58 patients (80.55 %), type II – 11 patients (15.27 %), type III – 2 patients (2.77 %), type IV – 1 patient (1.38 %).

The mandatory primary diagnostic method for all patients was abdominal ultrasound (US), which allowed the initial suspicion of MS. To clarify the diagnosis, determine the syndrome type, and plan the surgical treatment strategy, additional instrumental methods were used, such as magnetic resonance cholangiopancreatography (MRCP) – in 31 patients (43.05 %), multislice computed tomography (MSCT) – in 6(8.33 %), and endoscopic retrograde cholangiopancreatography (ERCP) – in 1 patient (1.38 %). All patients underwent a standard diagnostic set of examinations, which included complete blood count and biochemical blood tests, urinalysis, determination of blood group and syphilis screening, as well as testing for hepatitis and tumor markers.

Evaluation of treatment outcomes was carried out based on the analysis of postoperative complications (early bile leakage, formation of biliary fistulas, and others) and the overall effectiveness of the diagnostic-and-treatment strategy.

Data sources included medical records, imaging reports (US/MRCP/MSCT/ERCP), operative notes, and postoperative course documentation; key variables were age, sex, Csendes type, imaging performed and main findings, surgical approach and procedural details, postoperative complications, and mortality. Data were entered into a structured database, de-identified, stored on a password-protected device, and access was restricted to the research team. Statistical analysis was descriptive only: categorical variables were reported as n (%), continuous variables as mean ± SD (if approximately normal) or median (IQR) (if skewed), presented overall and, when relevant, stratified by Csendes type. The study was a retrospective chart review with no impact on patient management; all extracted data were anonymized/de-identified prior to analysis, and all included medical records contained signed consent for personal data processing and consent for surgical treatment.

Data extraction form (per patient): each patient was assigned a unique Study ID and no direct identifiers (full name, address, phone number) were recorded; files were stored separately and securely. Collected variables included Study ID (unique anonymized code; text, e.g., MS-001; source: study database), admission date (index; YYYY-MM-DD; chart), age (years; integer; chart), sex (F/M; chart), MS confirmation (yes/no; chart/operative note), Csendes type (I/II/III/IV; operative note/imaging), US performed (yes/no; imaging), US findings (free text; imaging), MRCP performed (yes/no; imaging), MRCP findings (free text; imaging), MSCT performed (yes/no; imaging), MSCT findings (free text; imaging), ERCP performed (yes/no; procedure), ERCP findings (free text; imaging), surgical approach (Lap/Open/Conv; operative note), postoperative complications (yes/no; chart), complication details (free text; chart), and mortality (yes/no; chart).

Research results and their discussion

During the retrospective analysis, Mirizzi syndrome (MS) was diagnosed in 72 patients, accounting for 6.05 % of all cases of gallstone cholecystitis. Of these, 51 were women (70.84 %) and 21 were men (29.16 %). The patients' ages ranged from 25 to 92 years.

The distribution of patients by MS type (according to the A. Csendes classification) showed a predominance of type I, which was observed in 58 patients (80.55 %). Type II MS was diagnosed in 11 patients (15.27 %), type III in 2 patients (2.77 %) and type IV in 1 patient (1.38 %) (Figure 1).

The primary method of initial diagnosis of Mirizzi syndrome (MS) was ultrasound (US), which made it possible to suspect the syndrome in all patients, namely a dilated cystic duct with a stone – 48 patients (66.66 %). However, the specificity of US for establishing the type of the syndrome and assessing the extent of involvement was insufficient. The additional use of magnetic resonance cholangiopancreatography (MRCP) made it possible to clarify the type and degree of involvement in 31 patients (43.05 %). Multislice computed tomography (MSCT) was effective in refining the diagnosis in 6 cases (8.33 %), and endoscopic retrograde cholangiopancreatography (ERCP) was used in 1 patient (1.38 %) and was accompanied by the development of acute post-procedural pancreatitis.

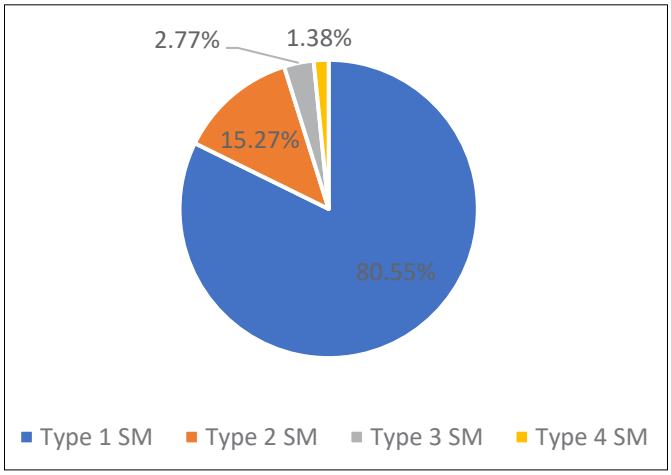

Fig. 1. Types of Mirizzi Syndrome

In two patients, contraindications to performing ERCP were identified in the form of parapapillary diverticula, and in one more patient repeated attempt to catheterize the papilla of Vater were unsuccessful.

Analyzing the surgical tactics, it was established that in type I Mirizzi syndrome laparoscopic cholecystectomy (LC) was the procedure of choice. Contraindications to LC in type I MS included a dense inflammatory infiltrate in the area of Calot's triangle and the inability to clearly visualize the anatomical structures, as well as the generally accepted contraindications to performing laparoscopic interventions. Laparoscopic cholecystectomy was performed in 58 patients (80.55 %). In patients with type II MS, open procedures were predominantly carried out: open (laparotomic) cholecystectomy with repair (plastic) of the common bile duct over a Kehr T-tube in 7 cases (9.72 %); external drainage of the common bile duct according to Vishnevsky in 2 cases (2.77 %); subtotal cholecystectomy with drainage of the gallbladder remnant in 2 patients (2.77 %); and, in patients with types III and IV MS, open cholecystectomy with the creation of a hepaticojejunostomy on a defunctionalized Roux-en-Y loop was performed in 3 patients (4.16 %) (Table 1).

Postoperative complications were observed in 28 patients (38.88 %), and there were no fatal cases. In 3 patients with type II MS, the complications were represented by bile leakage after subtotal cholecystectomy, in one patient with type I MS, after the laparoscopic cholecystectomy, experienced early bile leakage through the drain originating from the ducts of Luschka (4; 5.55 %), the formation of a postoperative biliary fistula after laparotomic cholecystectomy – in 2 patients (2.77 %). In addition, among patients with type II MS, incisional seromas were also observed in 4 patients (5.55 %) and postoperative right-sided pneumonia in 2 patients (2.77 %).

Analyzing the treatment outcomes of patients with MS who underwent laparoscopic surgery, the following complications were identified: lower-extremity deep vein thrombosis in 7 patients (9.72 %); superficial thrombophlebitis of the lower extremities in 5 patients (6.94 %); postoperative right-sided pneumonia in 2 patients (2.77 %); Cardiac rhythm disturbances in 2 patients (2.77 %); subsegmental pulmonary embolism (SSPE) in 1 patient (1.38 %) (Figure 2).

Pathogenetically justified conservative therapy allowed successful resolution of these complications in all patients. Such a number of complications may be due to the high comorbidity index in these patients, particularly involving the cardiopulmonary system. In such patients, the negative effects of high-pressure carboperitoneum during laparoscopic interventions become clinically significant.

The obtained results emphasize the necessity of the comprehensive use of modern diagnostic methods to determine the type of Mirizzi syndrome, which makes it possible to choose the optimal method of surgical intervention and to minimize the number of conversions, as well as to reduce the risk of intra- and postoperative complications. In our opinion, the widespread introduction into practical activity of MRCP with 3D reconstruction of the biliary tree can improve the preoperative diagnosis of MS without exposing patients to the risk of periprocedural complications as during ERCP.

Table 1

Surgical Treatment Methods for Mirizzi Syndrome

MS Type	Operation procedure	Number of Patients (n)	Percentage (%)
Type I	Laparoscopic cholecystectomy	58	80.55 %
Type II	Open cholecystectomy with bile duct reconstruction (Kehr drainage)	7	9.72 %
	External drainage of the common bile duct (Vishnevsky technique)	2	2.77 %
	Subtotal cholecystectomy with drainage of the gallbladder remnant	2	2.77 %
Type III–IV	Cholecystectomy with the creation of hepaticojejunostomy on a defunctionalized Roux-en-Y loop	3	4.16 %
Total		72	100 %

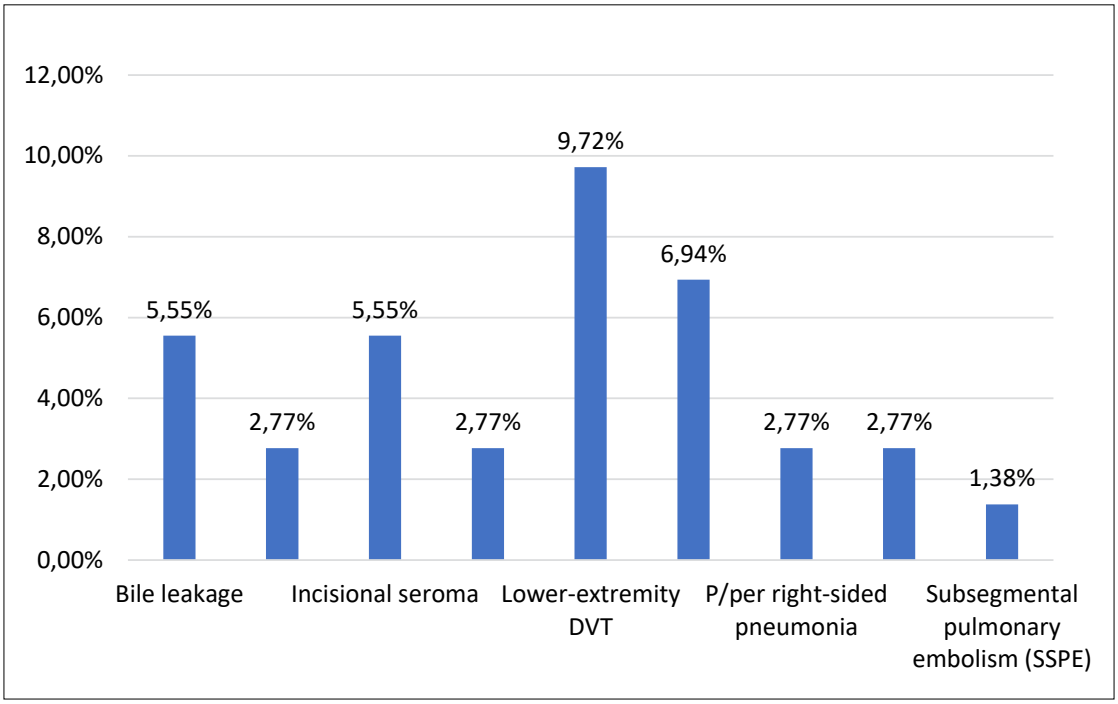

Fig. 2. Postoperative complications with Mirizzi Syndrom

In urgent conditions, given the lack of time for a full preoperative examination, clear visualization of the biliary and vascular structures has primary importance. The use of such novel techniques as fluorescent laparoscopy and the development of new methods for identifying the anatomical structures of Calot's triangle will make it possible to significantly increase the proportion of laparoscopic interventions in MS, preventing the risk of injury to the bile ducts and the hepatic artery. The development and application of gasless technologies for endovideosurgical interventions, taking into account the predominantly advanced age and severe polymorbid background in patients with acute cholecystitis complicated by MS, will make it possible to expand the group of patients operated on using laparoscopic methods.

Conclusions

1. Mirizzi syndrome is a rare but clinically significant complication of gallstone cholecystitis, detected in 6.05 % of the examined patients over the period from 2014 to 2024. The disease predominantly occurs in women.
2. The most common was type I MS (80.55 %), which in most cases is effectively treated with laparoscopic cholecystectomy. In more complex types (II, III, and IV), open surgical interventions with reconstructive procedures on the bile ducts predominate.
3. The primary method of initial diagnosis of Mirizzi syndrome remains ultrasound, however it requires mandatory supplementation with modern diagnostic methods (especially MRCP), which allow high-accuracy determination of the syndrome type and selection of an adequate treatment strategy.
4. Careful preoperative planning, with the use of modern diagnostic methods and the correct choice of surgical tactics, makes it possible to significantly reduce the risk of postoperative complications and to ensure successful treatment outcomes for patients with Mirizzi syndrome.

Thus, the results obtained underscore the importance of a multidisciplinary approach to the management of patients with Mirizzi syndrome and the need for further refinement of diagnostic and therapeutic algorithms for this challenging patient group.

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EFFICACY OF HYALURONIC ACID APPLICATION IN PATIENTS WITH PERIODONTITIS DURING THE HYGIENIC PHASE OF TREATMENT

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Introduction. The problem of treating periodontal diseases, particularly generalized periodontitis, remains relevant worldwide. Therefore, there is still a need to continue the search for new therapeutic approaches for this pathology. In recent years, hyaluronic acid has gained popularity as a treatment modality for periodontal diseases, which supports the ongoing investigation of the efficacy of its various forms.

Objective of the study. To evaluate the clinical effectiveness of locally applied hyaluronic acid in combination with standard therapy during the hygienic phase of treatment for generalized periodontitis in young adults.

Materials and methods. The study included 68 patients aged 26 to 35 years, who were divided into two groups: a main group of 35 individuals and a control group of 33. The assessment of periodontal status in both groups was performed using periodontal tests and by calculating the following indices: the OHI-S index, the PBI bleeding index, the PMA index, the PI index, and the Schiller–Pisarev test. The condition of the periodontal tissues was evaluated before treatment and at 3 days, 2 weeks, and 1 month after treatment.

Results and discussion. The results of the study indicate that the use of hyaluronic acid contributes to a more rapid normalization of the periodontal tests and indices used for the objective assessment of periodontal tissue status during the hygienic phase of treatment of generalized periodontitis. The positive dynamics observed in the PMA and PBI indices, as well as the Schiller-Pisarev test, demonstrate a significant anti-inflammatory and anti-edematous effect of the hyaluronic acid hydrogel on the periodontal tissues, which is capable of stabilizing periodontal tissue condition after initial treatment of generalized periodontitis already within the earliest follow-up periods.

Conclusions. The local application of hyaluronic acid in the form of a hydrogel contributes to significant improvement of periodontal tissue status.

Keywords: periodontitis; topical therapy; hygienic phase; hyaluronic acid; periodontal indices.

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ЕФЕКТИВНІСТЬ ЗАСТОСУВАННЯ ГІАЛУРОНОВОЇ КИСЛОТИ У ХВОРИХ НА ПАРОДОНТИТ НА ЕТАПІ ГІГІЄНІЧНОЇ ФАЗИ ЛІКУВАННЯ

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Статтю присвячено порівняльній оцінці клінічної ефективності місцевого використання гіалуронової кислоти та стандартної терапії на етапі гігієнічної фази лікування генералізованого пародонтиту в осіб молодого віку. До дослідження було залучено 68 пацієнтів у віці від 26 до 35 років, які увійшли до двох груп: основної з 35 осіб та контрольної – з 33. Після проведення маніпуляцій за сучасними протоколами пацієнтам контрольної групи призначено ротові ванночки з 0,12 % розчином хлоргексидину протягом 14 днів, а пацієнтам основної – з 0,025 % розчином гіалуронової кислоти в аналогічному режимі. Отримані результати свідчать, що гіалуронова кислота сприяє більш швидшій нормалізації пародонтальних проб та індексів, що використаних для об'єктивної оцінки стану тканин пародонта на етапі гігієнічної фази лікування генералізованого пародонтиту.

Ключові слова: пародонтит, місцеве лікування, гігієнічна фаза, гіалуронова кислота; пародонтальні індекси.

Introduction

Despite substantial advances in theoretical and clinical dentistry, periodontal diseases remain a significant problem worldwide due to several objective factors, including their high prevalence (about 11 % of the population; the sixth most prevalent disease worldwides) [1], progressive course, limited effectiveness of current therapies, and their marked negative impact on patients' psycho-emotional status and somatic health [2].

In Ukraine, the epidemiologic situation is discouraging. In recent years the number of adults, including young individuals, with generalized periodontitis (GP) has steadily increased [3]. Over the past decade, the prevalence of inflammatory and inflammatory-dystrophic periodontal

diseases among young adults has risen by 15 %. Although this increase is attributable to the initial gingivitis stage, gingivitis is a precursor of periodontitis.

Periodontal diseases are multifactorial, and their pathogenesis is extremely complex. Although the microbial factor is recognized as pivotal in GP etiopathogenesis, antimicrobial therapy combined with calculus removal alone does not prevent further inflammatory-destructive processes in periodontal tissues or achieve stable remission [4; 5].

A wide range of dental care is required for such patients – from various preventive programs and dispensary follow-up to comprehensive multidisciplinary rehabilitation. Nevertheless, dentists, therapists, and periodontists traditionally focus most on local pharmacotherapy of GP, as local treatment can deliver active agents directly to periodontal structures – from soft tissues (gingiva, periodontal ligament) to hard tissues (alveolar bone and cementum).

Accordingly, optimizing local treatment to enhance GP treatment effectiveness in young adults remains an urgent issue in contemporary dentistry.

A reduction in epithelial barrier and defensive functions owing to impaired tight intercellular contacts, facilitating penetration and spread of pathogens and their toxins, plays a certain role in GP pathogenesis [6; 7]. Hyaluronic acid (HA), a natural, non-sulfated glycosaminoglycan, is the principal component of the intercellular matrix and underlies numerous connective-tissue functions: structural integrity, trophic and transport activity, regulation of cellular differentiation, and maintenance of water and plasma protein homeostasis [8; 9]. Stabilizing the intercellular substance and preserving structural and homeostatic integrity may therefore reduce bacterial invasion and modulate the protective effects of HA on periodontal tissues.

In addition, HA supports tissue hydration, cellular resistance to mechanical damage, and bone regeneration, shows high biocompatibility with minimal adverse effects, and even exhibits antibacterial potential, which has attracted considerable interest across medical fields, including dentistry [9–14].

In recent years, HA has gained recognition as an adjuvant for treating chronic inflammatory diseases [15], warranting further evaluation of its various formulations.

Objective. To compare the clinical efficacy of local HA application with standard therapy during the hygienic phase of GP treatment in young adults.

Materials and Methods

Sixty-eight patients aged 26–35 years were enrolled and divided into a study group (n = 35) and a control group (n = 33). Groups were age- and gender-matched (Table 1).

Inclusion criteria were Stage I, Grade A GP (Figure 1) without any treatment in the preceding year; compliance with physicians' recommendations; and consent to attend follow-up visits. Exclusion criteria were decompensated systemic diseases, multiple dental defects and malocclusions, severe uncompensated occlusal anomalies, antibiotic or immunosuppressant use within the past 6 months, allergy to study medications, pregnancy or lactation, and non-compliance or missed visits.

Table 1

Characteristics of groups by age and gender, abs./%

Group	Women		Men		Total
	< 30 years	> 30 years	< 30 years	> 30 years	
Study					
n	8	10	8	9	35
%	22.9	28.5	22.9	25.7	100
Control					
n	8	9	8	8	33
%	24.2	27.4	24.2	24.2	100
Total					
n	16	19	16	17	68
%	23.5	27.9	23.5	25.1	100

The study design is presented in Figure 2.

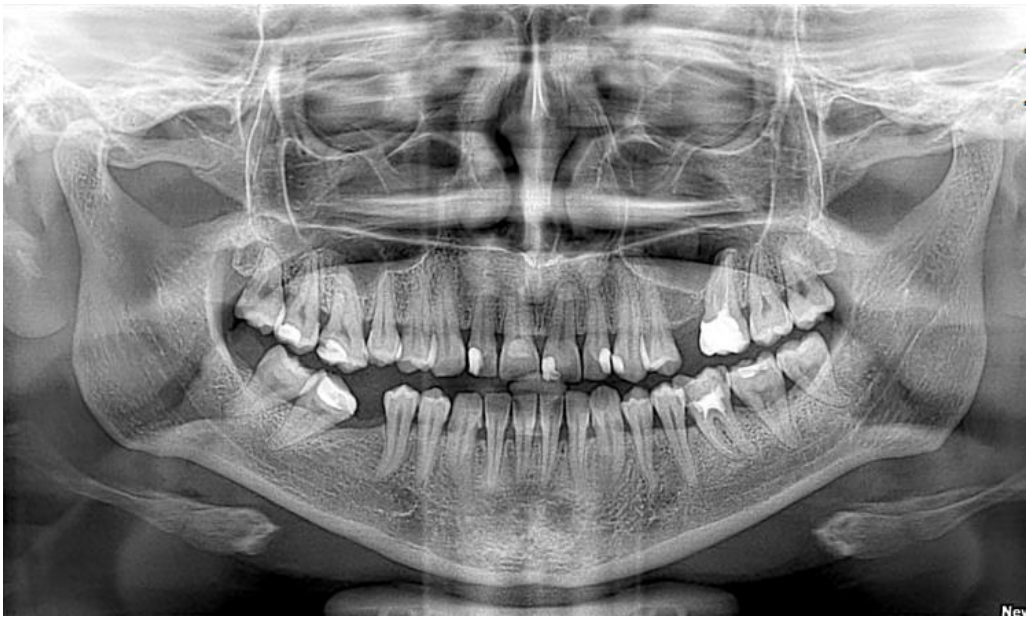

Fig. 1. Panoramic radiograph of a 32-year-old patient (participant in the study group). Stage I, Grade A generalized periodontitis

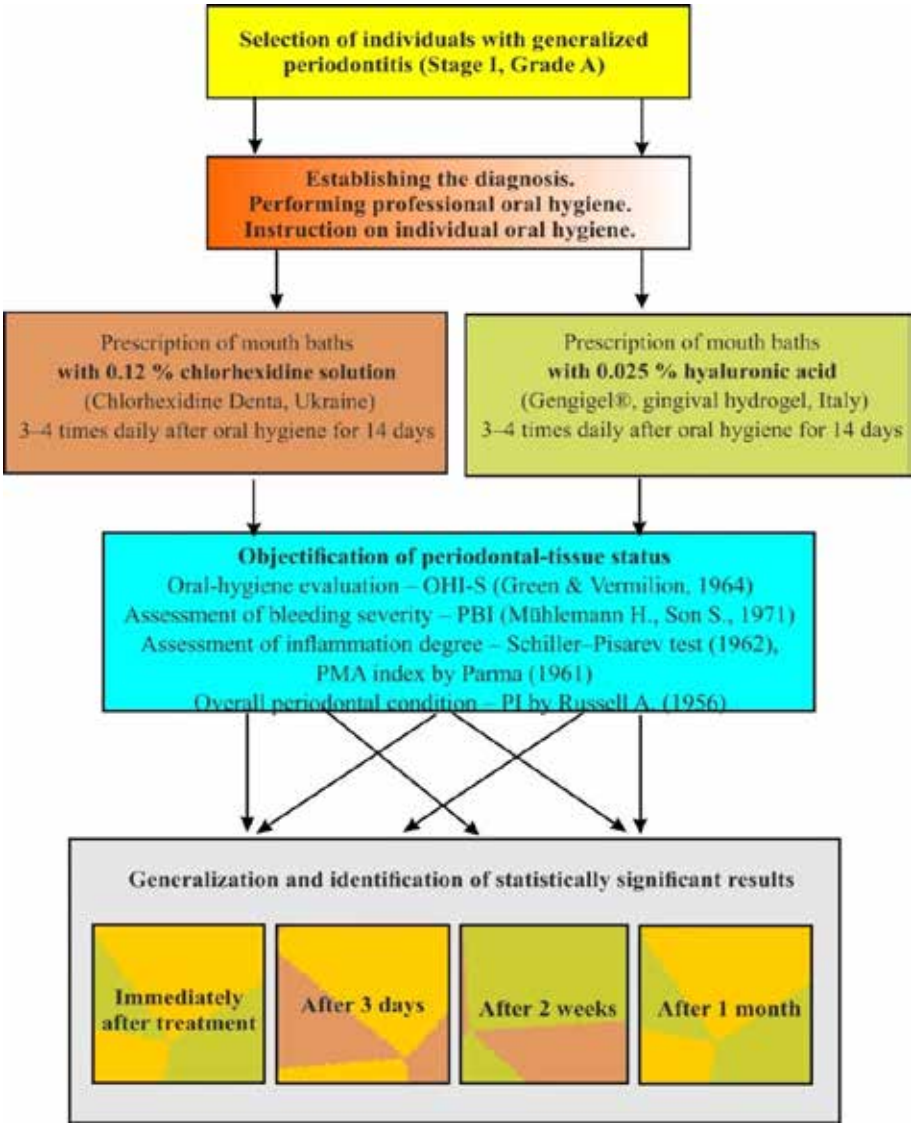

Fig. 2. Study design

All patients provided written informed consent in accordance with the Kharkiv National Medical University Bioethics Committee requirements (minutes No. 6 dated 04.06.2025). Dental Chart No. 043/o and a WHO-recommended individual card were used. The 2017 EFP/AAP periodontal disease classification [16] established the diagnosis.

After diagnosis, supra- and subgingival scaling and root planing (SRP) with biofilm removal via air-abrasive technique were performed. Patients then received individualized oral-hygiene instructions (toothpaste, brush selection, mouth-rinse regimen). The control group patients used 0.12 % chlorhexidine solution (Chlorhexidine Denta, Ukraine) as mouth baths 3–4 times daily for 14 days; the study group patients used 0.025 % HA oral gel (Gengigel®, Italy) on the same schedule. Both solutions were recommended to be held in the oral cavity for 1–2 min (10 mL) with no eating or drinking for 30 min thereafter.

Periodontal status in the control and study groups was assessed using a set of tests and indices: OHI-S (Green & Vermilion, 1964) for oral hygiene; PBI (Mühlemann & Son, 1971) for gingival bleeding; the Schiller–Pisarev iodine test (1962) and PMA index (Parma, 1961) for gingival inflammation; and the PI (Russell, 1956) as an overall periodontal index. Measurements were taken at baseline and after 3 days, 2 weeks, and 1 month. Data were processed using standard statistical methods [17].

Research results and their discussion

During the initial oral examination and evaluation of periodontal tests and indices in the selected cohort of patients with periodontitis, the correctness of group formation was confirmed. Specifically, the values of the OHI-S, PMA, PBI, and PI indices, as well as the Schiller–Pisarev test, showed no statistically significant differences either between the groups or between sexes ($p > 0.05$) (Table 2).

Regarding the dynamics of the analyzed indices, they evolved as follows (Table 2). The OHI-S index, which indicates the state of oral hygiene, had already improved markedly by Day 3 after treatment ($p < 0.01$), despite the presence of some signs of gingival trauma, in both the control group (1.9-fold in women and 1.7-fold in men) and the study group (1.9-fold in women and 1.8-fold in men),

Table 2

The condition of periodontal tissues in patients with GP at the stages of initial treatment (M ± m)

Index	Time point	Women		Men	
		Group			
		control	study	control	study
OHI-S (points)	Before treatment	1.57 ± 0.14	1.58 ± 0.13	1.66 ± 0.12	1.69 ± 0.15
	Day 3	0.81 ± 0.06[1]	0.83 ± 0.05[1]	0.98 ± 0.07[1]	0.93 ± 0.06[1]
	Week 2	0.78 ± 0.04[1]	0.69 ± 0.04[1.2]	0.88 ± 0.05[1]	0.74 ± 0.04[1.2.3]
	Month 1	0.72 ± 0.03[1]	0.58 ± 0.02[1.2.3]	0.84 ± 0.04[1]	0.68 ± 0.03[1.3]
PMA (%)	Before Treatment	54.3 ± 2.3	52.8 ± 2.1	58.7 ± 2.4	59.3 ± 2.5
	Day 3	48.3 ± 2.0[1]	47.2 ± 1.9[1]	51.2 ± 2.2[1]	49.4 ± 2.1[1]
	Week 2	31.4 ± 1.8[1.2]	24.3 ± 1.2[1.2.3]	36.8 ± 1.9[1.2]	28.5 ± 1.4[1.2.3]
	Month 1	25.3 ± 1.3[1.2]	15.4 ± 1.3[1.2.3]	28.7 ± 1.5[1.2]	18.7 ± 1.4[1.2.3]
Schiller –Pisarev test (points)	Before treatment	2.35 ± 0.21	2.41 ± 0.25	2.76 ± 0.28	2.77 ± 0.26
	Day 3	2.03 ± 0.19	1.55 ± 0.15[1.3]	2.28 ± 0.25	1.74 ± 0.15[1.3]
	Week 2	1.47 ± 0.10[1.2]	1.21 ± 0.08[1.2.3]	1.56 ± 0.11[1.2]	1.27 ± 0.09[1.2.3]
	Month 1	1.35 ± 0.07[1]	1.12 ± 0.05[1.3]	1.34 ± 0.08[1]	1.16 ± 0.05[1.3]
PBI (points)	Before treatment	2.45 ± 0.5	2.47 ± 0.16	2.57 ± 0.18	2.59 ± 0.19
	Day 3	2.36 ± 0.13	2.11 ± 0.09[1]	2.27 ± 0.11	2.05 ± 0.08[1]
	Week 2	2.03 ± 0.10[1.2]	1.75 ± 0.09[1.2.3]	1.95 ± 0.07[1.2]	1.76 ± 0.06[1.2.3]
	Month 1	1.53 ± 0.08[1.2]	0.67 ± 0.03[1.2.3]	1.59 ± 0.05[1.2]	0.81 ± 0.04[1.2.3]
PI (points)	Before treatment	1.97 ± 0.39	1.95 ± 0.39	2.09 ± 0.42	2.05 ± 0.41
	Day 3	1.73 ± 0.36	1.64 ± 0.31	1.81 ± 0.38	1.79 ± 0.35
	Week 2	1.52 ± 0.21	1.35 ± 0.16	1.68 ± 0.33	1.48 ± 0.21
	Month 1	1.17 ± 0.11[1]	0.82 ± 0.08[1.2.3]	1.23 ± 0.13[1]	0.91 ± 0.08[1.2.3]

Notes: [1] – $p < 0.05$ vs baseline; [2] – $p < 0.05$ vs previous time point; [3] – $p < 0.05$ vs control group.

which reflects the effectiveness of individualized hygiene instruction. Two weeks after the start of treatment, the trend toward improved oral hygiene persisted in all patients, although it was not as marked as at the previous observation point; nevertheless, statistically significant differences were still evident ($p < 0.05$), and certain distinctive features were noted. Specifically, in the control group the OHI-S index values for both sexes differed significantly from the corresponding pre-treatment values ($p < 0.05$). In the study group, significant differences were recorded both relative to baseline (women $p < 0.05$, men $p < 0.01$) and, for men, relative to the control group ($p < 0.01$). After one month of observation the earlier trends persisted, albeit with further deceleration. In women in the study group, the OHI-S index remained significantly different from its pre-treatment value, from the earlier observation points, 1 and from the control group ($p < 0.05$). In men the same index also showed statistically significant differences compared with the pre-treatment state and with the control group ($p < 0.05$).

The PMA index, which reflects the degree of gingival inflammation, showed a downward trend in all groups of patients with GP. In women of the control group, PMA values fell by 1.1-, 1.5-, and 1.2-fold on Day 3, at 2 weeks, and 1 month after the start of treatment, respectively, whereas in women of the study group the reductions were 1.1-, 1.9- ($p < 0.01$ vs control), and 1.6-fold ($p < 0.05$ vs control), respectively. It should be emphasized that although on Day 3 the dynamics and absolute PMA values were similar between groups ($p > 0.05$), by the 2-week mark a clearly greater decrease in gingival inflammation was evident in the study cohorts – 1.9-fold in women ($p < 0.01$) and 1.7-fold in men ($p < 0.01$) – relative to both sexes in the control group and the preceding observation point. This accelerated normalization of PMA in both sexes in the study group persisted after 1 month: a 1.6-fold reduction in women (versus 1.2-fold in the control group, $p < 0.01$) and a 1.5-fold reduction in men (versus 1.3-fold in the control group, $p < 0.01$).

The Schiller–Pisarev test, which provides information on the presence, intensity, and extent of inflammation, exhibited the following dynamics. Changes in the test values were recorded as early as Day 3 of observation. In the control group the test value decreased 1.2-fold in both women and men relative to baseline ($p > 0.05$), whereas in the study group it declined 1.6-fold in both sexes ($p < 0.05$). It should also be noted that by the first follow-up visit a statistically significant difference between the Schiller–Pisarev test values of the study and control subjects had already been established ($p < 0.01$). Two weeks after the start of treatment, a positive trend toward normalization of gingival status was observed in all patients of both groups, and the Schiller–Pisarev test values differed significantly both from the previous observation point and between groups of the same sex ($p < 0.05$). The decrease in the degree of inflammation persisted one month after initiation of treatment, with a significant difference between the study and the control groups ($p < 0.05$), although without statistical differences relative to the preceding observation time.

An objective indicator of inflammation is the degree of gingival bleeding, quantified by the PBI index. Its dynamics were favorable in all groups by Day 3 of observation, but only in the study group did the change reach statistical significance relative to the pre-treatment value ($p < 0.05$). Two weeks after the start of observation, the values for

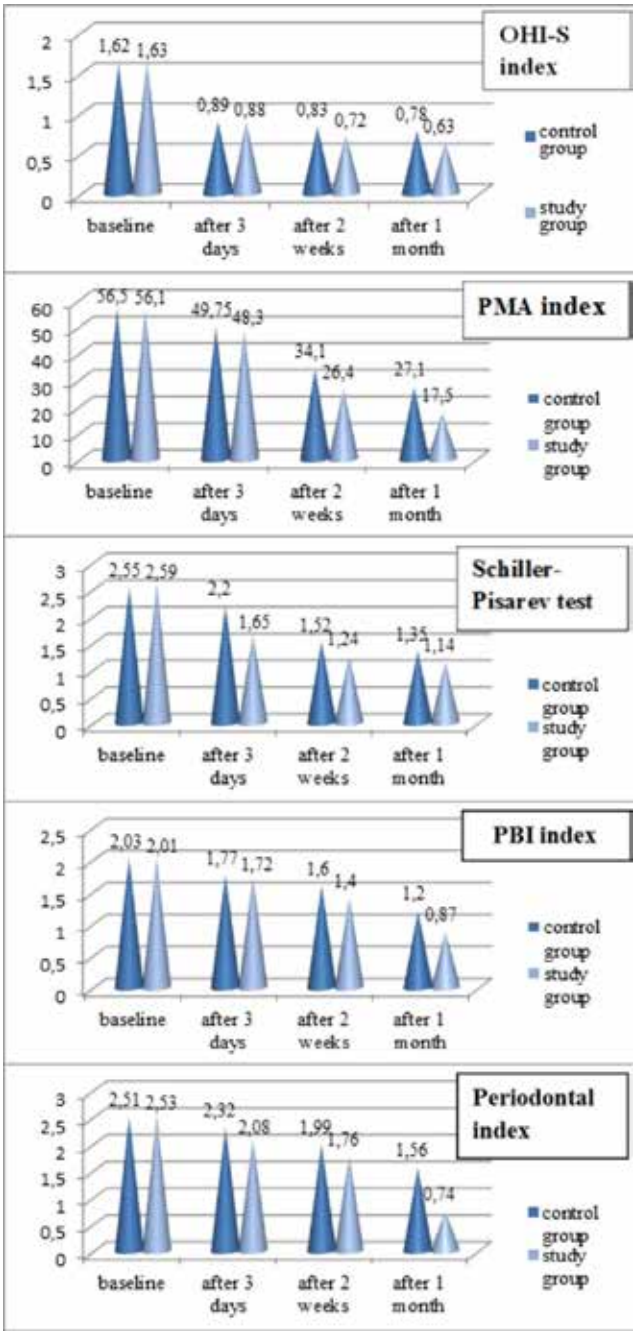

Fig. 3. Dynamics of periodontal tests and indices in individuals of the control and study groups

both sexes in the control group differed significantly from baseline and from the preceding data point, whereas in the study group the improving PBI dynamics were further accompanied by a significant difference from the control group ($p < 0.05$). The same trend was documented one month after treatment initiation: in the control group the PBI values differed significantly from those before treatment for both sexes, at Day 3, and at two weeks ($p < 0.05$), while in the study group, in addition to these differences, a significant disparity versus the control group persisted, with bleeding reduced 2.3-fold in women and 1.9-fold in men ($p < 0.01$).

The periodontal index (PI) provides a comprehensive evaluation of periodontal tissue status. PI values improved progressively at every observation point in the patient cohort, although its dynamics showed certain differences. In women in the control group, PI decreased 1.1-fold (on Day 3 and at 2 weeks) and 1.3-fold one month after the start of treatment. In men in the control group, the reductions were 1.2-fold (Day 3), 1.1-fold (Day 3 and 2 weeks), and 1.4-fold one month after the start of treatment. It should be noted that, in the control group, statistical significance between baseline and post-treatment PI values was recorded only at the final follow-up – 1 month ($p < 0.05$).

In the study group, normalization of periodontal tissues proceeded more rapidly: a 1.2-fold reduction at Day 3 and 2 weeks and a 1.6-fold reduction 1 month after the start of treatment in women, and likewise a 1.2-fold reduction at Day 3 and 2 weeks and a 1.6-fold reduction 1 month after the start of treatment in men. At the last follow-up visit, PI values differed significantly not only from baseline but also from the preceding observations and from the corresponding control-group data ($p < 0.05$–$p < 0.01$).

Visualization of the dynamics of periodontal tests and indices is presented in Figure 3.

Analyzing the obtained results, we can state that HA enabled a more rapid normalization of the periodontal tests and indices chosen for the objective evaluation of periodontal tissue condition during the hygienic phase of generalized periodontitis treatment. The favorable dynamics of the PMA and PBI indices and of the Schiller–Pisarev test indicate a pronounced anti-inflammatory and anti-edematous effect of the hyaluronic-acid hydrogel on periodontal tissues, stabilizing their status soon after the initial therapy. Improvement in the PI index is also indisputable; however, its complete normalization requires a longer follow-up – at least 6-8 weeks – to permit re-epithelial attachment to the root surface.

Participants also reported that the hyaluronic-acid gel was easy to apply and pleasant to use.

Consequently, periodontal diseases, and generalized periodontitis in particular, remain a focal point of active scientific investigation and of practical dental efforts both globally and in Ukraine. Unfortunately, they have not yet been fully brought under control; therefore, the search for optimized treatment protocols for generalized periodontitis is a pressing challenge today.

Over recent decades, considerable experience has been gained regarding the use of HA in the comprehensive treatment of generalized periodontitis. For example, Jentsch H. et al. (2003) and Johannsen A. et al. (2009) reported improvements in the PI index and the bleeding-on-probing index (BOP) after twice-daily topical application of 0.2 % HA for three weeks in patients with periodontitis. Subsequent studies [18; 19] demonstrated that subgingival administration of HA after SRP favorably affected periodontal tissues in generalized periodontitis, reducing the PI and BOP indices as well as periodontal pocket depth. Bertl K. et al. [20] further noted that local use of HA resulted in fewer sites requiring repeat SRP at three months and a higher frequency of pocket closure at 12 months.

Conclusions

1. Topical application of HA in hydrogel form improves periodontal tissue status, as confirmed by the favorable

dynamics of the OHI-S, PMA, PBI, and PI indices and the Schiller–Pisarev test.

2. Incorporating hyaluronic-acid hydrogel into comprehensive therapy for generalized periodontitis provides greater clinical efficacy than standard topical treatment alone.

3. Local use of hyaluronic-acid hydrogel may be recommended during the first, that is, the hygienic phase of generalized periodontitis management.

Future research should focus on studying the effects of HA on the condition of periodontal tissues during the maintenance phase of therapy.

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LIVER DAMAGE IN PATIENTS WITH GASTRIC AND DUODENAL ULCERS IN CHRONIC HELICOBACTER PYLORI INFECTION

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LIVER DAMAGE IN PATIENTS WITH GASTRIC AND DUODENAL ULCERS IN CHRONIC HELICOBACTER PYLORI INFECTION

Odesa National Medical University, Odesa, Ukraine

The purpose. To identify and determine the state of the liver according to the activity of hepatic enzymes and ultrasound diagnostic data in patients with gastric and duodenal ulcers in chronic helicobacteriosis.

Materials and methods. 54 gastroenterological patients (21 men and 34 women) with gastric and duodenal ulcer caused by chronic *Helicobacter pylori* infection and a control group of patients (n = 20) have been examined. Control group patients additionally underwent biochemical blood tests.

Results. During a comprehensive examination of the main group patients concomitant pathology was detected: chronic pancreatitis, chronic acalculous cholecystitis, post-cholecystectomy syndrome, arterial hypertension, ischemic heart disease, chronic kidney disease was diagnosed in patients.

The average degree of contamination of the gastric mucosa with inactive forms of *Helicobacter pylori* infection by topographic zones was analyzed. In the majority of gastric and duodenal ulcer patients in chronic *Helicobacter pylori* infection, concomitant changes in the gallbladder, pancreas, and liver were observed.

Conclusions. The results of our own studies indicate a high frequency of pathological changes in the ultrasound picture of the liver parenchyma, the structure of the gallbladder and pancreas in patients with gastric and duodenal ulcer disease in chronic *Helicobacter pylori* infection.

The results of clinical and laboratory studies showed that in the main group patients signs of cytolysis are determined in the form of a significant increase in transaminases, namely alanine transaminase and aspartate transaminase, indirect bilirubin, thymol test. The signs of cholestasis – an increase in gamma-glutamyltransferase and bilirubin, both direct and indirect, were present as well.

Keywords: Gastric ulcer, duodenal ulcer, chronic *Helicobacter pylori* infection, liver, *Helicobacter Pylori.*

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УРАЖЕННЯ ПЕЧІНКИ У ХВОРИХ НА ВИРАЗКОВУ ХВОРОБУ ШЛУНКА ТА ДВАНАДЦЯТИПАЛОЇ КИШКИ ПРИ ХРОНІЧНОМУ ГЕЛІКОБАКТЕРІОЗІ

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Метою дослідження стало виявлення та визначення стану печінки за показниками активності печінкових ферментів та даних ультразвукової діагностики у хворих на виразкову хворобу шлунка та дванадцятипалої кишки при хронічному гелікобактеріозі.

Результати власних дослідження свідчать про високу частоту патологічних змін ультразвукової картини паренхіми печінки, структури жовчного міхура та підшлункової залози, а також визначаються признаки цитолізу в вигляді підвищення показників трансаміназ, а саме аланінтрансамінази та аспартаттрансамінази, непрямого білірубіну, тимолової проби, та признаки холестазу – підвищення показників гамма-глутамілтрансферази та білірубіну як прямого так і непрямого у хворих на виразкову хворобу шлунка та виразкову хворобу дванадцятипалої кишки при хронічному гелікобактеріозі.

Ключові слова: виразкова хвороба шлунка, виразкова хвороба дванадцятипалої кишки, хронічний гелікобактеріоз, печінка, Helicobacter Pylori.

Introduction

According to various literary data, the atypical course of gastric and duodenal ulcer in chronic *Helicobacter pylori (HP)* infection is determined in 8 – 25 % of patients [3; 4; 9; 12; 14], mainly in women. Half of them complain of a "cholecyst-like" variant of ulcer disease course. At the same time, signs of chronic non-calculous cholecystitis are detected in 53 % of cases [1; 6–8], and the combination of inflammatory and ulcerative lesions of the stomach and duodenum with cholelithiasis occurs in 21–25 % of cases [10, 13, 18].

Therefore, on the example of patients' specified contingent we are dealing with the comorbid pathology formation which manifestation characterizes by a changed

nature of the inflammatory damage of anatomically closed stomach and duodenum and its spread to gastrohepatopancreatoduodenal region parenchymal organs [2]. In such cases, the diagnostic search in patients is quite complicated, since at the specific moment of the doctor's visit, any organ can give an inflammatory reaction exacerbation with all the pathophysiological mechanisms inherent in this and the "vicious circle" of enteral activity dysregulation [16].

Such a situation, unfortunately, is frequent, in modern practice of family medicine and, in particular, gastroenterology as evidenced by statistical indexes [7]. We are experienced in certain part of patients with gastric and duodenal ulcers with concomitant liver involvement in the pathological process examination and treatment. Some similar clinical cases were already analyzed, however, there were isolated publications [11]. That's why we consider it fundamentally justified and clinically important to analyze the pathogenetic contribution of inflammatory liver parenchymal lesions to gastroduodenal ulceration clinical manifestation.

The purpose. To identify and determine the state of the liver according to the activity of hepatic enzymes and ultrasound diagnostic data in patients with gastric and duodenal ulcers in chronic helicobacteriosis.

Materials and Methods

54 patients (21 men and 34 women) aged 62 to 54 years (the average age was equal to 38.6 ± 4.4 years) with gastric and duodenal ulcer in chronic HP infection were under observation during the 2022–2025 years in therapeutical department the Municipal Non-Profit Enterprise "Odessa Regional Clinical Medical Center".

As a control group we examined clinically 20 practically healthy individuals without pathological changes in abdominal organs and hepatobiliary system.

Patients were examined and anamnesis was taken in accordance with the Declaration of Helsinki. All patients and healthy volunteers were informed about their objective examination results use with scientific purposes. Written agreement was signed by each of them.

The following criteria were used to include patients in the study: established clinical diagnosis of chronic non-atrophic gastritis, gastric ulcer, duodenal ulcer (confirmed by endoscopic and histological examination with the HP presence in active or inactive forms on the gastric mucosa); disease duration from 6 months to 12 years; the patients comprehensive examination including biochemical blood test, esophagogastroduodenoscopy (EGD) and the abdominal organs ultrasound diagnostics).

The criteria for patients excluding from the study were the following: the above-mentioned diagnosis without HP active or inactive forms confirmation on the gastric mucosa; short disease duration (up to 3 months); incomplete patients' comprehensive examination; presence of oncological disease of the gastrohepatoduodenal organs.

HP infection was verified as etiological factor with further confirmed endoscopially biopsy material. Urease and microbiological tests for HP were positive in all patients. For this aim double testing for HP was used (the urease test and stained smears microscopy).

All patients of the control and clinical groups were undergone to blood biochemical investigation upon admission to the clinic and before the start of treatment. Patients who were referred for biochemical blood tests had not been on anti-Helicobacter therapy over the past 6 months.

The patients' comprehensive examination included pH-metry, EGD (using the end-face fibrogastroduodenoscope FG-29V, "PENTAX", Japan) and ultrasound examination of the abdominal organs (using portable ultrasound device "LOGIC eR8", GE Healthcare, USA).

An ultrasound examination (USE) was performed using generally accepted method, on an empty stomach, with patients' position on back, on the left side and after changing position. The condition of the liver, gallbladder walls, its shape and size (volume), motor activity, nature of the contents (presence of sediment, polyps and concrements), pancreas, spleen, abdominal vessels were studied and analyzed.

The sequence of the examination was as follows: pH-metry was performed firstly, then EGD with biopsy material for PH testing and gastric mucosa histological studies. The examinations were done in the morning, on an empty stomach, 12-14 hrs after the last food intake.

Anti – helicobacter therapy is the treatment standard for chronic non-atrophic gastritis, gastric and duodenal ulcer associated with HP. It includes proton pump inhibitors (PPIs) in a standard dose twice a day + clarithromycin 500 mg twice a day + amoxicillin 1000 mg or metronidazole 500 mg twice a day. The duration of the course of threatment is 7 days. The functional state of the hepatobiliary system was examined at the stage of anti-helicobacter therapy in the main group patients.

The obtained results were statistically analysed using the one0way ANOVA parametric criterion. The minimum statistical significance threshold was set at $p < 0.05$.

Research results and their discussion

Gastric and duodenal ulcer patients in chronic HP infection complain of heartburn in 71.9 % of cases, acid regurgitation in 66.6 %, pain, feeling of heaviness in the epigastric region had 81 % of patients, nausea was present in 83.7 % of patients, vomiting in 2.6 %, flatulence in 10.8 %, stomach upset (constipation, diarrhea) in 77.9 %, manifestations of intoxication were observed in 98.5 % of cases.

A comprehensive examination of gastric and duodenal ulcer patients in chronic HP infection revealed concomitant pathology. 23 patients had chronic pancreatitis, 29 had chronic acalculous cholecystitis, post-cholecystectomy syndrome was present in 2 persons, arterial hypertension had 14 patients, ischemic heart disease – 6, chronic kidney disease – 9 patients.

Based on the data obtained, we considered it necessary to draw attention to the state of the hepatobiliary system in chronic HP infection. In connection with the above, functional and biochemical studies of the state of the hepatobiliary system were conducted.

The results of the mucous membrane of various topographic zones of the stomach with active and inactive forms of HP infection with microscopy of stained smears – prints in patients with chronic HP infection and the degree their contamination are presented in Fig. 1.

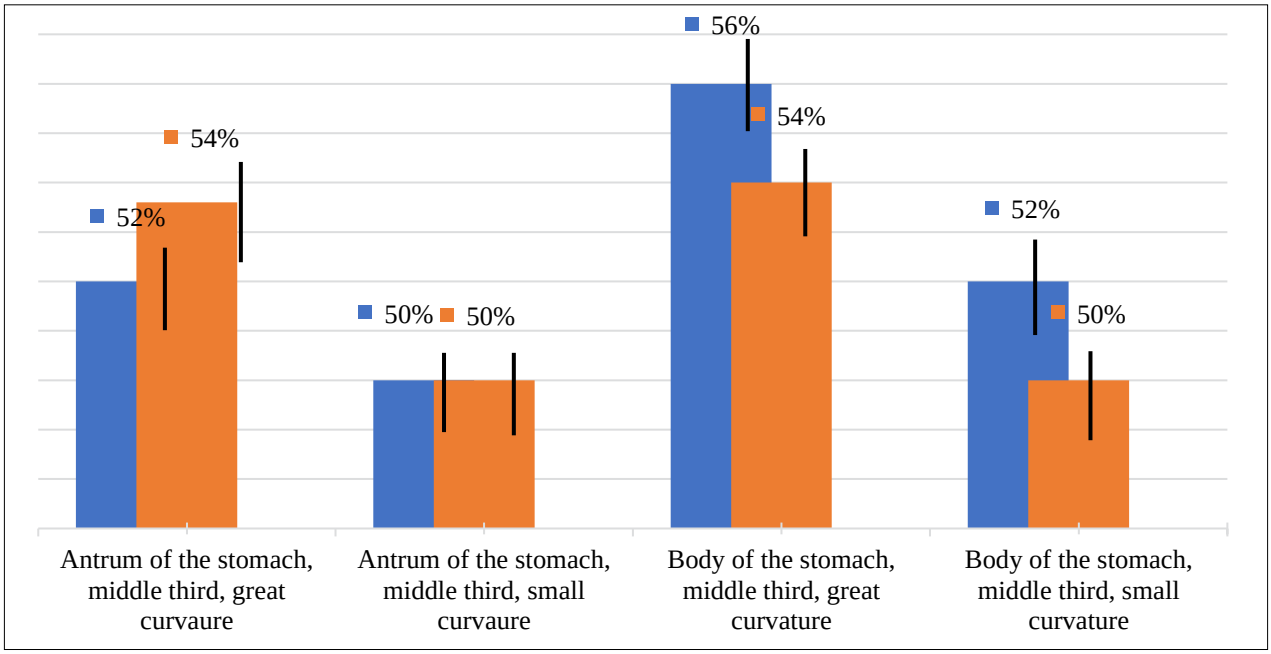

Fig. 1. Frequency of detection and degree of contamination of the gastric mucosa with active and inactive forms of HP infection by topographic zones in patients with chronic Helicobacter pylori (n = 54)

In total, 58 % of cases of intracellular "depot" of HP infection were detected in the gastric mucosa.

When compare the average degree of gastric mucosa contamination with active and inactive forms of HP infection by topographic zones, a significantly ($p < 0.05$) higher degree of contamination was detected in the body of the stomach along the greater curvature in relation to the topographic zones of the antrum, while there were no significant differences between the zones of the antrum or between the zones of the stomach body ($p > 0.05$).

Analysis of the results obtained showed that in chronic HP infection patients, precancerous changes in the gastric mucosa (atrophy, dysplasia, colonic metaplasia) in the antrum took place in 55.8 % of cases; in the middle – upper third of the stomach body along the greater curvature they were met in 30.7 % of cases and along the lesser curvature in 27.8 % of cases.

Ultrasound examination showed minor signs of the hepatobiliary system damage in chronic HP patients at the stage before the prescrition of anti-helicobacter therapy, mainly these were diffuse changes in the liver parenchyma – 35.4 % and fatty infiltration of the liver – 37.9 %.

At the initial stage of examination (before treatment), biochemical blood test was performed on 54 chronic HP patients (21 men, 34 women) and on 20 control group patients.

Patients who were referred for biochemical blood tests had not taken drugs included in the anti-HP therapy (AHPT) regimen, which is the standard of care for chronic non-atrophic gastritis, gastric and duodenal ulcer associated with HP, for the past 6 months (Table 1).

An increase in alanine transaminase, aspartate transaminase, alkaline phosphatase by 1.5–2 times was noted in patients after the specified treatment (Table 2).

Table 1

Biochemical test results in patients with chronic non-atrophic gastritis, gastric ulcer and duodenal ulcer in chronic *Helicobacter pylori* infection before the prescription of anti-Helicobacter therapy

Indicators	Control (n=20)	Before prescription of anti-HP therapy (n=54)
Total bilirubin, μmol/l	14,05±2,35	16,61±3,58*
Direct bilirubin, μmol/l	4,04±0,79	3,16±1,67
Inderect bilirubin, μmol/l	10,82±2,41	11,31 ±3,51
ALT, U/l	21,49±1,87	17,51±2,63 *
AST, U/l	19,51±3,19	22,84±2,34*
Alkaline phosphatase, U/l	167,68±11,39	188,53±12,89
Thymol test, U	1,66±0,77	1,67±0,81
Urea, mmol/l	5,41±0,41	5,46±0,63
Glucose, mmol/l	5,21±0,83	5,26±1,81
Total protein, g/l	74,62±1,71	77,13±5,25
Cholesterol, mmol/l	4,87±0,92	5,18±1,87

Note: n – number of studies;

*statistically significant changes vs the control group, $p < 0.05$

Table 2

Biochemical state of the liver in patients of the study group with chronic *Helicobacter pylori* infection during anti-Helicobacter therapy on the 7th and 15th day (M ± m)

Indicators	Control (n=20)	During anti-HB therapy, 7 days (n=54)	After anti-HB therapy, 15 days (n=54)
Total bilirubin, μmol/l	14,05±2,35	30,31±3,52*	34,21±2,64*
Direct bilirubin, μmol/l	4,04±0,79	9,11±1,06*	9,52±0,46*
Indirect bilirubin, μmol/l	10,82±2,41	23,34±1,07 *	25,19±2,13*
ALT, units/l	21,49±1,87	106,09±4,93*	186,21±5,44*
AST, units/l	19,51±3,19	64,04±3,26*	72,07±4,76*
Alkaline phosphatase, units/l	167,68±11,39	289,19±16,54*	317,81±15,14*
Thymol test, units	1,66±0,77	3,16±1,93	3,21±0,73
Urea, mmol/l	5,41±0,41	5,33±1,07	5,43±1,24
Glucose, mmol/l	5,21±0,83	5,26±0,71	5,24±0,59
Total protein, g/l	74,62±1,71	78,31±3,56	78,43±5,28
Cholesterol, mmol/l	4,87±0,92	5,41 ±1,19	5,59±1,46

Note: n – number of studies;

*statistically significant changes vs the control group, $p < 0.05$

This indicates a violation of the functional state of the hepatobiliary system mainly by the mechanism of cytolysis – the activity of transaminases increased, especially alanine transaminase, by 5 times.

It is known that the imbalance of intestinal microflora most often develops when macrolides (clarithromycin, azithromycin) and tetracycline are prescribed. They have the most detrimental effect on the intestinal flora, including *E. coli.* This can lead to a disruption of the bacterial balance and dysbacteriosis symptoms development

Indeed, the results obtained showed that during and especially after anti-helicobacter therapy, 42 % of patients complained of flatulence and bloating, 46.8 % – of pain along the intestinal loops, 42 % had complaints of rumbling in the stomach after eating, constipation had 34.7 % of patients, diarrhea 13.9 %. This indicated a disruption of the intestinal microbiocenosis balance. Also, according to the results of US-examination in 21 days after the start of anti-helicobacter therapy, hepatic parenchyma diffuse changes were observed in 72.3 % of patients and fatty infiltration of the liver in 64.9 %.

Additional confirmation of cholestasis presence was an increase of gamma-glutamyltransferase level by 10 times during anti-helicobacter therapy on the 7th day and its increase by 20 times on the 15th day from the start of eradication therapy in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic helicobacteriosis (Fig. 2).

Thus, the main idea of the obtained data analysis is that the anti-helicobacter therapy use in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic helicobacteriosis was accompanied by even more expressed symptoms of hepatobiliary system damage. This may be a consequence of both the direct hepatotropic effect of drugs included in the anti-helicobacter therapy regimen and the development of intestinal microflora disorders, which was detected in the patients under observation.

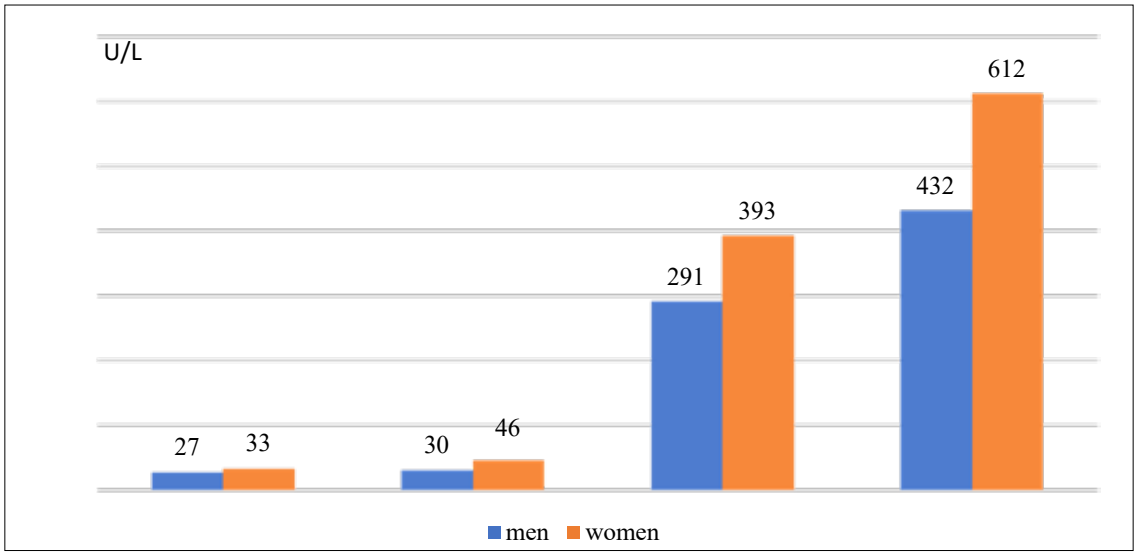

Fig. 2. Dynamics of gamma-glutamyltransferase in patients of the groups under observation, on the 7th and 15th day from the start of AGBT

*statistically significant changes relative to the control group, $p < 0.05$

To discuss the data obtained we would like to accent attention on the following three items. Firstly, we outline the liver involvement into the pathophysiological cascade of chain reactions in patients with stomach and duodenum ulceration is due to its critical functional role in organisms' both metabolism and detoxification [10]. Moreover, its extremely close anatomical location with the stomach and intestines predisposes it to shared pathophysiological mechanisms of responses to alternating inflammatory stimuli. Situations of concomitant liver parenchymal damage resulting from the inappropriate or erroneous prescription or administration of pharmacological agents with hepatotoxic effects are extremely dangerous [17].

The second, one could register the enteral dysbacteriosis in the selected patients development with progressive hepatic parenchyma failure. HP is well known to be the initial link of a long pathogenetic chain that leads to the development of the gastrointestinal tract dysbacteriosis [5, 15].

Long-term persistence of HP infection in the gastrointestinal tract accompanied by the development of chronic helicobacteriosis, massive eradicative antibiotic therapy causes possible secondary immunodeficiency due to the suppression of primarily bifidoflora with subsequent colonization of the mucous membrane by opportunistic and pathogenic microflora. This leads to a decrease of the microorganism resistance to infection due to the suppression of immune reactivity. Under the influence of HP, local immunodeficiency of the gastrointestinal tract mucous membrane may develop. This can close the pathogenic vicious circle of the inflammatory process on the mucous membrane of the digestive organs.

It is known that the microbiocenosis through various mechanisms participates in almost all human's body processes. This applies to both the metabolism of food components and the maintenance of the activity of the central nervous system. Further study of the gastrointestinal tract microflora allows us to discover new mechanisms of its influence on the body functions.

Thirdly, the severity of the clinical condition of our patients and the general pathological dysregulation with the disruption or absence of compensatory mechanisms contributed to the development of cholelithiasis that was as indicated by a 3-fold increase in the amount of direct bilirubin with a simultaneous increase in the activity of alkaline phosphatase, indirect bilirubin and thymol test. Cholestasis and cytolysis phenomena led to a decrease in the functional capabilities of the liver.

The detected phenomena of cytolysis indicate the hepatotoxic effect of drugs included in the treatment regimen for chronic helicobacteriosis. Thus, we noted an increase in the level of transaminases, with a predominant increase in alanine aminotransferase by 5 times on the 7th day and 9 times on the 15th day of anti-helicobacter therapy compared to the control group indicators. We believe that cytolysis is the cause of the decrease in the functional activity of hepatocytes, as indicated by an increase in the content of indirect bilirubin and the thymol test indicator twice during anti-helicobacter therapy. Hepatocyte damage probably leads to impaired bile passage due to increased pressure in the bile ducts, the criteria for which are increased direct bilirubin and alkaline phosphatase activity.

The changes in the functional and biochemical state of the liver are most likely associated with the hepatotropic effect of drugs used in anti-helicobacter therapy, which can be combined with the etiotropic effect of HP, after effective therapy on day 15, judging by clinical data and complete eradication – HP was not detected in patients by any of the methods.

At the same time, data indicating that the phenomena of cytolysis and cholestasis remain almost the same were obtained. An increase in gamma – glutamyltransferase indicators is an additional confirmation of the development of cholestasis

Resuming, we summarize the need for diagnostic measures strengthening in patients with gastrointestinal tract prolonged ulcerative lesions with the obvious abdominal ultrasound investigation focusing on the hepatobiliary system. Such a methodological approach will optimize the management of this patients' contingent and refine the comprehensive, pathogenetically based treatment schemes for concomitant liver dysfunction associated with gastrointestinal tract ulcerative lesions.

Conclusions

Our ultra-sound-examinations detected hepatic parenchyma changes in patients with chronic non-atrophic gastritis, gastric ulcer and duodenal ulcer with chronic helicobacteriosis. This coincides with the literature data.

Hepatic laboratory tests in patients with chronic non-atrophic gastritis, gastric and duodenal ulcer with chronic helicobacteriosis reveal signs of cytolysis, namely a significant increase in alanine and aspartate transaminase, indirect bilirubin and a positive thymol test.

At the same time, increases in the indicators of gamma-glutamyl transferase and bilirubin, both direct and indirect, indicates the presence of cholestasis. During anti-helicobacterial therapy these indicators are increasing even more.

Based on the results of our research, it is recommended to include in the complex treatment of patients with chronic non-atrophic gastritis, gastric and duodenal ulcer in chronic *Helicobacter pylori* ultrasound examination of the hepatobiliary system, as diffuse changes in liver tissue and its fatty infiltration were detected.

Thus, based on changes in laboratory and biochemical indicators that characterize the hepatic condition and are combined with the structural features of the organ, having been revealed by ultrasound, we can confirm the presence of pathological changes developing in the liver.

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ВИПАДОК ІЗ ЛІКАРСЬКОЇ ПРАКТИКИ

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КЛІНІЧНИЙ ВИПАДОК ВГС-АСОЦІЙОВАНОГО КРІОГЛОБУЛІНЕМІЧНОГО ГЛОМЕРУЛОНЕФРИТУ

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КЛІНІЧНИЙ ВИПАДОК ВГС-АСОЦІЙОВАНОГО КРІОГЛОБУЛІНЕМІЧНОГО ГЛОМЕРУЛОНЕФРИТУ
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У статті наведено опис клінічного випадку кріоглобулінемічного гломерулонефриту, асоційованого з вірусом гепатиту С (ВГС). Діагноз підтверджено виявленням РНК ВГС методом полімеразної ланцюгової реакції (ПЛР) та результатами патоморфологічного дослідження біоптатів нирок. Після проведення етіотропної терапії прямої противірусної дії (ППД) спостерігалися клінічне покращення, нормалізація лабораторних показників і підвищення якості життя. Представлений клінічний випадок підкреслює важливість ранньої діагностики та початку етіотропної терапії у пацієнтів з ВГС-асоційованим кріоглобулінемічним гломерулонефритом.

Ключові слова: ВГС, кріоглобулінемічний гломерулонефрит

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CLINICAL CASE OF HCV-ASSOCIATED CRYOGLOBULINEMIC GLOMERULONEPHRITIS
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In two-thirds of patients with chronic hepatitis C virus (HCV) infection, extrahepatic manifestations are observed, often serving as the first and only clinical signs of the disease.

The purpose of this study is to analyze the features of early diagnosis and treatment following a specific case of cryoglobulinemic glomerulonephritis associated with Hepatitis C virus (HCV).

Materials and methods. A clinical case of cryoglobulinemic glomerulonephritis associated with HCV in a 36-year-old male patient is presented.

The results. The diagnosis of HCV-associated cryoglobulinemic glomerulonephritis was confirmed by the detection of HCV RNA via polymerase chain reaction (PCR), a positive cryoglobulin test, rheumatoid factor (RF) and findings from a pathological examination of kidney biopsy specimens. The patient received etiotropic therapy with direct-acting antiviral agents (DAAs) for 12 weeks. Upon completion of treatment, the patient experienced clinical improvement and normalization of laboratory blood and urine parameters. However, after three years of follow-up, the patient exhibited signs of progressive renal dysfunction, characterized by increased creatinine levels and decreased glomerular filtration rate (GFR).

Conclusions. This clinical case underscores the importance of early diagnosis and initiation of etiotropic therapy in patients with HCV-associated cryoglobulinemic glomerulonephritis. It also highlights the potential role of antiviral treatment in preventing the progression of renal insufficiency. Long-term monitoring is essential, and additional therapeutic interventions may be required to prevent the development of chronic complications.

Keywords: HCV, Cryoglobulinemic Glomerulonephritis, direct-acting antiviral agents.

Вступ

За даними Всесвітньої організації охорони здоров'я у світі на хронічний гепатит С (ХГС) хворіє близько 58 мільйонів людей, при цьому щорічно реєструється близько 1,5 мільйона нових випадків інфікування [1]. Рівень серопозитивності до ВГС є ще вищим – близько 100 мільйонів осіб у світі (1,6 % [95 % ДІ 1,3–2,1 %] від загальної чисельності населення) [2].

Практично дві третини пацієнтів з ВГС-інфекцією мають позапечінкові прояви [3], які нерідко є першою і єдиною клінічною ознакою захворювання. Клінічна картина цих проявів може варіювати від безсимптомного перебігу до розвитку серйозних імунологічних порушень і, як наслідок, впливати на якість життя і рівень смертності серед даної категорії пацієнтів, створюючи при цьому значне навантаження на системи охорони здоров'я в усьому світі [4].

Вважається, що провідне місце в розвитку хвороби нирок (ХН) у пацієнтів із ХГС-інфекцією посідає мембранозно-проліферативний гломерулонефрит, який у переважній більшості випадків пов'язаний із кріоглобулінемією [5].

Терапевтичний підхід до лікування пацієнтів з ВГС-асоційованим кріоглобулінемічним гломерулонефритом передбачає декілька варіантів, як-от глюкокортикостероїди, плазмаферез, моноклональні антитіла (ритуксимаб), але призначення етіотропної терапії є першочерговим вибором у лікуванні цієї категорії хворих [6]. Літературні дані свідчать, що лікування ВГС-асоційованої кріоглобулінемії ППД з досягненням стійкої вірусологічної відповіді (СВВ) призводить до повного клінічного одужання у 63,7–90,2 % пацієнтів [7]. Наразі залишається багато прогалин у розумінні патогенезу, підходів до лікування, персоніфікації терапії, що потребує подальшого вивчення цього питання.

Мета роботи – дослідити особливості діагностики та лікування позапечінкових проявів ХГС на клінічному прикладі тяжкого перебігу ВГС-асоційованого кріоглобулінемічного гломерулонефриту.

Матеріали та методи дослідження

Матеріалом був клінічний випадок ВГС-асоційованого кріоглобулінемічного гломерулонефриту у 36-річного пацієнта.

Дослідження проведено відповідно до принципів біоетики, викладених у Гельсінській декларації «Етичні принципи медичних досліджень за участю людей» та «Загальній декларації про біоетику та права людини (ЮНЕСКО)» (протокол № 3 від 03.04.2023).

Результати дослідження та їх обговорення

Пацієнт К., 1983 року народження, госпіталізований до нефрологічного відділення Вінницької обласної клінічної лікарні ім. М. І. Пирогова 16.01.2019 з попереднім діагнозом «Нефротичний синдром неуточненого генезу».

Скарги: загальна слабкість, набряки під очима, набряки нижніх кінцівок, підвищення артеріального тиску, зменшення кількості сечі.

Анамнез хвороби: у грудні 2019 року перебував на лікуванні в ЛОР-відділенні з приводу перелому кісток носу. Під час виконання лабораторного дослідження сечі виявлено зміни. Для подальшого обстеження та лікування направлений на консультацію до нефролога.

Анамнез життя: супутньої патології не має. Алергологічний анамнез не обтяжений. Шкідливі звички заперечує.

Епідеміологічний анамнез: оперативні втручання, переливання крові та її компонентів, вживання наркотичних препаратів заперечує. Періодично проходив лікування у стоматолога.

Дані фізикального обстеження: під час огляду стан хворого оцінюється як середньої тяжкості. Температура 36,7 °С. Шкірні покриви та видимі слизові блідо-рожевого кольору. Висипів, геморагій немає. Щитовидна залоза не збільшена, м'яко-еластичної консистенції, клінічних ознак порушення функції щитовидної залози немає. Тони серця чисті, ослаблені. АТ – 160/100 мм рт. ст., пульс 72 уд/хв. З боку органів дихання, шлунково-кишкового тракту, опорно-рухового апарату, нервової системи клінічно-значимих патологічних змін не виявлено. Нирки не пальпуються, ділянка безболісна. Спостерігаються набряки нижніх кінцівок.

Пацієнту було проведено первинні лабораторні обстеження, за результатами яких у загальному аналізі крові мали місце незначна анемія (112 г/л), підвищений рівень сечовини (18,2 ммоль/л), креатиніну (272 мкмоль/л), зниження ШКФ (26 мл/хв), гіпопротеїнемія (55 г/л). Печінкові проби (білірубін, АЛТ, АСТ, ГГТ, лужна фосфатаза), рівень калію, натрію, глюкози, білкові фракції, показники згортання крові, ліпідного обміну – без особливостей. у загальному аналізі сечі протеїнурія (16,5 г/л), лейкоцитурія (6–10 в п/з), еритроцитурія (еритроцити не змінені – 60 у полі зору, еритроцити змінені – 10–15 у полі зору), циліндрурія (гіалінові 0–1–2 – у полі зору, зернисті 0–1–2 – у полі зору). Добова протеїнурія: кількість сечі на добу – 1200 мл, білок на добу – 11 880 мг. Для виключення або підтвердження етіологічних чинників ураження нирок проведено серологічні обстеження: HBsAg, AB-HIV – не виявлено, AB-HCV – виявлено. 18.01.2021 виконано додаткові методи діагностики – Ig G HCV Cor, NS3, NS4, NS5 – виявлено, ПЛР – RNA HCV – виявлено, генотип 3а, РФ – ++++ (> 100 МО/мл).

Під час проведення інструментальних методів діагностики виявлено такі зміни:

Фіброгастродуоденоскопія, висновок: рефлюкс-езофагіт. Еритематозна гастродуоденопатія. Висновок УЗД: ехоознаки асциту, двобічного гідротораксу, помірних дифузних змін у паренхимі печінки, підшлункової залози, ураження паренхіми обох нирок (збільшення товщини та паренхіми нирок). ЕКГ: виявлено помірні зміни в міокарді. УЗД серця: помірна концентрична гіпертрофія лівого шлуночка (ГЛШ). Методом непрямої еластометрії визначена еластичність печінки, медіанне значення якої становить 5,6 кПа, що відповідає стадії фіброзу F0-F1 (за шкалою METAVIR).

Пацієнт був оглянутий окулістом – патологічних змін не виявлено.

На основі вищезазначених даних було встановлено діагноз: ХХН IY (ШКФ 26 мл/хв), гломерулонефрит, нефротичний синдром, вторинна артеріальна

гіпертензія. СН І. Анемія легкого ступеня. HCV-інфекція. Хронічний вірусний гепатит С, мінімальна активність запального процесу, F0-F1 (за шкалою METAVIR). Призначено лікування: свіжозаморожена плазма, гіпотензивна та сечогінна терапія.

Отже, у пацієнта з ХГС тяжкість загального стану обумовлена проявами ниркової недостатності на тлі гепатиту з мінімальним цитолітичним синдромом, мінімальним фіброзом, що корелює з результатами багатьох клінічних досліджень, які вказують на те, що ниркові ускладнення можуть проявлятися у пацієнтів з ХГС навіть за відсутності явних ознак ураження печінки [8].

З огляду на різні механізми ураження нирок у пацієнтів з ВГС-інфекцією для проведення диференційної діагностики було рекомендовано дослідження сироватки крові на кріоглобуліни та проведення біопсії нирок для визначення морфологічного варіанту гломерулярного ураження.

Дослідження сироватки на кріоглобуліни (10.02.2019). Наявність кріоглобулінів підтвердилася шляхом проведення тесту з дотриманням необхідних умов забору крові. Наявність кріопреципітату було підтверджено візуальним спостереженням.

Біопсію нирки з гістологічним дослідженням тканини було проведено в Інституті нефрології НАМНУ12.02.2019. Морфологічне дослідження біоптату передбачало пряме імунофлюоресцентне дослідження з антитілами, міченими ФІТЦ до важких ланцюгів імуноглобулінів α, γ μ, легких ланцюгів імуноглобулінів κ і λ, компонентів комплементу C1q і C3c та фібриногену. Клубочки: усі з дифузним глобальним виразним перикапілярним гранулярним світінням IgG, IgM і легких ланцюгів імуноглобулінів κ і λ. у просвіті капілярів нечасто гіалінові депозити. у канальцях та інтерстиції – нечасто краплі реабсорбції в епітелії проксимальних звивистих канальців, розширення та клітинна інфільтрація інтерстицію (рис. 1 A, B, C). За даними літератури, результати імунофлюорисцентної мікроскопії, а саме виразне перикапілярне світіння IgG, IgM, C3c і легких каппа- і лямбда-ланцюгів, є характерним для кріоглобулінемічного гломерулонефриту [9].

За результатами проведення світлової мікроскопії: клубочки 1 – з клітинним, 1 – з фіброзно-клітинними півмісяцями, інтерстиційний фіброз, гіалінові депозити (рис. 1 D), потовщення гломерулярної базальної мембрани (ГБМ), звуження та облітерація просвіту капілярів (рис. 1 E), гіаліновий тромб, гіперцелюлярність інтерстицію (рис. 1 F). Під час проведення світлової мікроскопії коркової речовини нирки (рис. 1 H) виявлено збільшення клубочків, потовщення ГБМ, ендокапілярну гіперцелюлярність. В окремих петлях інтракапілярні депозити. За результатами дослідження канальців та інтерстицію – набряк, виразна мультифокальна мононуклеарна інфільтрація інтерстицію.

За даними літератури, особливістю гломерулонефриту, асоційованого з кріоглобулінемією, за результатами проведення світлової мікроскопії є ендокапілярна гіперцелюлярність зі звуженням та облітерацією просвіту капілярів під час дослідження клубочків, потовщення ГБМ, а також наявність інтракапілярних депозитів. Виявлення в просвіті капілярів гіалінового тромбу також вказує на кріоглобулінемічний варіант ураження нирок [9]. Отже, за результатами патоморфологічного опису підтверджено діагноз кріоглобулінемічного гломерулонефриту.

З метою проведення диференціальної діагностики з аутоімунними захворюваннями пацієнту були проведені лабораторні дослідження на антинуклеарні антитіла (ANA) та антимітохондріальні антитіла (AMA-M2). Результат – антитіла не виявлені. Для оцінки функціонального стану та можливого кріоглобулінемічного ураження щитоподібної залози визначали рівень гормонів Т3, Т4, ТТГ, антитіла до тиреопероксидази (АТПО): лабораторних відхилень від норми не виявлено.

10.03.2019 на основі клінічних даних і результатів отриманих досліджень було встановлено остаточний діагноз: ХХН IV (ШКФ 26 мл/хв), кріоглобулінемічний гломерулонефрит, нефротичний синдром, вторинна артеріальна гіпертензія. Анемія легкого ступеня. ВГС-інфекція. Хронічний вірусний гепатит С, мінімальна активність запального процесу, F0-F1 (за шкалою METAVIR). Рекомендовано проведення етіотропної терапії ВГС ППД. Однак лікування не було розпочато через низькі показники ШКФ (26 мл/хв) і відсутність доступу пацієнта до препаратів. З огляду на це рекомендовано продовжувати гіпотензивну та сечогінну терапію. Протягом наступних тижнів стан пацієнта прогресивно погіршувався – наростали набряки кінцівок, анасарка. За результатами лабораторного дослідження крові відмічено зниження рівня гемоглобіну (87 г/л), наростання креатиніну крові (379,5 мкмоль/л), зниження ШКФ (18 мл/хв). Показники цитолізу (АЛТ, АСТ) зберігалися в межах норми. За результатами проведення рентгенологічного обстеження органів грудної порожнини в прямій проєкції відмічалися застійні явища в малому колі кровообігу з наявністю рідини в лівому синусі (до рівня 5-го ребра) та збільшення кількості рідини в правому синусі. Хворий продовжував приймання гіпотензивних і сечогінних препаратів, інфузії альбуміну та плазми. 03.04.2019, враховуючи наявність препарату в рамках Національної програми щодо лікування вірусних гепатитів та стабілізацію функціонального стану нирок (ШКФ збільшилася до 36 мм/хв), призначено софосбувір 400 мг на добу щоденно та даклатасвір 60 мг один раз на добу щоденно. 16.04.2019 під час дослідження крові методом ПЛР РНК вірусу гепатиту С не визначали. Однак, незважаючи на проведення етіотропної терапії та елімінацію вірусу, стан хворого погіршувався, спостерігалося підвищення рівня креатиніну (266,4 мкмоль/л) і зниження ШКФ (27 мм/хв), наростали набряки нижніх кінцівок, асцит, гідроторакс, гідроперикард. За результатами проведення ренгенографії ОГК (17.04.2019) – негативна динаміка, посилення застійних явищ у малому колі кровообігу, збільшення лівобічного гідротораксу, зниження пневматизації з обох боків у верхніх легеневих полях. Серце розширене в поперечнику. УЗД серця: гідроперикард помірний – по задній стінці лівого шлуночка (ЗСЛШ) 8 мм, по задній стінці лівого передсердя (ЗСЛП) 6 мм^3. Водночас спостерігалася позитивна лабораторна динаміка за кількістю

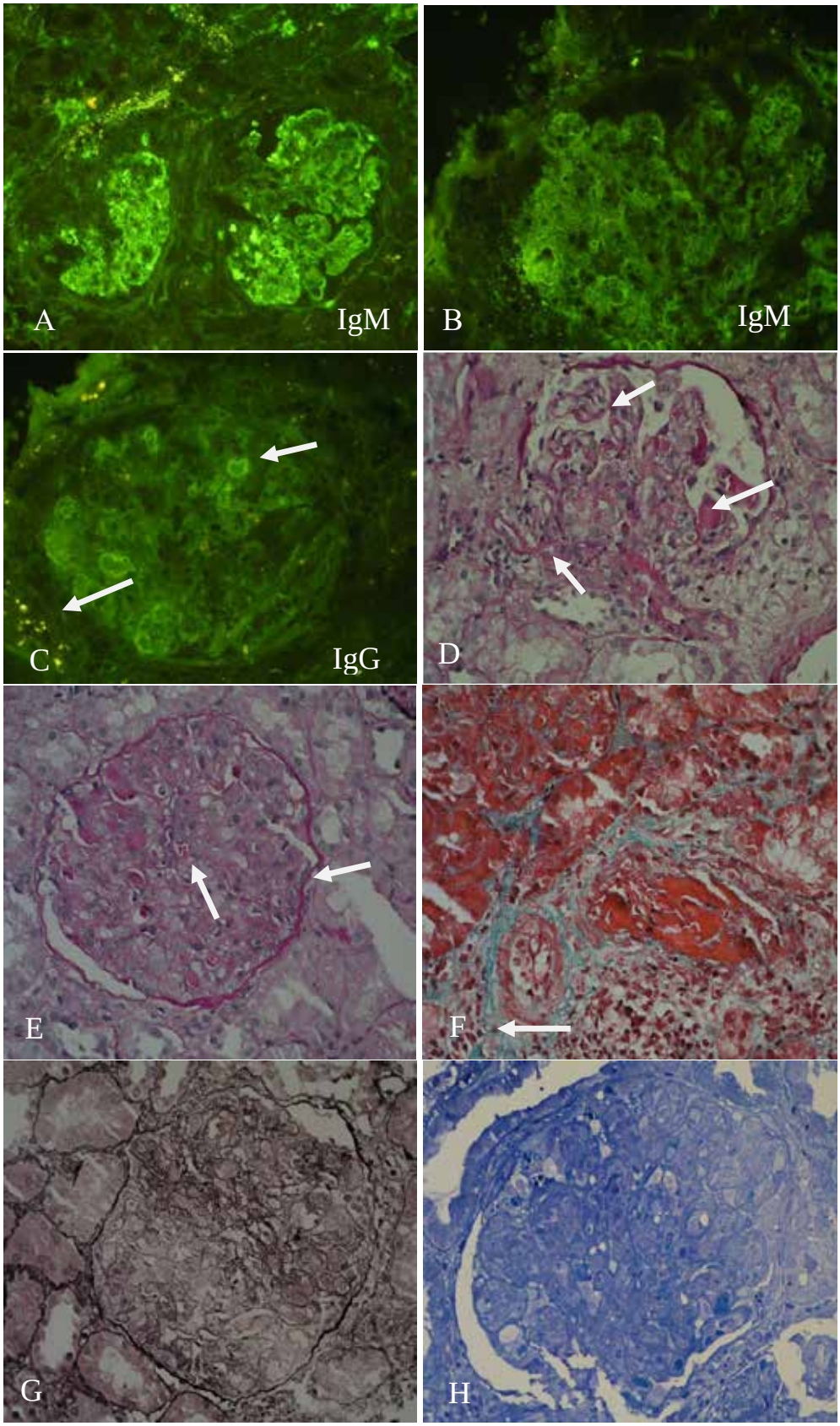

Рис. 1. Імунофлюоресцентна мікроскопія (A, B, C): кріоматрикс: ОСТ-середовище; серійні кріостатні зрізи завтовшки 3–4 мкм. Світлова мікроскопія (D, E, F, G): коркова і мозкова (1 : 1) речовина нирки (серійні мікротомні парафінові зрізи забарвлені гематоксиліном і еозином (3 мкм), трихромом (3 мкм), Шифф-йодною кислотою, конго червоним основним, пікросіріусом та імпрегновані метенаміновим сріблом за Джонсом. Світлова мікроскопія напівтонких зрізів (H): коркова речовина нирки (ультратомні зрізи завтовшки 0,7–1,5 мкм, забарвлені метиленовим синім)

еритроцитів – 2,1–3,46 х 10^{12}/л, лейкоцитів – 16,9–11,65 х 10^{9}/л та рівнем гемоглобіну – 60–100 г/л. Спостерігалася тенденція до нормалізації результатів дослідження сечі: у загальному аналізі – зниження рівня протеїнурії з 6,6 до 3,3 г/л та еритроцитурії з 80–100 до 40–60 у полі зору; добова протеїнурія зменшилася з 8415 до 3630 мг/добу. Показники АЛТ, АСТ, білірубіну, натрію, калію, хлору, глюкози крові не мали відхилень від норми, за винятком незначної гіпопротеїнемії. 02.05.2019, враховуючи виражений набряковий синдром, провели 9 сеансів гемодіалізу з ізольованою ультрафільтрацією. 21.05.2019 у пацієнта виникло гостре порушення мозкового кровообігу (ГПМК) за геморагічним типом у лобних долях і базальних ядрах із проривом крові в шлуночкову систему. Приймання противірусних препаратів було тимчасово призупинено. Після стабілізації стану з 04.06.2019 по 07.07.2019 пацієнт продовжив етіотропну терапію софосбувіром і даклатасвіром, приймання гіпотензивних, сечогінних препаратів та антикоагулянтів. Клінічно відмічалося покращення стану, зменшення задишки, тенденція до зменшення набряків. На момент закінчення лікування пацієнт почував себе задовільно, набряків не було. Наприкінці лікування рівень креатиніну, ШКФ, показники загального аналізу крові та сечі не мали суттєвих відхилень від норми (зберігалася незначна протеїнурія), ПЛР крові HCV RNA (10.07.2019) – негативний.

Отже, отримані результати підтверджують думку багатьох дослідників, що першочерговим вибором у лікуванні пацієнтів з ВГС-асоційованим кріоглобулінемічним ураженням нирок є етіотропна терапія [6; 10; 11].

З 2020 по 2022 рік пацієнт перебував під динамічним спостереженням сімейного лікаря, почував себе добре, продовжував приймання гіпотензивних препаратів та антиагрегантів. За результатами аналізу лабораторних досліджень крові спостерігалася тенденція до підвищення рівня креатиніну та зниження ШКФ, загального аналізу сечі – незначна протеїнурія.

11.10.2023 хворий звернувся на консультацію до нефролога в обласну лікарню ім. М. І. Пирогова. Скарги на підвищення артеріального тиску. За результатами лабораторного дослідження крові спостерігалося підвищення рівня креатиніну до 137,1 мкмоль/л та зниження ШКФ до 59 мл/хв. За результатами загального аналізу сечі – незначна протеїнурія. ПЛР крові HCV RNA (16.10) – негативний. РФ – ++++ (> 100 МО/мл). 16.10.2023 було виконано транзієнтну еластометрію печінки на апараті FibroScan, визначено стадію фіброзу F0-1 за METAVIR, середнє медіанне значення щільності 4,5 кП. Проведено дослідження крові на кріоглобуліни: кріопреципітат не візуалізується.

На рис. 2 та в табл. 1 наведено динаміку ШКФ, рівня креатиніну, гемоглобіну, рівнів протеїнурії та мікрогематурії до-, через 2 тижні після початку, після закінчення та через 1, 2 та 3 роки після завершення терапії ППД.

Пацієнта поінформовано про необхідність подальшого спостереження сімейним лікарем і нефрологом для моніторингу рівня креатиніну з розрахунком ШКФ, рівня РФ, компонента комплементу С3 та протеїнурії. Також пацієнта ознайомлено з можливими перспективами інших видів лікування, зокрема із застосуванням глюкокортикостероїдів та моноклональних антитіл (ритуксимабу).

Отже, у представленому клінічному випадку продемонстровано, що у пацієнта з ВГС-асоційованим кріоглобулінемічним гломерулонефритом зафіксовано значне клінічне та лабораторне покращення після проведення етіотропної терапії ППД з отриманням СВВ. Однак протягом наступних трьох років було

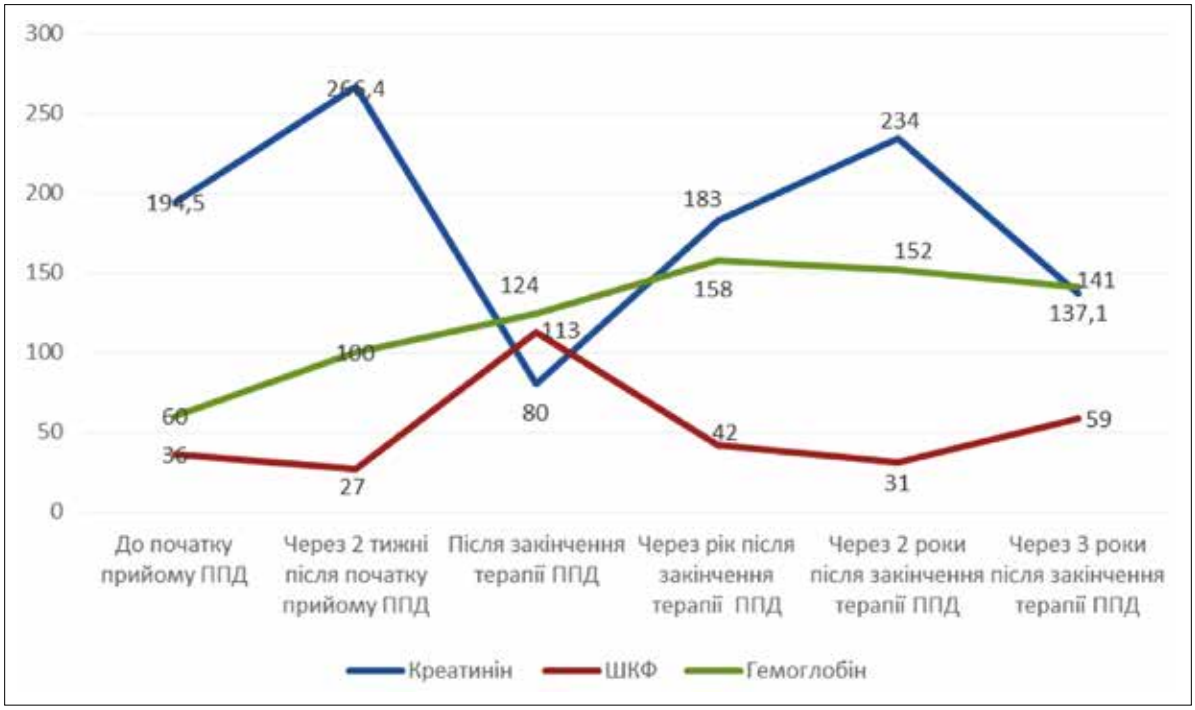

Рис. 2. Динаміка рівня креатиніну крові (мкмоль/л), ШКФ (мл/хв), гемоглобіну (г/л)

Таблиця 1

Динаміка показників добової протеїнурії, загального аналізу сечі до-, через 2 тижні після початку та -через 1, 2 та 3 роки після завершення терапії ППД

Показники	До початку приймання ППД	Через 2 тижні після початку приймання ППД	Після закінчення приймання ППД	Через 1 рік після закінчення приймання ППД	Через 2 роки після закінчення приймання ППД	Через 3 роки після закінчення приймання ППД
Добова протеїнурія	8415	3630	*	*	*	1386
Білок у загальному аналізі сечі (г/л)	6,6	3,3	0,066	0,099	0,33	0,99
Еритроцити не змінені	80–100	40–60	0	0	0–1	0
Еритроцити змінені	0	2–5	4–5	2–3	0	0
Циліндри гіалінові	0–1–2	1–3	0	0	0	0
Циліндри зернисті	1–2–4	2–4	0	0	0	0

Примітка: * – не визначалася.

відзначено поступове підвищення рівня креатиніну та зниження ШКФ, що вказує на можливе прогресування ХХН. Подібна динаміка перебігу захворювання спостерігається у 4–18 % пацієнтів із кріоглобулінемічним васкулітом [7; 12]. На думку дослідників, це може бути пов'язано зі збереженням циркулюючих клонів В-лімфоцитів, проліферація яких стає незалежною від наявності вірусу гепатиту С. Visentini і співавт. спостерігали персистування В-клітинних клонів у пацієнтів з ВГС-асоційованою кріоглобулінемією протягом 12 місяців після ерадикації вірусу [13]. Крім того, існують дослідження щодо того, що РНК ВГС може не виявлятися в сироватці крові, але водночас бути присутнім у гепатоцитах і мононуклеарних клітинах периферичної крові (прихована або латентна інфекція). Незважаючи на високу ефективність ППД в ерадикації ВГС з периферичної крові, питання її впливу на резервуари вірусу в гепатоцитах та мононуклеарних клітинах периферичної крові залишається відкритим [11]. Наявна у пацієнта артеріальна гіпертензія також може сприяти прогресуванню ХХН. Тому існує потреба в проспективних мультицентрових дослідженнях для повнішого розуміння механізмів персистенції вірусу гепатиту С у клітинних резервуарах, вивчення імунної відповіді в контролі персистенції чи елімінації вірусу, впливу різних факторів ризику на перебіг захворювання.

Представлений клінічний випадок із пацієнтом з ВГС-асоційованим, кріоглобулінемічним гломерулонефритом підкреслює необхідність призначення етіотропної терапії ВГС з подальшим тривалим спостереженням, навіть після досягнення клінічної, вірусологічної та лабораторної ремісії. Для запобігання прогресування ХХН необхідний комплексний підхід, який передбачає: регулярний моніторинг ниркової функції (визначення рівня креатиніну, ШКФ, протеїнурії), контроль артеріального тиску, приймання гіпотензивних препаратів, корекцію факторів ризику (дисліпідемії, цукрового діабету).

Висновки

Виходячи з аналізу вищевикладених результатів дослідження, автори статті дійшли таких висновків:

1. Пацієнти, що мають клінічні чи лабораторні ознаки ураження нирок, мають бути обстежені на наявність маркерів вірусних гепатитів.
2. Пацієнтам із ХГС мають бути виконані лабораторні обстеження сечі (визначення протеїнурії, мікрогематурії, циліндрурії в загальному аналізі сечі та в разі виявлення клінічно-значущих відхилень – добова протеїнурія) та біохімічні дослідження крові з визначенням рівня креатиніну, ШКФ.
3. Пацієнтам із ХГС та кріоглобулінемічним гломерулонефритом розглянути питання про першочергове призначення етіотропної терапії із застосуванням ППД.
4. Пацієнтам із ВГС-асоційованим (у т. ч. кріоглобулінемічним) ураженням нирок необхідне тривале клінічне спостереження з контролем рівнів РФ, С3 та С4 компонентів комплементу, кріоглобулінемії та вимірюванням артеріального тиску навіть після досягнення стійкої клінічної, лабораторної та вірусологічної ремісії.

Конфлікт інтересів

Автори заявляють про відсутність конфлікту інтересів.

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THE IMPACT OF PARTICIPATION OF PATIENTS WITH CARDIOVASCULAR DISEASES IN THE GOVERNMENT PROGRAM "AFFORDABLE MEDICINES" ON THEIR ADHERENCE

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THE IMPACT OF PARTICIPATION OF PATIENTS WITH CARDIOVASCULAR DISEASES IN THE GOVERNMENT PROGRAM "AFFORDABLE MEDICINES" ON THEIR ADHERENCE

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Introduction. High drug costs are one of the main barriers to achieving adherence, which jeopardizes the effectiveness of pharmacotherapy for chronic diseases. The general conclusion of a number of studies indicates a shortage of methods for increasing adherence. In order to reduce the financial burden on patients and increase the availability of medicines in Ukraine, the National Prescription Drug Cost Reimbursement Affordable Medicines Program (AMP) was launched. In 2018, the AMP received positive feedback on various criteria, but its impact on patient adherence hasn't been studied.

The aim of the study was to examine the impact of participation of patients with cardiovascular diseases (CVD) in the AMP on their adherence and to develop proposals for increasing adherence.

Results. Against the background of the overall low adherence of patients with CVD, the adherence of patients participating in the AMP was higher. The study found a weak, significant positive correlation ($r = 0.194$; $p \leq 0.05$) between patients' participation in the AMP and their level of adherence. Study results don't allow us to establish a clear dependence on the type of CVD and the adherence level of patients.

Conclusion. The results of the study demonstrated a significant positive effect of CVD patients' participation in the AMP on their adherence. The AMP may be an important tool for increasing adherence by expanding the range of drugs for the treatment of CVD through fixed combinations in a "single" pill that will meet all current guidelines for the provision of medical care for CVD, especially arterial hypertension.

Keywords: adherence, Affordable Medicines program, cardiovascular diseases, reimbursement.

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ВПЛИВ УЧАСТІ ПАЦІЄНТІВ ІЗ СЕРЦЕВО-СУДИННИМИ ЗАХВОРЮВАННЯМИ В УРЯДОВІЙ ПРОГРАМІ «ДОСТУПНІ ЛІКИ» НА ЇХ КОМПЛАЄНС

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Високі витрати на ліки є одним з бар'єрів для досягнення комплаєнсу, що ставить під загрозу ефективність фармакотерапії хронічних захворювань. З метою зменшення фінансового навантаження на пацієнтів та збільшення доступності ліків в Україні була започаткована урядова програма «Доступні ліки». Дослідження впливу участі пацієнтів із серцево-судинними захворюваннями (ССЗ) в програмі «Доступні ліки» на їх комплаєнс дасть можливість розробити шляхи підвищення комплаєнсу. На тлі загального низького комплаєнсу пацієнтів із ССЗ комплаєнс пацієнтів, які брали участь у програмі «Доступні ліки», був вірогідно вищим. Встановлено позитивний вірогідний зв'язок між участю в програмі та комплаєнсом пацієнтів. Вид ССЗ у пацієнтів не впливав на їх комплаєнс. Програма «Доступні ліки» може стати інструментом підвищення комплаєнсу пацієнтів після включення до неї фіксованих комбінації в «одній» таблетці та оптимізації відсотку доплати за ліки.

Ключові слова: комплаєнс, урядова програма «Доступні ліки», серцево-судинні захворювання, реімбурсація.

Introduction

High drug costs are one of the main barriers to achieving adherence to long-term treatment in patients with chronic diseases, particularly cardiovascular diseases (CVD). In turn, low patient adherence jeopardizes the effectiveness of pharmacotherapy for chronic diseases and adversely affects the financial sustainability of healthcare systems.

Almost all countries have systems for reimbursing the cost of drugs to the population, the main task of which is to minimize the costs of citizens and the state budget for the purchase of medicines [1]. In 2017, the Ministry of Health of Ukraine launched the National Prescription Drug Cost Reimbursement Affordable Medicines Program (AMP). The main goal of the AMP is to reduce the financial burden on patients and increase the availability of medicines [2]. Patients with CVD (including coronary artery disease (CAD), arterial hypertension (AH), atherosclerosis), chronic lower respiratory tract diseases, endocrine diseases (including diabetes mellitus), neurological diseases, and patients requiring palliative care can participate in the program [2].

Adherence is defined as patients' tendency to adhere to clinical recommendations and treatment and it can be driven by many elements, including a patient's socioeconomic status, chronic conditions, patient-provider discordance, and healthcare access [3]. In recent years, various authors have been actively studying methods that increase patient adherence [4–6]. The general conclusion of all studies indicates a shortage of methods for increasing adherence and the need to develop a set of criteria for evaluating such methods.

The study of the adherence of patients with different chronic diseases has long attracted the attention of researchers. Alqarni A. M., Alrahbeni T., Qarni A. A. et al. [7] in their study showed that the level of adherence was suboptimal even when free medicines were available with a high level of health care access through government programmes. S. Panahi's research with colleagues suggested that a lower level of general adherence exists among elderly patients of the free clinic [8]. Among the factors influencing adherence in patients with AH, financial constraints were identified with 74.4 % of patients considering medications too expensive) [9]. Similar data were obtained in the study by Asgedom S. W. at al. [10]: adherence of patients with hypertension who received medication free of charge was 97.8 %, while adherence of those who paid for medication themselves was almost half as high – 43.9 %.

Some researchers have studied the impact of reimbursement methods on patient adherence. One such study [11] found low patient adherence across pharmacological classes, but no significant effect of reimbursement type (immediate or deferred) on adherence was found. One more study [12] showed that medication adherence improved with a reduction in the patient's share of the cost of medication, but found that patients who received their medication completely free of charge also had poorer adherence.

In 2018, the results of the study "AMP: Results and Recommendations for Progress in Achieving Universal Health Coverage" were published [13]. The AMP was evaluated based on the following criteria: effectiveness (organizational aspects), access for patients, quality from the perspective of stakeholders, acceptance (by stakeholders, patients). The AMP received positive ratings for all indicators. The program received positive ratings on all indicators. However, no information was found in the available literature on the study of the impact of the AMP specifically on patient adherence. In our opinion, studying the relationship between patient participation in the AMP and the level of their adherence is relevant and will allow us to propose new approaches to increasing the adherence of patients with chronic diseases.

Our study was aimed to examine the impact of CVD patients' participation in National Prescription Drug Cost Reimbursement AMP on their adherence and to develop proposals for modernizing the Program to increase adherence among CVD patients.

Materials and Methods

The study was conducted in a pharmacy that has an agreement with the National Health Service of Ukraine to participate in the AMP during 6 months in 2024. 124 patients with CVD participated in the study. The criteria for including patients in the study were consent to participate in the study; age at least 18 years; diagnosis of AH or CAD; receiving antihypertensive and/or anti-ischemic pharmacotherapy. The exclusion criteria were: inability to communicate due to physical or mental problems; pregnant women.

Depending on whether CVD patients participated in the AMP, they were divided into two groups. Group I consisted of patients participating in the AMP. Group II included patients not taking advantage of this program. Adherence was assessed using the Morisky–Green scale: a version consisting of 4 questions was used (MMAS-4) [14].

Statistical data processing was performed using programs MS Excel for Windows XP, SPSS 10.0.5 and STATISTICA 5.0. Clinical, nonparametric descriptive and mathematical statistics were used to analyze the data. Descriptive statistics, such as means, were used to assess personal characteristics and adherence variables. Statistical characteristics of variables were presented using percentages, mean values (M), and their standard errors (m). To estimate the frequency of occurrence of the factor, the "Fisher's angular transformation" was used. The results of all statistical procedures were considered significant at $p < 0.05$. Correlation analysis was performed to confirm the proposed hypothesis. All methods applied during the study complied with requirements of the Declaration of Helsinki of the World Medical Association.

Research results and their discussion

The study included 124 patients with CVD aged 30 to 90 years, the mean age was 70.75 ± 10.3. The gender distribution of the study participants was as follows: 44 males (35.49 %) and 80 females (64.51 %). 32.26 % of patients had higher education, 39.52 % had secondary specialized education, and 28.21 % had secondary education.

Among the surveyed patients, 50 % had AH, 8.06 % had CAD, and 41.94 % had comorbid pathology – a combination of AH and CAD (Fig. 1).

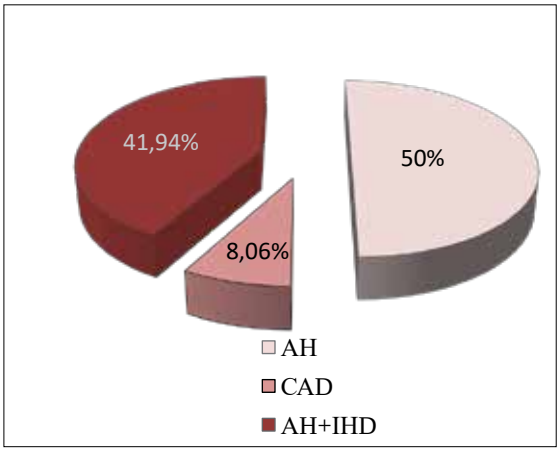

Fig. 1. Distribution of patients by type of CVD

All patients underwent blood pressure (BP) measurement. The target BP level of < 130/80 mm Hg was achieved in 33.33 % of all hypertensive patients (in 24 patients with AH and 14 patients with combination of AH and CAD).

All surveyed patients with various CVDs assessed their well-being using the criteria "good", "satisfactory", "partially satisfactory" and "unsatisfactory". The vast majority of patients reported frequent and unsatisfactory well-being (Fig. 2).

Depending on their participation in the AMP, all patients were divided into two groups. Group I consisted of 74.2 % (92) patients participating in the AMP. Among them were 46 patients with AH, 10 (all) patients with CAD, and 36 patients with comorbid pathology – AH and CAD. The duration of participation in the AMP was up to 1 year in 15.21 % patients, from 1 to 2 years in 34.79 % patients, and more than 2 years in 50 % patients. Group II included 25.8 % (32) patients who did not participate in the AMP. This Group consisted of 15 patients with AH, 17 patients with comorbid pathology – AH and CAD.

According to the results of the survey using the MMAS-4 scale, we determined that the adherence of all patients with CVD was 48.39 %. This result is significantly lower than the generally accepted indicator described in the literature, 80 % [15]. Only one patient, which was about 1 %, was completely non-adherent.

According to the adherence level all patients were divided into 3 Subgroups. The Subgroup with a high adherence level (MMAS-4 = 4) consisted of 23.39 % patients, whose mean age was 71.53 ± 13.75. The Subgroup with moderate adherence level (MMAS-4 = 2–3) consisted of 25 % patients, whose mean age was 60.08 ± 11.57. The Subgroup with a low adherence level (MMAS-4 = 1) consisted of 50.81 % patients, whose mean age was 73.85 ± 13.18. The gender distribution of patients in all subgroups is shown in the diagram (Fig. 3).

When conducting correlation analysis, the following results were obtained:

– Weak negative significant correlation ($r = –0.172$; $p < 0.05$) between patients' age and adherence level;

– Weak positive significant correlation ($r = 0.28$; $p < 0.05$) between the level of education and the adherence level;

– Weak positive significant correlation ($r = 0.243$; $p < 0.05$) between the duration of the disease and the adherence level;

– Weak positive significant correlation ($r = 0.117$; $p < 0.05$) between the well-being of patients and their adherence;

– Weak negative significant correlation ($r = –0.136$; $p < 0.05$) between the level of BP and the adherence level of hypertensive patients.

Further analysis of adherence of patients with CVD depending on their participation in the AMP showed that adherence of patients in Group I was approximately 56 %, and patients in Group II – approximately 37 %. Among patients in Group II, one patient was completely non-adherent. The study also found a weak, significant

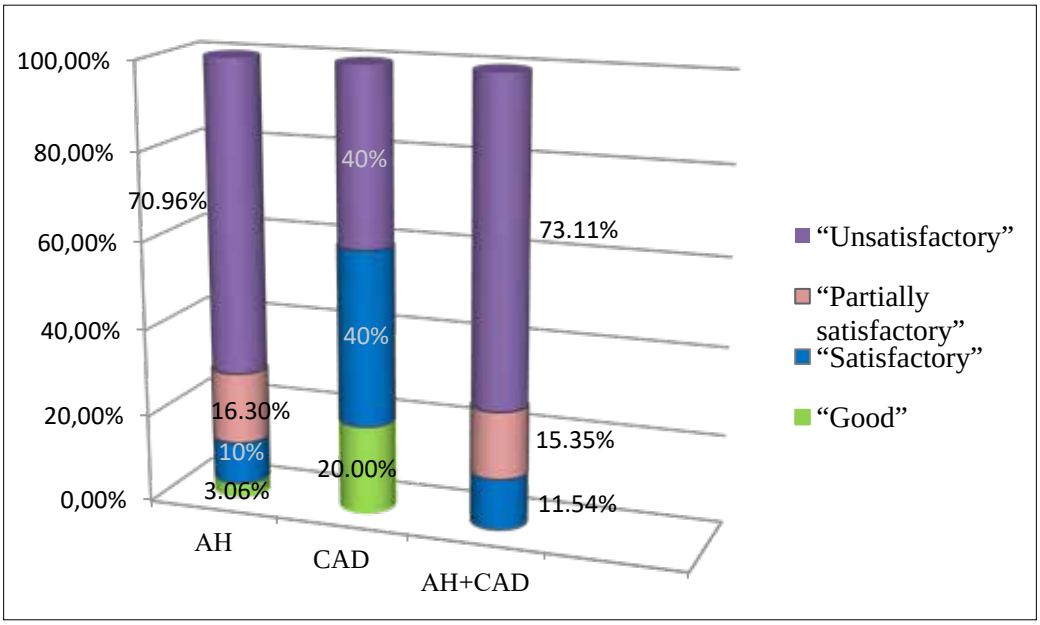

Fig. 2. Assessment of well-being in patients with various types of CVD

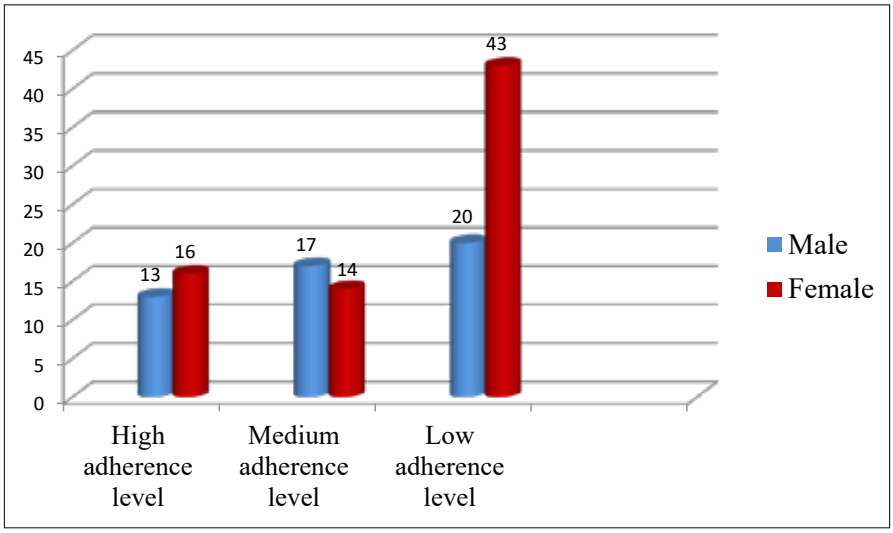

Fig. 3. Gender distribution of patients with different levels of adherence

positive correlation (r = 0.194; p ≤ 0.05) between patients' participation in the AMP and their level of adherence. Thus, adherence of patients participating in the AMP was significantly (p ≤ 0.05) higher than that of patients not participating in the AMP.

Among patients participating in the AMP, the numbers of patients with high and low adherence were significantly higher (p ≤ 0.01) than in patients not participating in the AMP (Table 1).

Analysis of the adherence level of patients with different CVDs depending on participation in the AMP showed that in patients with AH, the moderate and low adherence levels significantly predominated among Group I patients. In patients Group I with comorbid pathology – AH and CAD the high and low adherence level significantly predominated (Table 2).

Table 1

Analysis of patient adherence levels depending on participation in the AMP

Adherence level	Group I / Group II	
	$\varphi_{ем}$	p
High	2.543	0.0001*
Moderate	1.378	0.0841
Low	3.979	0.0001*

* p ≤ 0,01 – significant difference in data in comparison groups.

Table 2

Analysis of the adherence level of patients with various CVDs depending on participation in the AMP

Adherence level	Group I / Group II			
	AH		AH+CAD	
	$\varphi_{ем}$	p	$\varphi_{ем}$	p
High	0.568	0.2849	3.734	0.0001*
Moderate	2.185	0.0144*	0.568	0.2849
Low	1.941	0.0262*	2.191	0.0142*

* p ≤ 0.05 – significant difference in data in comparison groups.

Conclusions

The results of the study demonstrated an overall low level of adherence in patients with CVD. Assessment of the gender and age distribution of adherence showed a predominance of high adherence levels in female and younger individuals. The decrease in adherence with increasing age of patients may be associated with cognitive impairments that can develop in elderly and senile patients. The established relationship between adherence and patient education indicates a more conscious attitude towards their health status and understanding of the need for CVD treatment in patients with higher education. A marked increase in patient adherence with increasing disease duration may characterize patients' understanding that CVDs, in particular with comorbid pathology – AH and CAD, have a chronic course and only constant long-term administration of recommended medications can ensure control of the course of the disease and improve the well-being of patients. This assumption is supported by the relationship between patients' well-being and their adherence. The study results also demonstrated a relationship between lower BP levels and higher patient adherence, confirming the important role of patients' adherence to all recommendations for achieving target BP levels.

Against the background of a rather low adherence of all patients with CVD, the adherence of patients who participated in the AMP was higher compared to both all study participants and the group of patients who didn't participate in the AMP. The established positive significant relationship between participation in the AMP and adherence of patients with CVD and the significantly higher number of patients with a high adherence level indicates a positive impact of the AMP on patient's adherence. It should be noted that the results of the study could have been influenced by the conditions in which it was conducted: the survey was conducted in a pharmacy, where patients came to purchase the necessary medications, which, in general, indicates their high awareness level regarding the need for treatment of CVD.

Among patients with comorbid pathology – AH and CAD who participated in the AMP, the number of patients

with a high adherence level was significantly higher than in hypertensive patients alone. At the same time, the number of patients with a low adherence level didn't depend on the type of CVD and was significantly higher in patients who participated in the AMP. Such results don't allow us to establish a clear dependence on the type of CVD and the adherence level of patients.

The significantly higher numbers of both high and low adherence levels among patients with CVD who participated in the AMP indicate the need to expand the program's impact on adherence among all patients with CVD. The AMP can be an important tool for improving adherence by expanding the range of drugs for the treatment of CVD through *fixed-dose* combinations in a single-dose forms that will meet all modern guidelines for providing medical care for CVD, especially AH. Optimizing the list of drugs for which the patients make a surcharge and the percentage of co-payment can also contribute to improving adherence.

An expanded Register of Medicinal Products Subject to Reimbursement under the State Health Care Guarantee Program came into effect on January 1, 2025. The updated Register includes, in particular, *fixed-dose combination products* for the pharmacotherapy of CVD. Given that the present study was conducted in 2024, it would be promising to conduct further research aimed at assessing the changes in patient adherence as a result of the modernization of the AMP.

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Conflict of interests

The authors declare no conflict of interest.

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ANTIBIOTIC RESISTANCE: MOLECULAR MECHANISMS OF FORMATION AND MODERN MANAGEMENT STRATEGIES

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ANTIBIOTIC RESISTANCE: MOLECULAR MECHANISMS OF FORMATION AND MODERN MANAGEMENT STRATEGIES

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Background. Antibiotic resistance (ABR) is the greatest threat to human survival, leading to a loss of control over resistant bacterial strains. The aim of this work was to demonstrate the pathogenetic basis of ABR and potential solutions to this problem.

Methods. To achieve this goal, an analysis of current scientific publications regarding the mechanisms of ABR and innovative approaches to overcoming it was conducted.

Results. The main mechanisms of ABR include reduced membrane permeability, efflux pumps, modification of antibiotic targets, enzymatic inactivation, horizontal gene transfer, and the involvement of the host's immune system.

Conclusion. Controlling ABR requires the rational use of antibiotics, optimization of traditional antibiotic therapy, modulation of the immune response, microbiome modulation, and phage therapy.

Key words: antibiotic resistance, infection, immune protection, phagocytes, rational antibiotic therapy.

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М. Р. Хара, О. М. Олещук, С. М. Марчишин, Г. О. Безкоровайна, О. О. Іскра

АНТИБІОТИКОРЕЗИСТЕНТНІСТЬ: МОЛЕКУЛЯРНІ МЕХАНІЗМИ ФОРМУВАННЯ ТА СУЧАСНІ СТРАТЕГІЇ МЕНЕДЖМЕНТУ

Тернопільський національний медичний університет імені І. Я. Горбачевського Міністерства охорони здоров'я України, Тернопіль, Україна

Актуальність. Антибіотикорезистентність (АБР) – найбільша загроза виживанню людини, що веде до втрати контролю над резистентними штамами бактерій.

Метою роботи було продемонструвати патогенетичне підгрунтя АБР та можливості вирішення цієї проблеми. Для реалізації мети було проведено аналіз сучасних наукових публікацій щодо механізмів АБР та інноваційних підходів до її подолання.

Результати. Основні механізми АБР передбачають знижену проникність цитолеми, ефлюксні помпи, модифікацію мішеней для антибіотиків (АБ), ферментативну інактивацію, горизонтальний перенос генів, участь імунної системи макроорганізму.

Висновки. Контроль АБР – це раціональне використання АБ, оптимізація традиційної антибіотикотерапії, модуляція імунної відповіді, модуляція мікробіому та фаготерапія.

Ключові слова: антибіотикорезистентність, інфекція, імунний захист, фагоцити, раціональна антибіотикотерапія.

Introduction

Antibiotic resistance is a global public health issue, attracting increasing attention due to its real threat to the human population. Although resistance to antibiotics (ABs) is an inevitable consequence of bacterial evolution and natural selection, the misuse and overuse of ABs in modern medicine and dentistry significantly contribute to the worsening crisis. ABR reduces the ability of medicine to control socially dangerous infections (tuberculosis, syphilis, gonorrhea), and worsens treatment outcomes in patients undergoing chemotherapy, cesarean sections, hip prosthetics, organ transplants, and other complex medical interventions. The problem is exacerbated by uncontrolled antibiotic use in agriculture and the food industry. According to WHO, ABR is a global issue driven by lack of access to clean water, inadequate hygiene and prevention, lack of quality and affordable vaccines, and absence or disregard of legal regulations [1]. For Ukraine, this problem has become particularly acute since July 2022 due to a large number of patients with complex war injuries requiring antibiotic therapy.

Aim of the Study. The aim of the study was to present currently known molecular mechanisms of bacterial adaptation to antibiotics, to elucidate the role of the host organism in the pathogenesis of antibiotic resistance development, and to analyze scientific data on potential strategies for effective targeting of pathogens and enhancing the efficacy of antibiotic therapy using the existing arsenal of drugs.

Materials and Methods
Research results and their discussion

To achieve this aim, a review and integrative analysis of scientific publications available in bibliometric databases was conducted. The selected sources reflect the underlying causes and mechanisms of antibiotic resistance, as well as approaches to addressing this global challenge.

Epidemiology of ABR and Issues Across Medical Fields. The discovery of antibiotics marked a crucial milestone in medicine, saving and continuing to save millions of lives annually. However, their effectiveness is threatened by the ability of bacteria to adapt to hostile environments and diminish or neutralize treatment. ABR arises from numerous mechanisms that enable certain bacteria to survive after the application of specific antibiotics, and the resulting resistance can be passed on to other bacteria as they reproduce [2; 3].

According to the European Centre for Disease Prevention and Control (ECDC), more than 35,000 people die each year in Europe due to ABR [2]. The overall epidemiological situation in the EU remains concerning. Although the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is gradually decreasing, the prevalence of carbapenem-resistant strains of *Klebsiella pneumoniae* has increased by more than 50 % since 2019 [4].

According to WHO, in 2019, ABR caused more than 1.27 million deaths globally [1], and by 2050, this number may exceed 39 million (Lancet prognosis). The economic consequences of such trends include an annual loss of $3.4 trillion and more than 24 million people falling into extreme poverty [5; 6].

The consequences of ABR are already evident in many areas of medicine. Excessive or unjustified use of antibiotics for viral infections contributes to the growth of ABR. This is especially relevant in pediatrics, where about 30 % of antibiotics are prescribed without proper indications or while ignoring local sensitivity data [7].

Chronic respiratory diseases (such as cystic fibrosis and COPD) require prolonged antibacterial treatment, which promotes the development of complex forms of ABR. Traditional susceptibility testing does not always reflect the actual conditions in the lungs, so comprehensive resistome analysis is key to developing personalized therapeutic strategies [8]. Obstetrics and surgery are also affected by the consequences of ABR, as antibiotics are frequently used not only for treatment but also for the prevention of infections [9]. In dermatoveneorology, antibiotics are widely applied to treat socially significant sexually transmitted infections (syphilis, gonorrhea) [10], as well as severe forms of acne, rosacea, and other skin infections [11]. Tuberculosis occupies a distinct place in this issue, being a historical example of both natural and acquired ABR. Treatment of drug-sensitive forms requires the administration of multiple medications over a period of 6–9 months, which is often interrupted by patients, thus promoting the emergence of drug-resistant forms [12; 13]. Drug-resistant tuberculosis (resistant to at least one of the first-line drugs) is transmitted just as easily as drug-sensitive forms, but its diagnosis and treatment are significantly more challenging. The rapid rise in the number of multidrug-resistant forms threatens the global capacity to control this disease [14; 15].

Microorganisms of Concern in Antibiotic Resistance. A significant step in addressing ABR was the establishment by the World Health Organization (WHO) in 2017 of a priority list of the most dangerous antibiotic-resistant microorganisms. This list is divided into three priority tiers: critical, high, and medium. The *critical priority group* includes bacteria posing the highest threat, such as *Acinetobacter baumannii* (carbapenem-resistant), *Pseudomonas aeruginosa* (carbapenem-resistant), and members of the *Enterobacteriaceae* family, particularly those producing extended-spectrum β-lactamases (ESBL) or exhibiting carbapenem resistance. These microorganisms are the leading cause of healthcare-associated infections, especially in patients with catheters or on mechanical ventilation. *The high-priority group* includes pathogens that are already widespread in the population and are progressively developing resistance to standard treatment regimens: *Enterococcus faecium* (vancomycin-resistant), *Staphylococcus aureus* (including MRSA and VRSA), *Helicobacter pylori*, *Campylobacter, Salmonella*, and *Neisseria gonorrhoeae*. *The medium-priority group* comprises pathogens that are already showing alarming resistance trends, including *Streptococcus pneumoniae, Haemophilus influenzae*, and *Shigella spp.* [16–18].

ESKAPE Pathogens. Particular attention is currently drawn to a group of pathogens known by the acronym ESKAPE – *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter spp* [17; 19]. This group of bacteria was named for their ability to 'escape' the effects of available antimicrobial agents, making them some of the most dangerous pathogens in clinical practice [18; 19]. Their survival is due to high genetic plasticity, the ability to horizontally transfer resistance genes, biofilm formation, and resilience in hostile environments, particularly in hospital settings. They are the main representatives of nosocomial infections [20]. The greatest danger is associated with their resistance to last-line ABs, particularly carbapenems. In 2020, every fifth case of urinary tract infections caused by *Escherichia coli* was resistant to standard AB. *Klebsiella pneumoniae* also demonstrates growing antimicrobial resistance. This forces doctors to resort to reserve ABs, which accelerates the formation of resistant strains [18]. In addition, the spread of new invasive pathogens, such as *Candida auris* – a fungus resistant to several classes of antifungal drugs, capable of causing outbreaks of nosocomial infections – is increasing [21; 22].

Interestingly, ESKAPE bacteria, which are responsible for the development of bacteremia, ventilator-associated pneumonia, endocarditis, and infections of the urinary tract, skin, and soft tissues, do not always behave as pathogens. They can colonize the skin or mucous membranes without causing disease. Problems arise when these microbes enter sterile areas of the body, such as the blood or cavities, where they quickly cause severe, often treatment-resistant infections. The unique ability of ESKAPE pathogens to evade AB action and colonize a wide range of environments makes them the main drivers of the modern ABR crisis [23].

Types and Mechanisms of ABR. ABR exists in natural and adaptive forms. Natural ABR can be intrinsic or induced.

Intrinsic ABR is always universal within a bacterial species, doesn't depend on prior exposure to ABs, and isn't linked to horizontal gene transfer. Induced ABR is initiated by genes consistently present in bacteria, but their expression to ABR levels is triggered by ABs [24; 25]. The most common mechanisms of intrinsic ABR are reduced permeability of the bacterial outer membrane (due to lipopolysaccharides in Gram-negative bacteria) and the natural activity of AB efflux pumps, which are also a common mechanism of induced AMR [25; 26]. Acquired ABR develops through the acquisition of genetic material via all major pathways – transformation, transposition, and conjugation – collectively known as horizontal gene transfer (HGT). Additionally, bacteria can undergo mutations in their own chromosomal DNA. In this case, ABR can be temporary or permanent [27]. Adaptive AMR occurs when the amount of ABs increases during treatment; it's characterized by rapid resistance development and a swift return to a non-resistant phenotype after the AB is removed from the environment [28]. The mechanisms of ABR in pathogenic bacteria form the basis of multidrug resistance. Depending on the chemical structure of the AB, bacteria employ various counteracting mechanisms, including low outer membrane permeability, drug efflux pumps, AB inactivation, and modification of drug targets [29; 30].

Low Permeability of the Outer Membrane is a survival mechanism that microorganisms developed through evolution to protect themselves from toxic substances, including natural ABs. This mechanism involves a complex located on the outer and inner membranes of bacteria. This complex consists of lipid A, an oligosaccharide core, and O-antigen, which act as recognizers of anything foreign outside the bacterium. Through stabilization by Ca and Mg ions, lipopolysaccharide molecules connect, forming negatively charged phosphate groups that repel hydrophobic AB molecules. Hydrophobic ABs (like rifampicin and fluoroquinolones) can penetrate this lipid bilayer by diffusion. However, for hydrophilic ABs and nutrients, access is only possible through porin channels. These porins are less common in *mycobacteria* and allow for significantly lower uptake rates than in Gram-negative bacteria, which substantially limits drug entry [31].

Efflux pumps are another key mechanism in the development of ABR. These are transport proteins (transporters) involved in eliminating toxic substances from bacteria. These proteins are found in Gram-positive and Gram-negative bacteria, as well as in eukaryotes. There are five main families of efflux transporters: MF, MATE, RND, SMR, and ABC. The ABC family is powered by ATP hydrolysis, while all other families use a proton gradient [32]. For example, the cell wall of *P. aeruginosa* bacteria contains two efflux pumps: MexAB-OprM and MexXY. The MexAB-OprM pump spans both the inner and outer membranes of the bacterium and effectively expels toxins and ABs from the cell, reducing their concentration to an ineffective level. This complex consists of three key components: MexB – an RND family protein embedded in the inner membrane, responsible for recognizing and transporting harmful substances; MexA – a periplasmic protein that connects MexB to the outer channel; OprM – an outer membrane protein that forms the exit channel. The MexXY pump plays an important role in P. aeruginosa's resistance, specifically to aminoglycosides. Its unique feature is that this protein complex does not have its own outer membrane channel. Instead, it utilizes OprM from the MexAB-OprM complex and is activated by the inactivation of the MexZ repressor, which in turn activates the MexXY gene. This leads to the active elimination of ABs by the MexXY/OprM pump, which lowers their concentration inside the bacterium and renders the ABs ineffective [33].

Porin Channels. In bacteria, especially Gram-negative ones with a large outer membrane, many substances, including ABs, enter the cell through special protein channels called porins. Typically, these channels allow hydrophilic molecules to pass through. Bacteria develop ABR by affecting porins in two main ways. First one, decreasing the number of porins or blocking their synthesis: Bacteria can reduce the total number of porins in their outer membrane or block the production of specific types. Members of the *Enterobacteriaceae* family often use this mechanism to acquire ABR, particularly to carbapenems. The fewer "entry gates" there are, the less AB can get into the bacterium. And second one, initiating mutations that alter porin channel structure: This method either reduces or completely prevents the entry of certain ABs while still allowing essential nutrients to pass. For example, such mutations in *E. aerogenes* have caused ABR to imipenem and some cephalosporins. Similarly, in *Neisseria gonorrhoeae*, a mutation in loop 3 of the penB locus led to resistance against beta-lactams and tetracycline [34; 35].

Induction of Chromosomally-Encoded β-Lactamases. When there's a downregulation or absence of outer membrane OprD porins, beta-lactam antibiotics can still get into the bacterial cell. Once inside, they can induce the chromosomally-encoded β-lactamase AmpC. This essentially "turns on" the AmpC gene, leading to the production of a large amount of inducible cephalosporinase, which then breaks down the ABs. Additionally, the blaOXA-50 gene is consistently produced in bacteria, encoding a constitutively expressed oxacillinase (OXA-50). This enzyme also destroys ABs that are susceptible to its action [36]

Horizontal gene transfer is a mechanism through which ABR genes spread among bacteria. It involves the transmission of genetic material to a bacterium that is not its offspring via conjugation, transformation, or transduction. *Conjugation* is a contact-dependent process whereby mobile genetic elements, such as plasmids, integrative and conjugative elements (ICEs), are transferred through a pilus or pore between adjacent bacteria, either within the same genus or across different species. This enables the rapid dissemination of ABR genes. *Transformation* involves the uptake by recipient bacteria of extracellular DNA released from donor bacteria lysed by antibiotics. Once absorbed, this DNA integrates into the recipient bacterium's genome, conferring new traits, including ABR. *Transduction* refers to the use of a temperate bacteriophage as a vector for transferring both chromosomal and extrachromosomal DNA from donor to recipient bacteria, thereby conferring new characteristics [37].

Modification of antibiotic targets. Bacteria possess numerous cellular components that serve as targets for

antibiotics. In the case of ABR, the quantity and/or structure of penicillin-binding proteins in the bacterial cell wall and membrane are altered due to the acquisition of van genes. Changes also occur in the structure of peptidoglycans and the surface charge of the bacterial membrane, which may become more positive. In ribosomes, mutations can lead to methylation of the ribosomal subunit or the protection of ribosomes by specific proteins. Target modification also encompasses metabolic alterations, including the synthesis of nucleic acids through changes in DNA gyrase or topoisomerase IV, and altered metabolism due to mutations in genes encoding enzymes involved in folate synthesis (DHPS, DHFR) [27; 38].

Inactivation of ABs. Bacteria have developed effective strategies to counteract ABs, among which inactivation plays a key role. This process occurs either through hydrolysis of the AB by β-lactamases [38–40], or via the chemical modification of antibiotics by the addition of acetyl, phosphoryl, or adenylyl groups, which renders the compound inactive [27].

Biofilm formation. Due to the protective properties of their matrix and physiological changes in the cells – leading to the development of metabolically dormant cells – biofilms exhibit exceptional resistance to various chemical and physical environmental factors. Initially, planktonic microorganisms reversibly adhere to biological surfaces within seconds of contact. This is followed, within minutes, by irreversible attachment of the microorganisms. The subsequent stage of biofilm formation involves cell growth and division, occurring over the course of several hours. In the following days, exopolysaccharides are produced, and water channels begin to form. These structures hinder the penetration of ABs through the mucosal surfaces of organs and into the deeper layers of the biofilm. The slow diffusion of ABs through the biofilm, combined with the action of bacterial enzymes and chemical substances, results in the inactivation and degradation of the ABs. Over the ensuing months, additional bacteria adhere to the biofilm layers and disperse across its surface. Moreover, bacteria within biofilms utilise horizontal gene transfer mechanisms, which further enhance their resistance to ABs [41].

*The Role of the Host Organism in the Development of ABR.*The host immune system, particularly phagocytic cells, plays a crucial role in the pathogenesis of ABR. Macrophages and neutrophils employ a wide range of antibacterial mechanisms, including reactive oxygen species (ROS), reactive nitrogen species (NO), proteolytic enzymes (e.g., cathepsins, lysozyme), antimicrobial peptides (such as LL-37), and phospholipases. The generation of ROS and RNS is mediated by the enzyme systems Nox2 and NOS2, respectively. The products of these reactions, including peroxynitrite, can damage bacterial cells but at the same time contribute to the development of ABR by inducing a state of metabolic dormancy [42]. In *Staphylococcus aureus*, for instance, peroxynitrite disrupts the function of aconitase, thereby blocking the tricarboxylic acid cycle and driving the bacterium into a therapy-resistant state. Similar effects have been observed in infections caused by *Mycobacterium tuberculosis* and *Salmonella typhimurium*, indicating a potentially universal mechanism. Neutrophil extracellular traps (NETs) and macrophage extracellular traps (mETs) further contribute to bacterial localisation and are essential for pathogen control under conditions where classical phagocytosis is impaired [43]. Of particular concern is the global spread of methicillin-resistant *S. aureus* (CA-MRSA), which is epidemiologically associated with severe skin infections and pneumonia, largely due to its high virulence. A major contributing factor is the strong selective pressure exerted by ABs on *S. aureus*, which activates both horizontal and vertical gene transfer mechanisms, leading to resistance against penicillins and structurally related β-lactam antibiotics. Phenol-soluble modulins of the alpha-type (PSMα), a novel group of S. aureus peptides, recruit, activate, and ultimately lyse human neutrophils, increasing bacterial virulence and reducing the efficacy of antimicrobial therapy [44]. Moreover, *S. aureus* is capable of evading the host immune response partly due to the anti-inflammatory cytokine IL-10, which promotes biofilm formation under conditions of macrophage anti-inflammatory programming (into the M2 subpopulation) [45]. *Mycobacterium tuberculosis* exploits both resident and recruited macrophages for survival, ultimately inducing their death. The released bacterial aggregates can evade phagocytosis and destroy macrophages in a contact-dependent manner by disrupting the plasma membrane, inducing calcium accumulation in the cytosol, and triggering pyroptosis. These effects are dependent on the Mtb ESX-1 secretion system and the presence of the surface lipid phthiocerol dimycocerosate [46].

Overcoming of the ABR Problem. Tackling ABR is a multifaceted challenge due to the complexity and diversity of resistance mechanisms. One promising approach under active investigation is the modulation of the host immune response. For instance, it has been demonstrated that streptazolin – a natural compound derived from *Streptomyces* – enhances the phagocytic activity of macrophages by activating the NF-κB signalling pathway, stimulating ROS production, and inducing cytokine secretion. Bosutinib, a SRC kinase inhibitor, has been shown to further augment phagocytic activity, ROS generation, and macrophage survival, thereby improving their capacity to eliminate resistant strains such as vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and *Pseudomonas aeruginosa*. The combined application of bosutinib and mitoxantrone has demonstrated an additive effect [47]. Antioxidants such as N-acetylcysteine (NAC) and tempol help to reduce oxidative stress and enhance AB efficacy, particularly against intracellular pathogens. Furthermore, immunomodulatory agents – including PPARγ agonists and glucocorticoids – facilitate macrophage adaptation for more effective pathogen clearance [48]. In one study, a nanoparticle named COSBN@CFS@PS was developed to combat recurrent infections caused by intracellular, antibiotic-resistant bacteria. This nanoparticle is pH- and H_2O_2-responsive, allowing for targeted action within macrophages. It is composed of chitosaccharides (COS), cefoxitin (CFS) – a β-lactam antibiotic – and a pinacol ester of phenylboronic acid (a β-lactamase inhibitor). The surface coating of phosphatidylserine (PS) facilitates the nanoparticle's uptake by macrophages. Once inside the macrophage, under acidic conditions and in the

presence of H_2O_2, the nanoparticle releases boronic acid, which inhibits β-lactamase and prevents degradation of the AB. This targeted delivery system significantly enhances the antibacterial efficacy of cefoxitin in the treatment of intracellular infections [49].

Drug repositioning is another promising approach in the fight against ABR. This strategy involves identifying new therapeutic applications for existing, already-approved drugs originally developed for other diseases. One particularly interesting direction is the investigation of antibiotics, traditionally used to treat bacterial infections, for their potential antiviral properties. Studies have indicated that certain classes of ABs, including macrolides, glycopeptides, tetracyclines, fluoroquinolones, and aminoglycosides, may exhibit antiviral activity against a range of RNA and DNA viruses, including SARS-CoV-2. Although the mechanisms underlying this antiviral activity are not yet fully understood, they are thought to involve both direct effects on the viral particles and indirect effects such as the immunomodulatory and anti-inflammatory properties of these ABs, which may influence the host's response to viral infection. Despite the promising nature of these findings, the use of antibiotics to treat viral infections remains controversial and is not currently accepted as standard medical practice. Robust clinical trials are required to confirm the efficacy and safety of antibiotics in this novel role. To date, no antibiotic has been officially approved for use as an antiviral agent [50].

Optimisation of Existing Antibiotics. In addition to the development of new drugs, considerable efforts are being directed towards the optimisation of treatment regimens using existing, or "old", antibiotics. In the United States, the National Institute of Allergy and Infectious Diseases (NIAID) is actively conducting research focused on refining the use of established ABs. This includes exploring novel routes of administration, determining the most effective and shortest possible duration of therapy, and evaluating combination treatment strategies – specifically, the concurrent use of two or more antibiotics [51; 52].

Microbiome-Based Approaches. Researchers are exploring non-traditional strategies for treating antibiotic-resistant infections, including the development of live microbiome-based therapeutics. Scientists from the NIAID have collaborated with researchers in Thailand on a project demonstrating that *Bacillus* – a "beneficial" bacterium commonly found in probiotic digestive supplements – can aid in eliminating *Staphylococcus aureus*. NIAID is also investigating the use of faecal microbiota transplantation as a treatment for recurrent *Clostridium difficile*-associated disease (CDAD), a potentially life-threatening form of diarrhoea. This procedure involves introducing stool from a healthy donor – screened for infectious agents and antibiotic-resistant organisms – into the recipient's colon to restore a healthy and diverse gut microbiome [53].

Phage Therapy. Bacteriophages (phages) are viruses that selectively infect and destroy bacteria. Phage therapy has been employed to treat patients suffering from severe, multidrug-resistant infections under compassionate use protocols, with encouraging outcomes. However, significant knowledge gaps currently hinder the development, standardisation, and regulatory approval of phage-based treatments [54]. While the complete elimination of antimicrobial resistance is unachievable – given that it is a natural evolutionary process – modifying our approaches to antibiotic use can have a substantial impact in slowing the spread of this global threat [55].

Adjuvant Coupling: Synergistic Therapy. The usage of adjuvants enables the restoration of bacterial sensitivity to existing antibiotics by blocking resistance mechanisms (e.g., efflux pumps) or facilitating drug penetration into the cell. Combining antibiotics with mucolytics (e.g., N-acetylcysteine) and enzybiotics (peptidoglycan-degrading enzymes) is effective for the disruption of bacterial biofilms. This allows the antimicrobial agent to penetrate the deep layers of the infectious focus [56].

Discovery of New Classes: Lantibiotics. It is a class of ribosomally synthesized antimicrobial peptides (bacteriocins) containing unconventional amino acids (lanthionines). They possess a unique, typically dual mechanism of action: binding to lipid II, which disrupts cell wall synthesis, and pore formation in the membrane. This renders the development of resistance extremely difficult. Representatives of this class, such as Nisin and the novel lichenicidins, are considered potent alternatives for combating methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE) [57].

Rational Use of Antibiotics in Medical Practice. To combat the growing threat of antibiotic resistance, the WHO has developed key strategies aimed at promoting the rational use of antibiotics [58]. In our view, the most essential and effective measures for healthcare systems include the following:

1. *Optimal dosing and treatment duration.* Inadequate antibiotic dosing or premature discontinuation of therapy may result in the survival and subsequent proliferation of resistant bacterial strains. Conversely, excessive use increases the risk of adverse effects for the patient and promotes the development of ABR [59].

2. *Use of antibiotics only when clinically indicated.* Antibiotics should be prescribed exclusively in cases where a bacterial infection has been confirmed or is highly suspected. Their use in viral illnesses – such as the common cold or influenza – is entirely inappropriate and counterproductive.

3. *Expansion of infection prevention systems.* The most effective way to reduce the need for antibiotics is to prevent infections in the first place. Vaccination (e.g., against influenza or pneumococcal disease) and proper hand hygiene play critical roles in this regard.

4. *Monitoring of ABR.* Systematic collection and analysis of data on microbial susceptibility allow for the adjustment of antibiotic prescribing guidelines at both local and national levels, enabling timely responses to evolving resistance patterns.

Regulatory Framework for Rational Antibiotic Therapy in Ukraine. Ukraine, recognising the global challenges posed by antimicrobial resistance, has taken active steps to promote the rational use of ABs. One of the most significant regulatory measures is the Order of the Ministry of Health of Ukraine No. 1513, dated 23 August 2023, entitled "*On the Approval of the Standard of Medical Care: Rational Use of Antibacterial and Antifungal*

Agents for Therapeutic and Prophylactic Purposes." This order serves as a foundational document, marking a substantial shift in the approach to prescribing and using antimicrobial agents within the Ukrainian healthcare system. Its adoption represents a crucial step in aligning Ukrainian legislation with international and European standards in the fight against ABR. The document clearly regulates the prescription of ABcs, emphasising the importance of using clinical protocols and microbiological test results, and restricts the uncontrolled use of broad-spectrum antibiotics. Furthermore, it introduces a system for ABR monitoring, enabling the collection, analysis, and exchange of data on microbial susceptibility – an essential element for formulating up-to-date recommendations and detecting emerging threats. In addition, the order establishes requirements for detailed accounting of antibiotic consumption and mandates regular reporting. The implementation of this regulation aims not only to reduce inappropriate antibiotic use and slow the progression of ABR but also to improve the quality of infectious disease treatment and alleviate the financial burden on the healthcare system.

Another critically important regulatory act addressing the rational use of antibiotics in wartime conditions in Ukraine is the Ministry of Health's Order No. 1004, dated 1 June 2023, entitled "*On Approval of the Standard of Medical Care 'Prevention of Infectious Complications of Combat Injuries with Antibacterial Drugs at the Pre-Hospital Stage*.'" This order holds exceptional relevance in the context of the ongoing full-scale military aggression against Ukraine. It governs the use of antibiotics under the extreme conditions of armed conflict, where timely and appropriate administration can be vital for saving the lives and preserving the health of the injured. The document clearly defines the circumstances under which prophylactic antibiotic use is justified and necessary already at the pre-hospital stage for patients with various types of wounds. It specifies the recommended antibiotics for prophylactic use, based on their spectrum of activity against the most likely pathogens associated with combat-related infections, and outlines the optimal routes of administration under field conditions. The primary goal of such prophylactic application is to minimise the risk of purulent-septic complications, which are common in combat trauma due to the high level of wound contamination. Early antibiotic intervention can prevent infection from spreading or becoming systemic.This order is of critical importance for safeguarding the lives and health of wounded military personnel and civilians, as timely and evidence-based antibiotic use in the pre-hospital phase can significantly improve clinical outcomes, reduce the need for complex surgical interventions, and shorten rehabilitation periods.

According to the Order of the Ministry of Health of Ukraine No. 1614 dated August 3, 2021, "On the Organization of Infection Prevention and Control in Healthcare and Social Assistance/Social Protection Institutions," a multidisciplinary team must be established in every hospital to implement the antimicrobial resistance containment strategy. This team must necessarily include a clinical pharmacist, who is responsible for the following processes:

- *Pre-authorization:* Approval of the prescription of "Reserve" group antibiotics;
- *Prospective Audit and Feedback:* Real-time review of prescriptions regarding their appropriateness, dosage, and duration;
- *Consultative Support:* Providing recommendations to physicians on drug selection based on the facility's local antimicrobial resistance profile;
- *Educational Function:* Training staff on the principles of rational antibiotic therapy.

These and other regulatory acts issued by the Ministry of Health of Ukraine form a robust foundation for a systematic approach to antibiotic therapy management. They integrate the principles of rational antibiotic use into routine clinical practice and ensure effective control over the circulation of these vital medications. The implementation of antimicrobial stewardship programs involves the coordinated efforts of physicians and clinical pharmacists. This ensures continuous oversight of the appropriateness of prescriptions, the selection of the optimal drug, and the monitoring of treatment efficacy at all stages of healthcare system.This is especially critical in the context of wartime, where the resilience of the healthcare system and the ability to effectively manage infectious complications are of paramount importance.

Conclusions

Antibiotic resistance represents a global public health crisis, driven both by the natural evolution of bacteria and the irrational use of antibiotics. Bacteria have developed sophisticated defence mechanisms, including reduced membrane permeability, active efflux of antibiotics, target site modification, enzymatic inactivation, horizontal gene transfer of resistance traits, and biofilm formation. Simultaneously, the human host, through complex inflammatory and immune responses, may also contribute to the emergence and persistence of antimicrobial resistance. Effective response to this threat requires a comprehensive and multifaceted approach. This includes modulation of the immune response, development of new drugs and pharmaceutical formulations, and the assessment and optimisation of existing antibiotic therapies. Microbiome-based strategies – such as the use of probiotics and faecal microbiota transplantation – alongside phage therapy, represent promising adjunctive approaches. Crucially, the rational use of antibiotics in medical practice remains a cornerstone of antibiotic resistance control. This involves appropriate dosing, treatment duration, and prescription based strictly on clinical indications. Infection prevention measures and state-level regulatory oversight, including the implementation of modern antibiotic resistance monitoring systems, are essential.The adoption of these strategies is vital not only for maintaining the effectiveness of antibacterial therapies but also for safeguarding global public health security in the face of an escalating antimicrobial resistance threat.

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ДЛЯ АВТОРІВ

«ОДЕСЬКИЙ МЕДИЧНИЙ ЖУРНАЛ»

Відомості про видання

«Одеський медичний журнал» було засновано в 1926 році. За кілька років він набув неабиякого авторитету серед науковців. у ньому друкували свої праці вчені, чиї імена були всесвітньо відомі вже того часу або які здобули визнання в майбутньому. Та згодом, на початку 1930-х років, видання журналу було припинено. Поновлений у 1997 році, він за короткий час відновив свій авторитет і посів чільне місце серед наукових видань країни.

Засновником і видавцем «Одеського медичного журналу» є Одеський національний медичний університет.

Головним редактором із часів відновлення випуску журналу є академік НАМН України, лауреат Державної премії України В. М. Запорожан. До складу редакційної колегії та редакційної ради входять відомі вітчизняні й зарубіжні вчені.

«Одеський медичний журнал» включений до Переліку наукових фахових видань України в категорії «А» (галузь – медичні науки, спеціальності – 221 «Стоматологія», 222 «Медицина», 226 «Фармація, промислова фармація», 228 «Педіатрія» (Наказ Міністерства освіти і науки України № 1721 від 10.12.2024, додаток 6; доступ за посиланням https://mon.gov.ua/static-objects/mon/uploads/public/675/c49/0fe/675c490fea3a6035511617.pdf) Щороку в журналі друкується близько дев'яноста статей і повідомлень. Він надходить до найвідоміших бібліотек країни, великих наукових центрів, десятків навчальних закладів. Його появу гідно оцінено за межами нашої країни – він занесений до Index Copernicus, Ulrich's Periodicals Directory, BASE-Search, Google Академії, «Наукової періодики України», Scopus Content Selection and Advisory Board (CSAB) розглянула заявку журналу «Одеського медичного журналу» та схвалила її для реферування в наукометричній базі Scopus 25.10.2023 р.

У серпні 2022 року наукове видання «Одеський медичний журнал» отримало тримісячну стипендію від проєкту «Підтримка українським редколегіям» (SUES – Support to Ukrainian Editorial Staff). SUES є ініціативою європейських установ та організацій, мета яких полягає в підтримці наукової спільноти України.

Розповсюджується за передплатою. Передплатити журнал можна в будь-якому передплатному пункті. Передплатний індекс – 48717.

Журнал виходить шість разів на рік.

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ПРАВИЛА ПІДГОТОВКИ СТАТЕЙ ДО «ОДЕСЬКОГО МЕДИЧНОГО ЖУРНАЛУ»

1. В «Одеському медичному журналі» публікуються теоретичні й оглядові статті, які відображають важливі досягнення науки, підсумки завершених оригінальних клінічних та експериментальних досліджень, основні результати дисертаційних робіт із медицини, стоматології та фармації, а також матеріали меморіального характеру.

2. До розгляду приймаються проблемні та оригінальні статті загальним обсягом 7–15 сторінок, огляди – до 12–20 сторінок.

3. Не приймаються статті, які вже були надруковані в інших виданнях або запропоновані до публікації кільком виданням водночас, а також роботи, які за своєю сутністю є переробкою опублікованих раніше статей і не містять нового наукового матеріалу або нового наукового осмислення вже відомого матеріалу.

4. у журналі друкуються:

а) результати оригінальних досліджень у пріоритетних напрямах розвитку медичних, стоматологічних та фармацевтичних наук;

б) роботи з фундаментальних та прикладних проблем із таких спеціальностей: 221 – стоматологія, 222 – медицина, 226 – фармація, промислова фармація, 228 – педіатрія:

– генетика та прикладні аспекти медичної генетики;

– біофізичні та морфофункціональні характеристики клітин організму при різних видах патології;

– роботи з новітніх клітинних технологій;

– новітні розробки в галузі загальної і клінічної фармакології та фармації;

– досягнення в галузі вивчення етіології, патогенезу та діагностики сучасних захворювань;

– профілактика захворювань, щеплення, запобігання особливо небезпечним захворюванням;

в) експериментальні дослідження, огляди, клінічні випадки, нові методи та технології з сучасних актуальних проблем стоматології, медицини, педіатрії та фармації;

г) інформація, хроніка, ювілеї, матеріали з історії науки та медицини, фармації, стоматології, рецензії.

5. Стаття надсилається до редакції в електронному варіанті зі сканом першої сторінки з підписами всіх авторів. Своїми підписами автори гарантують, що статтю написано з дотриманням правил підготовки статей до «Одеського медичного журналу», експериментальні та клінічні дослідження були виконані відповідно до міжнародних етичних норм наукових досліджень, а також надають редакції право на публікацію статті в журналі, розміщення її та матеріалів щодо неї на сайті журналу і в інших джерелах.

6. Стаття супроводжується сканом (1) направлення до редакції, завізованим підписом керівника та печаткою установи, де виконано роботу, (2) відомостями про авторів (з декларуванням участі кожного автора з деталізацією вкладу у підготовці статті), (3) декларацією щодо оригінальності тексту наукової статті, а для вітчизняних авторів також (4) експертним висновком, що дозволяє відкриту публікацію.

7. Якщо у статті використано матеріали, які є інтелектуальною власністю кількох організацій і раніше не публі-

кувалися, автор має одержати дозвіл на їх публікацію від кожної із цих організацій і надіслати його разом зі статтею.

8. Текст друкується через півтора інтервалу на стандартному машинописному аркуші (ширина полів: лівого, верхнього та нижнього – по 2 см, правого – 1 см) шрифтом Arial (Arial Cyr) або Times (Times Cyr) розміром 14 пунктів. Сторінка тексту повинна містити не більше 30 рядків.

9. Мова статей – англійська та українська (перевага віддається англомовним роботам).

10. Матеріал статті має бути викладений за такою схемою:

а) індекс УДК – зліва, відповідно до ключових слів;

б) ініціали та прізвище автора (авторів), ORCID ID кожного автора. Рекомендована кількість авторів статті має не перевищувати 5;

в) назва статті;

г) повна назва установи (установ), де виконано роботу, місто, країна. Якщо авторів кілька і вони працюють у різних установах, тоді необхідно арабськими цифрами позначити цифровий надрядковий знак, що відповідає установі, де працює кожний з авторів; а назва установи має бути вказана з відповідним цифровим позначенням, електронна адреса (адреси), номер телефону;

д) два резюме: українською мовою обсягом до 800 друкованих літер (0,45 сторінки) та англійською обсягом до 1800 друкованих літер (1 сторінка). Резюме українською мовою має складатися за такою схемою: індекс УДК, ініціали та прізвище автора (авторів), назва статті, текст резюме, ключові слова (не більше п'яти);

е) постановка проблеми в загальному вигляді та її зв'язок із важливими науковими та практичними завданнями;

ж) формулювання мети статті (постановка завдання);

з) матеріали і методи дослідження з описами методів дослідження, кількості та розподілу об'єктів дослідження. Має бути зазначено дотримання принципів Етичного кодексу Всесвітньої медичної асоціації (Гельсінська декларація) щодо досліджень, до яких долучають людей, або принципів Директиви Європейського Союзу 2010/10/63 EU щодо експериментів на тваринах;

и) виклад основного матеріалу дослідження з повним обґрунтуванням отриманих наукових результатів;

к) висновки з дослідження і перспективи подальших розробок у цьому напрямі;

л) літературні посилання в порядку їх цитування або за алфавітом.

11. Резюме англійською мовою має коротко повторювати структуру статті, включно зі вступом, метою та завданнями, методами, результатами, висновками, і містити ключові слова. Ініціали та прізвище автора (авторів) подаються у транслітерації, назва статті – у перекладі англійською мовою. Ключові слова й інші терміни статті мають відповідати загальноприйнятим медичним термінам, наведеним у словниках. Не слід використовувати сленг і скорочення, які не є загальновживаними.

12. Хімічні та математичні формули вдруковують або вписують. Структурні формули оформляють як рисунки. у формулах розмічають: малі та великі літери (великі позначають двома рисками знизу, малі – двома рисками зверху простим олівцем); латинські літери підкреслюють синім олівцем; грецькі – обводять червоним олівцем; підрядкові та надрядкові цифри та літери позначають дугою простим олівцем.

13. у статтях слід використовувати Міжнародну систему одиниць СІ.

14. Рисунки і підписи до них виконують окремо. На зворотному боці кожного рисунка простим олівцем слід указати його номер і назву статті, а в разі необхідності позначити верх і низ.

15. Таблиці слід друкувати на окремих сторінках, вони повинні мати нумерацію та назву. На полях рукопису необхідно вказати місце розміщення рисунків і таблиць. Інформація, наведена в таблицях і на рисунках, не повинна дублюватися.

16. Список літературних джерел повинен містити перелік праць за останні 10 років і лише в окремих випадках – більш ранні публікації. В оригінальних роботах цитують не більше 20 джерел, в оглядах – до 60. На кожну роботу у списку літератури має бути посилання в тексті рукопису. Література у списку розміщується згідно з порядком посилань на неї в тексті статті, які подають у квадратних дужках, або за алфавітом. Якщо наводяться роботи лише одного автора, вони розміщуються за хронологічним порядком. До списку літературних джерел не слід включати роботи, які ще не надруковані.

17. Список літератури оформлюється латиницею за нижченаведеними схемами англійською мовою або транслітеровані. Оформлювати їх необхідно згідно зі стандартом National Library of Medicine (NLM) або Vancouver style.

Для статей:

Povorozniuk VV, Balatska NI, Klymovytskiy FV, Synenkiy OV. Actual nutririon, vitamin D deficiency and bone mineral density in the adult population of different regions of Ukraine. *Trauma*. 2012;13(4):12–16. (In Ukrainian). Available from: http://www.mif-ua.com/archive/article/34633

Scott F, Mamtani R, Brensinger C, et al. The risk of a second non-melanoma skin cancer with thiopurine and anti-TNF use in inflammatory bowel disease. *Am J Gastroenterol*. 2014;109:S473. doi: 10.1016/S0016-5085(14)60282-1.

Прізвища авторів та назва журналу подаються латиницею у транслітерації, назва статті – у перекладі англійською мовою. Транслітерацію можна зробити автоматично на сайті http://ukrlit.org/transliteratsiia. у бібліографічному посиланні кожного джерела слід вказати всіх авторів, відокремлюючи один від одного комою і пробілом. Ініціали вказують після прізвища, знаками пунктуації не відокремлюються. Повні імена авторів не наводяться. у випадку **7 і більше** авторів ставиться посилання "et al." після перших трьох прізвищ. Якщо авторів **6 і менше**, "et al." не використовується. Після переліку авторів ставлять крапку і пробіл. Назва публікації наводиться англійською мовою повністю, без скорочень. Після назви статті ставлять крапку і пробіл. Назва періодичного видання наводиться англійською мовою або транслітерується символами латинського алфавіту. Дозволяється наводити зареєстровані скорочення назви періодичного видання. Зазвичай ця форма написання самостійно приймається виданням, її можна дізнатися на сайті журналу, видавництва, на сайті **ISSN** або необхідно наводити його повну назву без скорочення. Назви

вітчизняних журналів скорочувати не можна. Після назви видання ставлять крапку і пробіл. Інформація щодо видання: рік видання відокремлюється крапкою з комою, потім наводиться номер тому, якщо необхідно, у круглих дужках вказується номер журналу, після двокрапки наводиться діапазон сторінок. Для статті, що надрукована не англійською мовою, наприкінці сформованого посилання у круглих дужках вказується мова оригіналу. Додаткова інформація стосовно статті – номера DOI («DOI: https://doi.org/...»), PubMed ID, режим доступу до першоджерела тощо – наводиться наприкінці посилання у форматі активного гіперпосилання. Форма для пошуку DOI: Crossref system.

Для матеріалів конференцій:

Sulkowski M, Krishnan P, Tripathi R. Effect of baseline resistance-associated variants on SVR with the 3D regimen plus RBV. In: *Conference on Retroviruses and Opportunistic Infections (CROI)*. 2016 Feb 22–25; Boston, MA.

Bakeyeva LY, Saprunova VB, Pilipenko DI. Ultrastructure of mitochondria in endogenous oxidative stress, mitochondrial antioxidant protective effect SkQ1. In: *Proceeding of the IV congress of the Russian Society of Biochemistry and Molecular Biology*. 2008 May 11–15; Novosibirsk, Russian Federation. Novosibirsk; 2008. (in Russian).

Прізвища авторів подаються у транслітерації, назва праці – у перекладі англійською. Головне в описах конференцій – назва конференції мовою оригіналу (подається у транслітерації, якщо немає її англійської назви), виділяється курсивом. у дужках наводиться переклад назви англійською. Вихідні дані (місце проведення конференції, місце видання, рік, сторінки) – англійською.

Для монографій та інших книжок:

Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders; 2014. 2040 p.

Lutsik AD, Detyuk YS, Lutsik MD, autors; Panasyuk YN, editor. Lektiny v gistokhimii [Lektins in histochemistry]. Lviv: Vyscha shkola; 1989. 144 p. (in Russian).

Прізвища авторів подаються у транслітерації, назва книжки – у транслітерації з перекладом англійською мовою у квадратних дужках. Місце видання, рік видання, загальна кількість сторінок – англійською, назва видавництва – у транслітерації.

Зауважуємо: у списку латиницею потрібно зазначати всіх авторів літературного джерела, на яке Ви посилаєтесь. Також не слід у ньому застосовувати знаки розділення: // та –. Назву джерела (журнал, конференція, книга) завжди виділяють курсивом.

Наприкінці літературного джерела потрібно вказувати цифровий ідентифікатор статті DOI, якщо такий є. Дотримання цих правил забезпечить коректне відображення цитованих джерел у більшості реферативних наукометричних баз даних.

18. Скорочення слів і словосполучень подаються відповідно до ДСТУ 3582-97 і ГОСТ 7.12-93.

Для тих, хто не має доступу до повного тексту ДСТУ, на сайті Одеського медуніверситету наведено приклади оформлення бібліографічних записів. Доступ за посиланням http://libblog.odmu.edu.ua/p/blog-page_8912.html.

19. До друкованих матеріалів, виконаних із використанням комп'ютерних технологій, обов'язково додаються матеріали комп'ютерного набору та графіки в електронному вигляді.

Текст може бути таких форматів: Word for Windows, RTF (Reach Text Format).

Графічний матеріал слід подавати в окремих файлах форматів XLS, TIFF, WMF або CDR. Роздільна здатність штрихових оригіналів (графіки, схеми) форматів TIFF повинна бути 300–600 dpi B&W, напівтонових (фотографії та ін.) – 200–300 dpi Gray Scale (256 градацій сірого). Ширина графічних оригіналів – 5,5, 11,5 і 17,5 см.

20. Статті піддаються науковому рецензуванню, за результатами якого ухвалюється рішення про доцільність публікації роботи. Відхилені статті не повертаються і повторно не розглядаються.

21. Редакція залишає за собою право редакційної правки статей, яка не спотворює їх зміст, або повернення статті автору для виправлення виявлених дефектів.

22. Датою надходження статті до журналу вважається день отримання редакцією остаточного варіанта тексту.

23. Після отримання підтвердження від редколегії про прийняття статті до публікації надаються реквізити для сплати публікаційного внеску. Вартість публікації становить 2000 гривень (за 12 сторінок). За кожну додаткову сторінку необхідно додати до публікаційного внеску 40 гривень. Публікаційний внесок покриває витрати, пов'язані з коректурою і редагуванням статей, макетуванням журналу та розміщенням його електронної версії. За бажанням автор статті може замовити собі друкований примірник журналу. Вартість друкованого примірника – 800 гривень, які необхідно сплатити додатково до публікаційного внеску. Підтвердження проведеної оплати (відскановану квитанцію або її фотографію) автор надсилає в електронному вигляді на e-mail omj@onmedu.od.ua.

24. Редакція «Одеського медичного журналу»: Валіховський пров., 2, ректорат Одеського національного медичного університету, м. Одеса, 65082, Україна;

e-mail: redkolehiaOMJ@onmedu.edu.ua

Відповідальні секретарі журналу – доцент Грекова Алла, тел.: +38 (097) 938 30 52, доцент Юрченко Ірина, тел.: +38 (050) 815 53 05

Контактна особа (Видавничий дім «Гельветика») – Демченко Христина, тел.: +380 (93) 035 42 60; e-mail: omj@onmedu.od.ua

Науковий редактор – Антоненко Петро, тел.: +380 (97) 587 56 36

Сторінки журналу: journal.odmu.edu.ua, journals.onmedu.od.ua/index.php/med/home

25. Статті, що не відповідають цим правилам, не розглядаються. Передрук статей можливий лише з письмової згоди редакції та з посиланням на журнал.

Середній час очікування публікації (від дня подачі до дня публікації) – 2–8 місяців (залежно від фактичної кількості поданих авторами публікацій у конкретний випуск).

Додаток до Правил підготовки статей
до «Одеського медичного журналу»

ДЕКЛАРАЦІЯ
щодо оригінальності тексту наукової статті

Я(ми), ***(П.І.Б. автора або авторів – зазначаються всі автори наукової статті),*** декларую(ємо), що у статті ***(назва наукової статті)*** наявний оригінальний текст, отриманий у результаті власних досліджень (клінічних спостережень), ***відсутні*** некоректні цитування, запозичення іншого тексту**,** відомості, передбачені ст. 32 та 69 Закону України «Про вищу освіту».

Заявляю(ємо), що моя(наша) наукова робота виконана самостійно і в ній не містяться елементи плагіату.

Усі запозичення з друкованих та електронних джерел, а також із захищених раніше наукових робіт, кандидатських і докторських дисертацій мають відповідні посилання.

Я(ми) ознайомлений(і) з чинним Положенням про виявлення академічного плагіату, згідно з яким наявність плагіату є підставою для відмови прийняття наукової статті до опублікування в науковому журналі Одеського національного медичного університету.

Дата **Підпис(и)**

Примітки: 1. у Декларації повинні бути підписи всіх авторів наукової статті, які мають бути засвідчені установою, де вони працюють.

2. Якщо автори статті є співпрацівниками різних установ, то Декларація повинна бути з кожної установи.

ПОРЯДОК РЕЦЕНЗУВАННЯ
рукописів наукових статей, які надходять для публікації до редакції «Одеського медичного журналу»

Наукові статті, які надходять для публікації до редакції «Одеського медичного журналу», підлягають рецензуванню. Завданням рецензування є максимально об'єктивна оцінка змісту наукової статті, її відповідності вимогам журналу, аналіз її переваг та недоліків, винесення конкретних рекомендацій щодо її вдосконалення. Відповідальний секретар журналу проводить попередній аналіз статей, що надійшли до редакції, їхню відповідність тематиці та спеціалізації журналу. Рецензентів призначає головний редактор журналу. В окремих випадках за рішенням головного редактора призначення рецензента(ів) може бути доручене члену редакційної колегії або вирішене на засіданні редакційної колегії.

Рецензентами журналу є досвідчені фахівці – доктори наук, члени редколегії журналу та його редакційної ради. у разі потреби редакція залучає до рецензування сторонніх фахівців. Рецензенти мають відповідати кваліфікаційним вимогам згідно з Наказом МОН України від 15.01.2018 № 32. Наукові статті, що надійшли до журналу, спрямовуються на рецензію одному рецензенту, за необхідності – двом рецензентам. Для всіх статей, що надходять до журналу, визначається рівень їхньої унікальності за допомогою Системи програмно-обчислювального комплексу Strikeplagiarism.com.

Під час рецензування оцінюються відповідність статті тематиці журналу та її назві, актуальність і науковий рівень, переваги й недоліки, відповідність оформлення статті вимогам редакції. Наприкінці робиться висновок про доцільність публікації.

Рецензування проводиться конфіденційно за принципом подвійного «сліпого» рецензування (ані автор, ані рецензент не знають П.І.Б. одне одного). Рецензія надається автору статті на його запит без підпису, вказівки прізвища, посади і місця роботи рецензента. В окремих випадках на прохання рецензента та за узгодженням із редакційною колегією журналу взаємодія рецензента та автора може відбуватись у відкритому режимі. Така практика застосовується лише в тому випадку, якщо відкрита взаємодія забезпечить поліпшення викладу матеріалу роботи, що рецензується. Зазвичай рецензент робить висновок щодо можливості публікації статті протягом 14 діб.

Якщо рецензент рекомендує виправити або доопрацювати статтю, редакція відправляє автору текст рецензії для внесення в роботу відповідних змін. Статті, відіслані авторам на виправлення, слід повернути до редакції не пізніше ніж через сім днів після одержання. Коректури авторам не висилаються, проте якщо це не порушує графік виходу журналу, можливе надання препринту, у якому допустиме виправлення лише помилок набору і фактажу.

Автору, стаття якого не була прийнята до публікації, на його запит відправляється мотивована відмова. Рукопис статті не повертається.

Якщо автор не згоден із думкою рецензента, він може дати мотивовану відповідь.

У разі потреби за погодженням з автором може бути проведено додаткове рецензування рукопису іншим фахівцем.

Остаточне рішення про публікацію статті та її терміни приймає редакційна колегія.

В окремих випадках за наявності позитивної рецензії можлива публікація статті за рішенням головного редактора або його заступника.

Після ухвалення рішення про публікацію статті редакція інформує про це автора з указанням терміну публікації.

Оригінали рецензій зберігаються в редакції протягом 1 року.

INFORMATION ABOUT EDITION

"ODES'KIJ MEDIČNIJ ŽURNAL" ("Odesa Medical Journal")

Publication information

"Odes'kij medičnij žurnal" ("Odesa Medical Journal") was founded in 1926. During a few years it was highly appreciated by scientists. The works of the famous scientists had been published there. But then, at the start of 30-s, the publication of the Journal was stopped. It was renewed only in 1997, and very soon the Journal won its authority again and took a proper place among other scientific editions of the country.

The founder and publisher of "Odesa Medical Journal" is the Odesa National Medical University.

The editor-in-chief of the Journal since the time of its renewal is the academician of the NAMS of Ukraine, the Ukraine State Prize Winner V. M. Zaporozhan. The members of the editorial board and editorial council are the world-known scientists.

"Odesa Medical Journal" is included in the List of specialized scientific publications of Ukraine of category "A" (branch – medical sciences, specialties – 221 "Dentistry", 222 "Medicine", 226 «Pharmacy, industrial pharmacy», 228 "Pediatrics" (Order of the Ministry of Education and Science of Ukraine No. 1721 dated 10.12.2024, appendix 6; available at https://mon.gov.ua/static-objects/mon/uploads/public/675/c49/0fe/675c490fea3a6035511617.pdf).

About 90 articles are published in the Journal annually.

It comes to the most known libraries of the country, large scientific centers, some educational establishments. Its release is highly appraised outside of the country: the Journal is represented in Index Copernicus, Ulrich's Periodicals Directory, BASE-Search, Google Academy, "Scientific Periodics of Ukraine", "Scientific Periodics of Ukraine". The Scopus Content Selection & Advisory Board (CSAB) has reviewed application of the Odesa Medical Journal and approved it for coverage in Scopus database 25.10.2023.In August 2022, the scientific publication "Odesa Medical Journal" received a three-month scholarship from the "Support to Ukrainian Editorial Staff" (SUES – Support to Ukrainian Editorial Staff) project. SUES is an initiative of European institutions and organizations, the purpose of which is to support the scientific community of Ukraine.

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THE MANUAL OF ARTICLE STYLE FOR "ODES'KIJ MEDIČNIJ ŽURNAL" ("ODESA MEDICAL JOURNAL")

1. "Odes'kij medičnij žurnal" ("Odesa Medical Journal") publishes theoretical and review articles, which cover important achievements of science, results of completed original clinical and experimental researches, basic results of dissertations on medicine, dentistry and pharmacy, and also memorial materials.

2. Problem and original articles with total volume of 7–15 pages, reviews – up to 12–20 pages.

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– biophysical and morphofunctional analysis of cells of an organism at different types of pathology;

– works on modern cellular technologies;

– modern elaborations in the field of general and clinical pharmacology and pharmacy;

– achievements in the field of study of etiology, pathogenesis and diagnostics of modern diseases;

– prophylaxis of diseases, inoculation, prevention of especially dangerous diseases;

c) experimental manuscripts, reviews, clinical cases, novel methods and technologies on current issues of dentistry, medicine, pediatrics, and pharmacy;

d) information, chronicle, anniversaries, materials on history of science and medicine, farmacy, dentistry, reviews.

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the article in the Journal, placing it and its materials on the Journal's site and in other sources.

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c) the title of the article;

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e) two abstracts – in Ukrainian up to 800 printing letters (0.45 page) and in English up to 1800 printing letters (1 page). Ukrainian abstracts after the following scheme: UDC index, initials and the last name of author (authors), title of the article, text of the abstract, key words (no more than five);

f) statement of a problem in general and its connection with important scientific and practical tasks;

g) formulation of the aim of the article (raising a task);

h) research materials and methods with descriptions of research methods, number and distribution of the research objects. Compliance with the principles of the World Medical Association Code of Ethics (Helsinki Declaration) for human research or the principles of the EU Directive 2010/10/63 EU on animal experiments should be noted;

i) presentation of the main material of the study with a full justification of the obtained scientific results;

j) conclusions from the given research and perspectives of subsequent works in this direction;

k) references in the citation order or after the alphabet order.

11. The abstract in English should shortly reproduce the structure of the article, including introduction, purpose and task, methods, results, conclusions, key words. Initials and the last name of author (authors) are given in transliteration, the title of the article must be translated into English. The key words and other terms of the article should correspond to generally used medical terms cited in dictionaries. One should not use slang and abbreviations which are not in general use.

12. The chemical and mathematical formulas are inprinted or put down. The structural formulas are designed as figures. In formulas there are marked out: small and large letters (large ones by two hyphens from below, small ones – by two hyphens from above by a lead pencil); the Latin letters are underlined with a dark blue pencil; Greek ones – with a red pencil; subscript and superscript letters – by an arc line with a lead pencil.

13. The International System of Units (SI) should be used in the articles.

14. Figures and signatures to them are made separately. On the back side of every figure by a lead pencil one should indicate its number and title of the articles, and if necessary to note a top and bottom.

15. The tables should be placed on separate pages, be numbered and titled. The marginal notes should indicate the place of figures and tables. The information given in tables and figures must not be duplicated.

16. The references must contain the list of works for the last 10 years and only sometimes – more early publications. In the original works they quote no more than 20 sources, in the reviews – about 60. Every work in the references should be referred in the manuscript. The literature in the list is ordered according to reference to it in the text of the article, which is given in square brackets, or after the alphabet. If the works of one and the same author are presented, they take place after the chronological order. The references shouldn't contain works which have not been published yet.

17. The references should be arranged in Latin alphabet according to rules below in English or transliterated according to the National Library of Medicine (NLM) standard or Vancouver style.

For articles:

Povorozniuk VV, Balatska NI, Klymovytskiy FV, Synenkiy OV. Actual nutririon, vitamin D deficiency and bone mineral density in the adult population of different regions of Ukraine. *Trauma*. 2012;13(4):12–16. (In Ukrainian). Available from: http://www.mif-ua.com/archive/article/34633

Scott F, Mamtani R, Brensinger C, et al. The risk of a second non-melanoma skin cancer with thiopurine and anti-TNF use in inflammatory bowel disease. *Am J Gastroenterol.* 2014;109:S473. DOI: 10.1016/S0016-5085(14)60282-1.

The authors' surnames and the title of the Journal are given in Latin in transliteration, the title of the article is translated into English. Transliteration can be done automatically at the site: http://ukrlit.org/transliteratsiia. In the bibliographic reference of each source it is necessary to specify all authors, separating from each other a comma and a space. Initials are indicated after the surname, punctuation marks are not separated. The full names of the authors are not given. In the case of 7 or more authors, the reference "et al." after the first three surnames. If the authors are 6 or less, "et al." not used. After the list of authors a point and a space is put. The title of the publication is given in English in full, without abbreviations. After

the title of the article a point and a space are put. The title of the periodical is given in English or transliterated with the symbols of the Latin alphabet. It is allowed to cite the registered abbreviations of the title of the periodical. Usually this form of writing is accepted by the publication itself, it can be found on the website of the Journal, publisher, on the ISSN website, or it is necessary to give its full name without abbreviation. The names of domestic Journals cannot be abbreviated. After the title of the publication a point and a space are put. Information about the publication: the year of publication is separated by a semicolon, then the volum's number is given, if necessary, in parentheses indicate the number of the Journal, after the colon follows the range of pages. For an article that is not published in English, the language of the original is indicated in parentheses at the end of the generated link. Additional information about the article – DOI number («DOI: https://doi.org/...»), PubMed ID, source access mode, etc. – is provided at the end of the link as hyperlink. Search form for DOI: Crossrefsystem.

For materials of conferences:

Sulkowski M, Krishnan P, Tripathi R. Effect of baseline resistance-associated variants on SVR with the 3D regimen plus RBV. In: *Conference on Retroviruses and Opportunistic Infections (CROI).* 2016 Feb 22–25; Boston, MA.

Bakeyeva LY, Saprunova VB, Pilipenko DI. Ultrastructure of mitochondria in endogenous oxidative stress, mitochondrial antioxidant protective effect SkQ1. In: *Proceeding of the IV congress of the Russian Society of Biochemistry and Molecular Biology.* 2008 May 11–15; Novosibirsk, Russian Federation. Novosibirsk; 2008. (in Russian).

The last names of authors are given in transliteration, title of the work – in translation into English. The main thing in descriptions of conferences is the name of conference in the language of original (is given in transliteration if there is not its English title), indicated by italic. Translation of the title into English is given in brackets. Imprint (place of holding a conference, place of publication, year, pages) – in English.

For monographs and other books:

Mann DL, Zipes DP, Libby P, Bonow RO. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia: Saunders; 2014. 2040 p.

Lutsik AD, Detyuk YS, Lutsik MD, autors; Panasyuk YN, editor. Lektiny v gistokhimii [Lektins in histochemistry]. Lviv: Vyscha shkola; 1989. 144 p. (in Russian).

The last names of authors are given in transliteration, title of the book – in transliteration with translated into English in the square brackets. Place of publication, year of publication, total number of pages – in English, name of publishing house – in transliteration.

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