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Correspondence address: 4, Nauky Avenue, Kharkiv, 61022, Ukraine.
E-mail: ic.journal@knmu.edu.ua
as.shevchenko@knmu.edu.ua
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SUBOPTIMAL HEALTH AND CARDIOVASCULAR RISK: QUESTIONNAIRE-BASED ASSESSMENT USING SHSQ-25 AND SF-36

Burdina V.R.[1], Danylchenko S.I.[1], Yesselbayeva A.K.[2], Golovchenko I.V.[1], Morozenko D.V.[3], Aravitska M.G.[4], Shevchenko A.S.[5–7], Pertsev D.P.[5], Cherkova N.V.[7], Dushik L.N.[7]

[1]Kherson State University, Kherson–Ivano-Frankivsk, Ukraine
[2]Kazakh National Women's Teacher Training University, Almaty, Republic of Kazakhstan
[3]State Institution "Sytenko Institute of Spine and Joint Pathology of the National Academy of Medical Sciences of Ukraine", Kharkiv, Ukraine
[4]Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine
[5]Kharkiv National Medical University, Kharkiv, Ukraine
[6]Kharkiv Regional Institute of Public Health Services, Kharkiv, Ukraine
[7]V.N. Karazin Kharkiv National University, Kharkiv, Ukraine

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ABSTRACT

Background. Suboptimal health is considered an intermediate state between complete health and the early manifestations of chronic diseases. Its detection at the preclinical stage is important for the prevention of cardiovascular disorders and other chronic pathologies.

Aim. To systematize and analyze subjective health indicators in apparently healthy individuals and determine their relationship with cardiovascular risk factors using the SHSQ-25 and SF-36 questionnaires.

Materials and Methods. A total of 509 individuals aged [34.31±13.79] years were examined. The SHSQ-25 and SF-36 questionnaires were used to assess suboptimal health status and quality of life. Body mass index, blood pressure, glucose and total cholesterol levels, smoking index, and endothelial function were measured using computer photoplethysmography. Multifactorial discriminant analysis was applied for health status classification, and mathematical models were developed to assess the risk of arterial hypertension. Statistical analysis included descriptive statistics, correlation analysis, and group comparisons based on different levels of risk factors. The research was conducted as a private initiative of the authors, did not receive funding from grant programs, and the research topic was not officially registered in the state register of scientific topics.

Research Ethics. The study was conducted in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki (1964–2024) and European Community Directive 86/609 on the participation of humans in biomedical research.

Results. In the examined individuals, five health status clusters were identified: optimal health status, suboptimal health with low risk factors, suboptimal health with high risk factors, cardiovascular phenotype of suboptimal health with low risk factors, and cardiovascular phenotype of suboptimal health with high risk factors. Subjective health assessments obtained using the SHSQ-25 showed significant correlations with blood pressure (systolic and diastolic), endothelial function indicators, body mass index, total cholesterol, and glucose levels. High SHS scores were associated with reduced quality of life according to SF-36, particularly in the physical and mental health components, confirming the impact of suboptimal health on daily activity and psychological well-being.

Conclusions. The SHSQ-25 and SF-36 questionnaires are effective primary screening tools for identifying individuals with suboptimal health and increased risk of cardiovascular disorders. Their use in the clinical practice of physical therapists and occupational therapists allows timely identification of at-risk groups and planning of preventive or rehabilitative measures. Health status mathematical modeling improves the accuracy of risk assessment and can be integrated into the physiotherapy program.

Keywords: *physical therapy and rehabilitation, subjective health, cardiovascular risk factors, quality of life, chronic disease prevention.*

Introduction

Assessment of the CardioVascular System (CVS) is a vital step in physical and occupational therapy because it reflects the body's structural and functional reserves and helps determine the appropriate load for the patient [1–3]. Establishing a rehabilitation diagnosis is complicated because impairments are multifactorial, requiring the integration of data based on the International Classification of Functioning, Disability, and Health (ICF) [4; 5].

A modern, thorough patient evaluation includes standard clinical procedures such as medical history, symptom assessment, instrumental tests, and analysis of how impairments affect daily life, and also necessarily considers psychological and social factors, which are crucial for effective rehabilitation. The biopsychosocial model, introduced by Engel, stresses the importance of a holistic approach that goes beyond purely biomedical perspectives [6]. This framework is highly relevant to current rehabilitation practices.

A study by Oostendorp R.A. et al. showed that physical therapists tend to focus more on somatic factors, while psychological and social aspects are often less addressed, emphasizing the need for a more comprehensive history-taking approach [7]. Psychosocial factors, such as fear of movement, coping strategies, emotional state, and expectations for recovery, are remarkably influential on rehabilitation outcomes, especially in musculoskeletal injuries [8]. A comprehensive patient assessment involves taking a medical history, evaluating complaints, conducting clinical and instrumental examinations, and assessing how impairments affect daily activities. Modern approaches highlight the importance of considering not only physical deficits but also psychological and social dimensions, which significantly improve the effectiveness of rehabilitation programs [9].

Quality of Life (QoL) questionnaires, like Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) and Suboptimal Health Status Questionnaire-25 (SHSQ-25), systematically assess the effectiveness of physical and occupational therapy by capturing physical, psychological, and social aspects of functioning. The SF-36 is a widely used generic questionnaire covering eight domains, such as physical functioning, pain, social functioning, and mental health, and provides two composite scores: physical and mental [10]. Its reliability, validity, and sensitivity to change are well documented across diverse clinical and general populations [11, 12]. The SHSQ-25 is a self-report tool with 25 items across five areas: fatigue, cardiovascular health, digestion, immunity, and psychosocial well-being [13; 14].

Psychometric testing confirms its reliability and structural validity in different groups, including populations in China, Ghana, and Korea [15; 16]. The SHSQ-25 serves as an effective screening instrument for the early detection of suboptimal health, which is associated with a higher risk of cardiovascular disease [17]. Combining general and specific tools provides a comprehensive CVS assessment in patients, aiding in the design of tailored physical and occupational therapy plans that enhance their effectiveness and improve patients' quality of life.

The **aim** of the study was to comprehensively assess suboptimal health status using the SHSQ-25 and SF-36 questionnaires and to establish its relationship with cardiovascular risks.

Materials and Methods

The study involved 509 individuals (222 men and 287 women) who were receiving treatment at rehabilitation centers and hospital departments in Ivano-Frankivsk, Poltava, Kharkiv, and Mykolaiv. The average age of participants was [34.31± ±13.79] years. All individuals who considered themselves cardiologically healthy at the time of examination were included through a continuous sampling method. Exclusion criteria comprised the presence of chronic non-communicable diseases (except for patients with stage I arterial hypertension), comorbid conditions, medication use, and having sought medical care within the last three months.

In the present study, the 36-Item Short Form Health Survey (SF-36, Medical Outcomes Study) was used, which is one of the most widely used generic tools for assessing Health-Related Quality of Life (HRQoL). The questionnaire comes in two versions: the standard and the abbreviated form. The main difference is in the response scale for certain items, but both versions produce similar results. The standard version assesses health status over the past four weeks, while the short form is

Corresponding Author:
Danylchenko Svitlana – PhD, Associate Professor of the Department of Physical Therapy and Occupational Therapy, Kherson State University, Kherson–Ivano-Frankivsk, Ukraine.
✉ 14, Shevchenka str., Ivano-Frankivsk, 76018, Ukraine.
E-mail: svetlanaadanilch@gmail.com

typically used for short-term assessments, usually covering one week [9].

The SF-36 includes 36 items organized into eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Each domain is scored from 0 to 100, with higher scores indicating better health status. Additionally, the instrument provides two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [18].

Scores are reported for each of the eight domains and the two composite scores, offering a detailed profile of HRQoL. Higher scores consistently reflect better self-rated health and functioning [19]. The scoring methods and calculation procedures are detailed in *Table 1*.

Values for items 6, 9a, 9d, 9g, 9i, 10, and 11 are reversed scored [4].

The calculation formula is as follows:

$$\text{Score} = \frac{\text{Actual item value} - \text{Minimum possible item value}}{\text{Possible score range}} \times 100 \quad (1).$$

The Suboptimal Health Status Questionnaire-25 (SHSQ-25) is a self-administered tool designed to assess subclinical health issues and early signs of cardiovascular and systemic dysfunction. It includes 25 items divided into five domains: fatigue, cardiovascular health, digestion, immune function, and psycho-emotional well-being (*Table 2*).

Higher total or domain scores indicate more severe suboptimal health, pointing to early functional changes that may come before clinically visible disease. Psychometric studies validate the SHSQ-25's reliability, internal consistency, and construct validity across various populations, supporting its use in screening for suboptimal health in otherwise healthy adults [15; 16].

Each item is rated on a 5-point Likert scale (0–4), where higher scores indicate worse health. Domain scores are calculated by summing responses within each domain, and the total SHSQ-25 score is obtained by adding all domain scores. For comparability and interpretation, scores can be converted to a 0–100 scale using the same formula as the SF-36.

All study participants completed the questionnaires. Some individuals were identified with arterial hypertension and underwent additional examinations for further analysis. The suboptimal health status was assessed in otherwise healthy in-

Table 1. Main principles of calculating the SF-36 scale scores

Scale	Items	Min–Max Value	Possible Score Range
Physical Functioning (PF)	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	10–30	20
Role-Physical (RP)	4a, 4b, 4c, 4d	4–8	4
Bodily Pain (BP)	7, 8	2–12	10
General Health (GH)	1, 11a, 11b, 11c, 11d	5–25	20
Vitality (VT)	9a, 9b, 9c, 9d	4–24	20
Social Functioning (SF)	6, 10	2–10	8
Role-Emotional (RE)	5a, 5b, 5c	3–6	3
Mental Health (MH)	9e, 9f, 9g, 9h, 9i	5–30	25

Note: Items refer to the original numbering of the SF-36 questionnaire.

Table 2. Structure and scoring of the SHSQ-25 questionnaire

Domain	Items	Number of Items	Possible Score Range
Fatigue	1–5	5	0–20
Cardiovascular system	6–10	5	0–20
Digestion	11–15	5	0–20
Immune function	16–20	5	0–20
Psycho-emotional status	21–25	5	0–20
Total	1–25	25	0–100

Notes: Each item is rated on a 0–4 Likert scale. Domain scores are summed to obtain total and domain-specific scores, and can be transformed to a 0–100 scale for comparability.

dividuals, and their results were compared with those of participants with risk factors for arterial hypertension and those diagnosed with grade 1 hypertension.

Quality of life was evaluated using the SF-36 questionnaire for participants without hypertension and the SHSQ-25 for broader suboptimal health assessment. Endothelial function and biochemical parameters were examined in apparently healthy individuals, considering their overall health status. An Enzyme-Linked Immunosorbent Assay (ELISA) was performed to measure endothelin-1 levels, confirming endothelial dysfunction in participants with different health conditions. Cluster and discriminant analyses were used to develop a mathematical model for determining individual health status, integrating clinical, biochemical, and questionnaire data.

Study Design and Procedures

Stage 1: All participants completed a detailed questionnaire that included information about sex, age, occupation, and medication use. Based on this data, risk factors for arterial hypertension were assessed, including alcohol intake, smoking, overweight/obesity, sedentary lifestyle, and poor nutrition. Participants with arterial hypertension underwent further tests, including self-monitoring of blood pressure, ElectroCardioGraphy (ECG), EchoCardioGraphy (EchoCG), and Doppler or duplex scanning of the brachiocephalic arteries, as part of the initial and subsequent stages of routine health check-ups.

Stage 2: The suboptimal health status was evaluated in 509 participants, and a comparative analysis was carried out based on the presence of risk factors: healthy individuals without hypertension risk factors (n=200) and those with risk factors (n=288). These groups were also compared with participants diagnosed with grade 1 arterial hypertension (n=21). For SHSQ-25 validation, suboptimal health scores were correlated with the SF-36 quality of life index (n=82, excluding participants with hypertension).

Stage 3: Endothelial function and biochemical parameters (such as low-density lipoproteins and glucose) were measured in 348 apparently healthy individuals. Participants were then divided into two groups based on their total SHSQ-25 score (overall SHS): Group 1: total SHS less than 14 points; Group 2: total SHS of 14 or more points.

These groups' parameters were compared to those of participants with arterial hypertension. To confirm endothelial dysfunction, an Enzyme-Linked Immunosorbent Assay (ELISA) was performed to measure endothelin-1 levels (n=52) in healthy participants from both groups.

Final Stage: Cluster and discriminant analyses were used to create a mathematical model for determining individual health status (n=488, excluding participants with arterial hypertension).

Statistical Methods

Descriptive statistics (mean, standard deviation, median, interquartile range) were used for data analysis. The Shapiro-Wilk test was used to assess the distribution of variables. Quantitative indicators between groups were compared using Student's t-test or the Mann-Whitney U test (based on data distribution), while one-way ANalysis Of VAriance (ANOVA) was used for multiple comparisons. Spearman's correlation analysis evaluated relationships between variables. Cluster analysis identified suboptimal health status phenotypes, and discriminant analysis checked the accuracy of the classification. A p-value less than 0.05 was considered statistically significant. Data analysis was performed using SPSS software, version 26.0 (IBM, USA).

Results

Stage 1 – Questionnaire Survey and Risk Factor Assessment

During the initial phase of the study, several risk factors for arterial hypertension were identified among participants, including smoking, overweight/obesity, high blood cholesterol, unhealthy diet, elevated blood glucose levels, and insufficient physical activity. Analysis of these risk factors showed that nearly one-quarter of participants (71.8%, mostly men) were smokers. The proportion of smokers under 40 was 2.5 times higher than in those over 40. Overweight or obesity was found in one out of every four participants. Nutritional imbalances were present in 56.1% of participants, and 58.6% had insufficient physical activity. Nearly one-third of participants had elevated blood cholesterol, mainly women, with 32% showing total cholesterol levels above 5 mmol/L.

Almost all participants (99.6%) reported experiencing stress of varying levels; however, only a few, mostly office workers (n=6), reported constant stress. Among office workers, 38.5% experienced frequent or constant stress, compared to 48% of manual workers. Significant correlations were found between Blood Pressure (BP) and several variables: smoking index (r=0.36), age (r=0.49), Body Mass Index (BMI) (r=0.47), and Total Cholesterol (TC) (r=0.26), all with $p < 0.05$. No significant differences in BP were observed based on employment type. Two risk factors oc-

curred together in 22.2% of participants, while three risk factors were present in 3.7%, demonstrating the prevalence of risk factors for arterial hypertension. Overall cardiovascular risk was low (<5%) in 96.3% of participants. Only nine male smokers aged 55–60 years were identified with high cardiovascular risk, with estimated probabilities of 7% and 11%, respectively. Grade 1 arterial hypertension was diagnosed in 21 participants.

Stage 2 – Suboptimal Health Status (SHS) Assessment

During the second stage of the study, the SHSQ-25 questionnaire was administered to the study sample (n=509) to determine the Suboptimal Health Status (SHS) score. Additionally, SHS scores were compared among participants with different risk factor profiles for arterial hypertension (Table 3).

The overall Suboptimal Health Status (SHS total) score was [14.34±5.74] points. Significant differences in the total SHS were observed among individuals with overweight or obesity (p=0.026) and among smokers (p=0.03). Correlation analysis revealed associations between the total SHS and total cholesterol (r=0.48, p<0.05), BMI (r=0.25, p<0.05), and BP (r=0.20, p<0.05).

Comparison of SHSQ-25 scores with quality of life indices measured using the SF-36 questionnaire (*Table 4*) demonstrated significant associations. Correlation analysis showed that the overall SHS score was significantly related to several SF-36 domains, including "fatigue", "mental health", "cardiovascular system", "digestive system", and "immune function", as well as to the physical health component (r=–0.65, p<0.05) and the mental health component (r=–0.54, p<0.05).

Among the study participants with a SHS score above 14 points (36.6%, n=30), a significant decrease in quality of life was observed compared to those with an SHS score below 14. Notably, declines were most evident in areas related to the cardiovascular system, role functioning, and mental health. These findings may suggest deviations in suboptimal health linked to impaired emotional well-being.

A comparative analysis of groups, considering the presence of risk factors and hypertension, showed that the total SHS score in patients with hypertension was significantly higher than in individuals without risk factors or with only risk factors (20.67±9.81 points vs. [11.65±5.78] points, p<0.001, and [16.2±6.45] points, p<0.05, respectively). This underscores notable differences in suboptimal health status among individuals with risk factors and hypertension, indicating potential health deviations. Additionally, the hypertension and risk factor groups displayed higher total cholesterol levels, lower High-Density Lipoprotein (HDL) levels, and elevated triglycerides compared to participants without risk factors (*Table 5*).

Table 3. Suboptimal Health Status (SHS) Score

Criteria	Overall Suboptimal Health Score, mean±SD	p
Age 18–40 years (n=304)	13.78±4.96	0.003
Age >40 years (n=205)	15.34±6.82	0.58
Men (n=222)	14.28±6.42	0.58
Women (n=287)	14.00±4.29	0.58
Smokers (n=124)	15.25±6.69	0.03
Non-smokers (n=385)	14.01±5.32	0.03
Office workers (n=374)	14.44±5.90	0.53
Manual workers (n=135)	14.07±5.26	0.53
BMI <25 (n=345)	13.76±5.32	0.026
BMI ≥25 (n=164)	14.93±6.09	0.026

Table 4. Quality of life indices in participants with different Suboptimal Health Statuses (SHS)

SF-36 Questionnaire Domains	Group 1 – total SHS <14, n=52, points	Group 2 – total SHS ≥14, n=30, points	t	p
Physical Health Component	54.29±14.48	29.82±8.46	2.816	0.018
Mental Health Component	45.35±18.87	22.00±7.54	2.740	0.023

Table 5. Comparative analysis of hypertension risk factor markers

Parameter	Individuals without risk factors, n=200	Individuals with risk factors, n=288	Individuals with arterial hypertension, n=21
SBP, mmHg	115.14±12.86	127.95±12.79*	142.14±5.14**
DBP, mmHg	75.51±8.51	79.78±12.28*	86.05±8.0**
BMI, kg/m²	20.74±2.07	26.80±6.72*	26.56±4.1
Glucose, mmol/L	4.52±0.82	5.01±0.87*	4.63±1.86
Total cholesterol, mmol/L	5.38±1.15^	5.95±1.20^	6.28±0.95**
LDL cholesterol, mmol/L	2.85±0.17	3.01±0.37*	3.26±0.12
Triglycerides, mmol/L	1.11±0.57	1.56±0.87	2.21±0.64**

Notes: * – difference between groups 1 and 2, $p<0.01$; ^ – difference between groups 1 and 2, $p<0.05$; ** – difference between groups 2 and 3, $p<0.05$.

Thus, the SHS was linked to risk factors for arterial hypertension. Endothelial dysfunction is seen as a primary mechanism that contributes to the development of cardiovascular diseases [19; 20]. In this study, arterial stiffness and endothelial function were measured using computer photoplethysmography. It was observed that vascular elasticity indicators, such as arterial stiffness and pulse wave velocity, increase with age [21]. Our results confirmed this, showing an age-related decline in endothelial function in both men and women ($p<0.05$). Smoking also negatively affected vascular elasticity, with endothelial function being lower in smokers compared to non-smokers ([6.4±8.1]% vs. [15.1±9.9]%, $p<0.0001$). Excess body weight likewise impaired endothelial function: the Full Factor Experiment (FFE) in overweight individuals was [7.8±9.6]%, significantly lower than in normal-weight individuals, who had an FFE of [16.6±8.6]% ($p<0.0001$).

Correlation analysis revealed an inverse relationship between endothelial function and both blood pressure ($r=–0.44$, $p<0.05$) and total cholesterol ($r=–0.23$, $p<0.05$). Significant correlations were also found between endothelial function and the overall suboptimal health status ($r=–0.52$, $p<0.05$), as well as specific SHSQ-25 domains: fatigue ($r=–0.36$, $p<0.05$), mental health ($r=–0.29$, $p<0.05$), and cardiovascular system ($r=–0.36$, $p<0.05$). Regression analysis further confirmed a strong link between overall suboptimal health status and endothelial function (*Table 6*).

The analysis included the following parameters: overall SHS, Smoking Index (SI), BMI, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Endothelial Function (FFE), and age. The dependent variable was the overall SHS. The regression analysis revealed the strongest association to be between overall SHS and FFE. Specifically, individuals with higher SHSQ-25 scores (>14 points) had lower endothelial function.

Comparing groups divided by the mean SHS revealed significant differences in the following indicators: FFE ([16.4±8.6]% in Group 1 vs. [6.6±10.5]% in Group 2, $p<0.0001$), Cardiac Output Index (COI) ([71.7±12.4]% in Group 2 vs.

Table 6. Regression Analysis Results (Dependent Variable: Overall SHS)

Model	Unstandardized Coefficient		Standardized Coefficient	t	p
	B	Std. Error	Beta		
Constant	13.350	6.670	–	2.002	0.046
Smoking Index (SI)	0.034	0.085	0.026	0.398	0.691
BMI	0.139	0.145	0.079	0.958	0.339
Systolic BP (SBP)	0.069	0.054	0.102	1.288	0.199
Diastolic BP (DBP)	–0.040	0.049	0.052	–0.815	0.416
Endothelial Function (FFE)	–0.248	0.068	–0.284	–3.679	0.000
Age	–0.132	0.053	–0.209	–2.491	0.013

[68.1±12.2]% in Group 1, p<0.01), COI² ([59.1± ±11.3]% in Group 1 vs. [63.3±10.7]% in Group 2, p<0.001), and Pulse Wave Velocity (PWV²) ([8.2±4.1] m/s in Group 1 vs. [9.3±3.3] m/s in Group 2, p=0.01), indicating higher vascular tone and stiffness in individuals with higher suboptimal health status. FFE significantly differed between groups across all age categories (p<0.001). Participants with arterial hypertension had lower FFE compared to both Group 1 and Group 2 (*Table 7*).

Thus, the group with an overall SHS ≥14 can be considered as representing a transitional stage between health and disease.

Among the primary biochemical markers of endothelial dysfunction, endothelin-1 plays a particularly crucial role. The level of endothelin-1 in Group 2 (overall SHS ≥14) was significantly higher than in Group 1 (overall SHS <14), measuring 4.79 (2.5; 9.13) fmol/mL versus 1.34 (0.94; 1.72) fmol/mL, respectively (Z=5.37, p<0.001). Endothelin-1 demonstrated a significant correlation with FFE (rs=–0.87, p<0.05), overall SHS (rs=0.83, p<0.05), the SHS subscale for "cardiovascular system" (rs=0.74, p<0.05), as well as with age (rs=0.40, p<0.05) and systolic blood pressure (rs=0.34, p<0.05).

The correlation between the SHS and endothelin-1 once again demonstrates the sensitivity of the SHS assessment method in identifying the risk of cardiovascular disease.

To investigate integrative relationships among overall SHS, FFE, and risk factors for arterial hypertension, a multifactorial statistical analysis was performed with the following variables: SHSQ-25 scores (overall and by subscales), SBP, DBP, BMI, smoking index, FFE, total cholesterol, and glucose levels. A cluster analysis was conducted based on these parameters, dividing all participants into five distinct clusters.

The first cluster comprised 114 individuals under 40 years of age (61 men and 53 women). This cluster most commonly exhibited low overall SHS values: [5.6±3.97] points (men – [4.68±3.46] points; women – [6.3±4.21] points). The "cardiovascular system" subscale of SHS also showed low scores: [0.38±1.0] points (men – [0.26±0.8] points; women – [0.47±1.13] points). Individuals in this cluster had normal BMI values ([22.6± ±2.66] kg/m²), normal blood pressure ([110.6± ±10.6] / [75.3±9.14] mmHg), and no endothelial dysfunction (FFE=[20.66±6.08]%). Glucose ([4.48± ±0.67] mmol/L) and cholesterol ([4.7±0.66] mmol/L) levels were within normal ranges. Participants in this cluster can be characterized as "individuals with optimal health status".

The second cluster included 131 individuals (54 men and 77 women). This group also consisted predominantly of young participants under 40 years of age, with a mean age of [23.66±4.45] years (men – [24.7±5.07] years; women – [22.9±3.9] years). However, the overall SHS in this cluster was higher compared to Cluster 1, both for the group as a whole and separately for men and women, measuring [10.5±4.1] points (men – [10.5±4.4] points; women – [10.4±3.68] points). The "cardiovascular system" subscale score was also higher than in Cluster 1, reaching [0.93±1.07] points (men – [1.25±0.9] points; women – [0.74± ±1.11] points). BMI ([21.6±2.95] kg/m²) and blood pressure ([109.0±11.3] / [71.1±8.6] mmHg) remained within normal ranges. A moderate decrease in FFE was observed ([17.29±7.77]%),

Table 7. Comparative characteristics of study groups

Parameter	Group 1 (overall SHS <14, n=181)	Group 2 (overall SHS ≥14, n=146)	Hypertensive individuals (n=21)
FFE, %	16.4±8.6*^	6.6±10.5	0.54±7.31
BMI, kg/m²	24.25±4.51*^	25.31±6.34	26.56±4.1
SBP, mmHg	121.19±11.22*	121.48±10.16**	142.14±5.14
DBP, mmHg	78.90±9.42*^	74.29±18.52**	86.05±8.0
Smoking index, pack-years	0 (0; 0.4)^	0 (0; 9.6)	1.13 (0; 20)
Glucose, mmol/L	4.55±0.82	4.86±0.92	4.63±1.86
Total cholesterol, mmol/L	4.87±0.74*^	5.78±1.24	6.28±0.95
Overall SHS	10.04±2.10*^	18.18±4.12**	20.67±9.81

Notes: *– significant difference between Group 2 and hypertensive individuals, p<0.05; ^ – significant difference compared to Group 2, p<0.05; **– differences between Group 2 and individuals with hypertension, p<0.05.

while glucose ([4.7±0.45] mmol/L) and cholesterol ([4.6±1.0] mmol/L) levels were within the reference range. This cluster can be characterized as "suboptimal health status with a low level of risk factors".

The third cluster comprised 102 individuals (36 men and 66 women), with a mean age of [26.0±8.77] years. This cluster was distinguished from the previous two by higher overall SHS values ([16.27±3.75] points). Elevated smoking index ([4.3±15.6] pack-years) and higher total cholesterol levels ([5.1±0.65] mmol/L) were also noted. A significant reduction in FFE was observed ([13.6±6.6]%). This cluster can be described as "suboptimal health status with a high level of risk factors".

The fourth cluster consisted of 89 individuals (46 men and 43 women), predominantly aged 35 years and older, with a mean age of [46.6±10.9] years. The SHS exhibited intermediate values, both for the overall score ([21.6±7.6] points) and for the "cardiovascular system" subscale ([1.1± ±1.1] points). Participants in this cluster presented with 1–2 risk factors for arterial hypertension, primarily overweight or prolonged smoking history. BMI in this group was [26.9±4.19] kg/m² (men – [27.26±3.5] kg/m²; women – [26.4±5.06] kg/m²), and the smoking index was [15.6±29.9] pack-years (men – [22.2±32.0] pack-years; women – [6.6±23.2] pack-years). This cluster can be characterized as the "cardiovascular phenotype of suboptimal health with a low level of risk factors".

The fifth cluster included 52 individuals (13 men and 39 women), predominantly aged 40 years and older, with a mean age of [52.03±7.8] years. This group exhibited high overall SHS values ([27.4±5.45] points overall; men – [27.5±5.23] points; women – [27.38±5.6] points), and markedly higher scores on the "cardiovascular system" subscale compared to previous clusters ([3.07±2.01] points). Multiple risk factors for arterial hypertension were identified: smoking (mean smoking index [3.49±6.5] pack-years), overweight/obesity (BMI [31.5±4.8] kg/m²; men – [30.3±2.8] kg/m²; women – [31.9±5.3] kg/m²), and hypercholesterolemia (mean total cholesterol [6.5±1.8] mmol/L; men – [7.27±0.5] mmol/L; women – [6.3±1.1] mmol/L). Endothelial dysfunction was observed, with FFE values of [0.82± ±7.4]% overall (men – [–0.15±5.81]%; women – [16±7.88]%), significantly lower than in the first four clusters. This cluster can be defined as the "cardiovascular phenotype of suboptimal health with a high level of risk factors".

Discriminant analysis demonstrated the validity of the chosen classification into five clusters. The results of this analysis enable the development of a mathematical classification model, which may facilitate the early, preclinical detection of functional changes in organs in individuals presenting only with nonspecific complaints that fall within the suboptimal health status spectrum.

This objective was achieved by having participants complete the "Suboptimal Health Status Questionnaire (SHSQ-25)". Risk factors were assessed, including calculation of the smoking index, body mass index, and measurement of arterial blood pressure, as well as determination of blood glucose and total cholesterol levels. Endothelial function was evaluated using computerized photoplethysmography with a reactive hyperemia test, followed by computational processing of the data according to established equations:

1. OHS (Optimal Health Status):

OHS = 535.2 × Sex – 0.8 × Age – 4.5 × Fatigue – – 22.9 × PsychStatus + 12.5 × CVS + 8.2 × × Digestive – 5.8 × Immune + 6.3 × SHS_Sum + + 3.2 × SmokingIndex + 10.6 × BMI + 2.8 × × SBP + 5.8 × DBP – 2.5 × EndothelialFunc + + 6.7 × AI – 4.4 × AI2 – 0.6 × SI – 4.7 × SI2 + + 46.3 × Cholesterol + 22.8 × Glucose – – 28485.5 (2).

2. Suboptimal Health Status with Low Risk Factors (SHS-LR):

SHS-LR = 534.2 × G – 0.9 × A – 4.9 × F – 23.2 × × PS + 12.0 × CVS + 7.7 × DS – 16.1 × IS + + 6.8 × TS + 3.2 × SI + 10.5 × BMI + 2.8 × × SBP + 5.8 × DBP – 2.5 × EF + 6.7 × PI c4.5 × × PI2 - 1.1 × AS – 4.8 × AS2 + 47.5 × TC + + 23.2 × GL – 28364.1 (3).

3. SHS-HR (Suboptimal Health Status with High Risk Factors):

SHS-HR = 534.1 × G – 0.9 × A – 4.6 × F – 22.5 × × P + 12.6 × CV + 8.4 × D – 15.7 × IS + 6.7 × × TS + 3.2 × SI + 10.5 × BMI + 2.8 × SBP + + 5.8 × DBP – 2.6 × EF + 6.8 × PI – 4.5 × PI2 – – 1.2 × AS – 4.6 × AS2 + 47.8 × Ch + 23.4 × × Glu – 28366.7 (4).

4. CV-SHS-LR (Cardiovascular Phenotype of Suboptimal Health with Low Risk Factors):

CV-SHS-LR =534.48 × G – 0.6 × A – 5.2 × F – – 23.2 × PSY + 12.1 × CVS + 7.3 × DIG – 16.3 × × IMM + 6.9 × SUM + 3.3 × SI + 10.9 × BMI + + 2.9 × SBP + 5.5 × DBP – 2.6 × EF + 6.7 × PI – – 4.5 × PI2 – 1 × AS – 4.6 × AS2 + 47.2 × × CHOL + 24.5 × GLU – 28429.2 (5).

5. CV-SHS-HR (Cardiovascular Phenotype of Suboptimal Health with High Risk Factors):

CV-SHS-HR = 536.3 × Sex – 0.6 × Age – 5.3 × × Fatigue – 23.1 × MentalStatus + 13.3 × × CardioSystem + 7.1 × DigestiveSystem – 16.6 × × ImmuneSystem + 7.2 × SHS_Total + 3.2 × × SmokingIndex + 11.3 × BMI + 3 × × SystolicBP + 5.8 × DiastolicBP – 2.9 × × EndothelialFunction + 6.8 × PW_Index – 4.6 × × PW_Index2 – 1.1 × ArterialStiffness – 4.4 × × ArterialStiffness2 + 49.6 × Cholesterol + 25.6 × × Glucose – 28672.9 (6).

Notes (Parameter Definitions):

OHS – Optimal Health Status.

SHS-LR – Suboptimal Health Status with Low Risk Factors.

SHS-HR – Suboptimal Health Status with High Risk Factors.

CV-SHS-LR – Cardiovascular Phenotype of Suboptimal Health with Low Risk Factors.

CV-SHS-HR – Cardiovascular Phenotype of Suboptimal Health with High Risk Factors.

Sex – sex.

Age – age.

Fatigue – fatigue symptoms.

PsychStatus – psychological status symptoms.

CVS – cardiovascular system symptoms.

Digestive – digestive system symptoms.

Immune – immune system symptoms.

SHS_Sum – total SHS-25 questionnaire score.

SmokingIndex – smoking index (pack-years).

BMI – body mass index.

SBP – systolic blood pressure.

DBP – diastolic blood pressure.

EndothelialFunc – endothelial function.

AI – reflection index of pulse wave.

AI2 – reflection index after pulse wave test.

SI – stiffness index.

SI2 – stiffness index after test.

Cholesterol – total blood cholesterol.

Glucose – blood glucose.

Based on the highest value obtained from the equations, the examined individual will be assigned to one of five clusters: 1) Optimal Health Status (OHS); 2) Suboptimal Health Status with a low level of risk factors (SHS-LR); 3) Suboptimal Health Status with a high level of risk factors (SHS-HR); 4) Cardiovascular phenotype of Suboptimal Health Status with a low level of risk factors (CV-SHS-LR); 5) Cardiovascular phenotype of Suboptimal Health Status with a high level of risk factors (CV-SHS-HR). This proposed approach enables the assessment of both the state of a healthy individual (OHS) and that of an individual with health deviations at the preclinical stage of disease (SHS).

Discussion

The results obtained confirm that subjective health assessment shows strong correlations with risk factors for arterial hypertension and indicators of endothelial function. This aligns with previous studies emphasizing the importance of SHS as an intermediate phase between health and disease, which may serve as an early marker for the development of chronic conditions [13; 15].

Using the SHSQ-25 questionnaire in our study enabled us to identify a close link between subjective complaints, risk factors, and quality of life. Similar findings were reported in international validation studies, demonstrating that the SHSQ-25 has good validity and reproducibility across different populations, including in Saudi Arabia and Ghana [14; 15]. This indicates the method's universality and its potential broad use in clinical practice.

Our study also confirmed that high SHS scores are associated with a reduced quality of life according to SF-36 results, especially in physical and mental health domains. This is consistent with prior research showing correlations between the SHSQ-25 and SF-36 measures in patients with cardiovascular diseases [11; 12]. Therefore, combining these scales can provide a more accurate assessment of patients' status at the preclinical stage.

It is also important to highlight the identified link between suboptimal health status and traditional cardiovascular risk factors such as excess body weight, blood pressure, and cholesterol levels. Similar associations have been documented in studies involving the Chinese population, demonstrating that SHS is closely connected to cardiovascular risks and may predict their development [17].

Special attention should be given to the observed relationship between endothelial function and risk factors, including smoking, arterial hy-

pertension, and dyslipidemia. This corresponds with existing literature emphasizing endothelial dysfunction as an early marker of cardiovascular problems [19; 20]. Therefore, evaluating endothelial function alongside SHS may improve the prognostic power of screening programs.

The mathematical model developed, which combines clinical, laboratory, and questionnaire data, provides a comprehensive assessment of health status and predictors of arterial hypertension even in practically healthy individuals. Similar multifactorial approaches have been successfully used by other researchers to predict cardiovascular complications [21–23]. This method could serve as a useful tool for primary screening in the general population and can be incorporated into annual preventive health check programs.

Our findings confirm the feasibility of using questionnaires and surveys as tools for initial cardiovascular risk screening in physical and occupational therapy settings [24]. Unlike complex lab or instrumental methods, these tools allow quick data collection regarding a patient's condition, help identify individuals with suboptimal health, and guide further diagnostics and interventions. However, it is crucial to recognize that data collected from questionnaires cannot fully substitute clinical examinations and should be viewed as a complementary approach. Integrating questionnaires into comprehensive rehabilitation programs is also vital.

Recent studies [25; 26] highlight that combining subjective patient assessments with objective biomarkers and functional tests significantly improves the accuracy of predicting cardiovascular event risk. Our results are consistent with this evidence and show that, even in a relatively small sample, meaningful associations between self-rated health and cardiovascular risk factors can be identified.

Consequently, questionnaires have great potential for early detection of at-risk patients in the practice of physical and occupational therapists. Further research with larger samples and multicenter studies will help clarify the diagnostic and prognostic value of these tools and support their integration into standardized medical-rehabilitation protocols.

Conclusions

1. Questionnaire-based assessment proved to be an informative and accessible method for distinguishing between optimal health status and suboptimal health conditions with varying levels of cardiovascular risk factors.

2. The applied cluster approach made it possible to identify five distinct health profiles, which may serve as a basis for differentiated strategies in physical therapy and occupational therapy.

3. The findings suggest that questionnaires can provide valid information on cardiovascular health already at the preclinical stage, thus supporting their use for early detection and preventive interventions.

4. Further integrating questionnaire data with clinical and functional diagnostic methods could improve predictive accuracy and support the development of personalized rehabilitation programs.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Burdina V.R.	+	+	+	+	+	+
Danylchenko S.I.	+	+	+	+	+	+
Yesselbayeva A.K.			+			+
Golovchenko I.V.			+			+
Morozenko D.V.				+		+
Aravitska M.G.				+		+
Shevchenko A.S.			+		+	+
Pertsev D.P.				+		+
Cherkova N.V.			+			+
Dushik L.N.				+		+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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FRACTAL ANALYSIS OF MANDIBULAR BONE ARCHITECTURE: A NOVEL CONTOUR SMOOTHING ALGORITHM FOR WHOLE-SLICE QUANTIFICATION

Stepanenko O.Yu., Maryenko N.I.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. The study of mandibular bone architecture is crucial for understanding remodeling, osteogenesis, and resorption processes under normal and pathological conditions. Traditional morphometric methods often rely on limited regions of interest and do not account for the hierarchical self-organization of bone tissue or the complexity of its surface configuration. There is a need for a modified fractal analysis technique focused on assessing the surface complexity of the entire bone slice rather than just its volume filling.

Aim. To develop an original modification of the contour smoothing method for studying mandibular bone architecture on computed tomography images, enabling the analysis of whole bone slices independent of region of interest selection.

Materials & Methods. The methodological study utilized digital cone-beam computed tomography images of the mandibular bone. The fractal dimension was calculated using a custom "contour smoothing" algorithm across six stages with increasing smoothing radii (2, 4, 8, 16, 32 pixels). Statistical data processing included the calculation of linear regression and the coefficient of determination to assess fractal properties; calculations and graphical visualization were performed using Excel 2016 (Microsoft, USA). The study was conducted as part of the initiative research project "Development of clinical and morphological methods of researching the structures of the human body" (State Registration No.0123U100367, 2023–2025).

Research Ethics. The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University.

Results. The analysis revealed that the dependence of variables remained linear during the first four stages (smoothing radii 2–8 pixels). At these stages, the bone trabeculae demonstrated monofractal properties. At stages 5 and 6 (radii 16–32 pixels), linearity was disrupted due to the loss of cortical plate contours, leading to a decrease in the approximation coefficient. Consequently, the optimal scaling range for the mandibular bone was determined to be stages 1–4.

Conclusions. The developed contour smoothing algorithm effectively quantifies the complexity of endosteal surface configurations and internal bone contours. This method offers a robust, resolution-independent approach for evaluating bone remodeling and resorption activity, suitable for diagnosing osteoporosis and assessing implant integration.

Keywords: *theoretical and experimental medicine, mandible, bone architecture, morphometry, computed tomography, fractal dimension.*

Introduction

The investigation of mandibular bone architecture is crucial for understanding the processes of remodeling, osteogenesis, and resorption that occur both in healthy conditions and in pathological states, such as osteoporosis, inflammatory processes, trauma, or following dental interventions. The assessment of bone microstructure on radiographic and Computed Tomography (CT) images allows for the non-invasive investigation of its morphofunctional state, the detection of early signs of remodeling disorders, and the prediction of fracture risks [1–4].

Current methods for studying bone architecture include traditional morphometric approaches,

Corresponding Author:
Stepanenko Oleksandr Yu. – PhD, ScD, Professor of the Department of Histology, Cytology and Embryology, Kharkiv National Medical University, Kharkiv, Ukraine.
✉ 4, Nauki ave., Kharkiv, 61022, Ukraine.
E-mail: oy.stepanenko@knmu.edu.ua

specifically the determination of various indices such as bone volume density, bone surface density, trabecular plate number, trabecular thickness, trabecular separation, and the degree of anisotropy [5–7]. However, these methods often present several limitations: they require precise Region Of Interest (ROI) selection, rely on two-dimensional projections of complex three-dimensional structures, and fail to account for the hierarchical self-organization of bone tissue. Furthermore, classical morphometric parameters do not adequately reflect the complexity and irregularity of the bone surface architecture, which is significant for analyzing bone remodeling.

In this context, the application of fractal analysis represents a promising direction for the quantitative assessment of bone tissue morphological organization [8]. Fractal dimension – a parameter determined via fractal analysis – reflects the degree of an object's structural complexity and its space-filling capacity. The more structural elements an object possesses (in the case of bone tissue, bone trabeculae) and the more complex their spatial configuration, the greater the degree of space filling by bone trabeculae, and consequently, the higher the fractal dimension of the trabecular (cancellous) bone as a whole [8–10]. Typically, fractal dimension is used as a complementary morphometric criterion for assessing trabecular bone status, particularly in osteoporosis diagnosis, due to its sensitivity to the reduction in space filling by bone tissue observed in this condition [11; 12]. It has been demonstrated that a decrease in fractal dimension on radiographs or CT images correlates with reduced bone mass and deterioration of trabecular microarchitecture [10; 13].

Fractal analysis has been employed in numerous studies regarding the mandible, specifically for assessing bone tissue in healthy patients [14] and determining sexual dimorphism [15], evaluating changes in osteoporosis [16; 17], assessing bone status prior to implantation [18] and during healing after orthognathic surgery [19], as well as in renal transplant recipients [20] and patients undergoing systemic glucocorticoid therapy [21].

Nevertheless, existing methodologies for bone fractal analysis have significant limitations. They are typically applied to limited ROI and are sensitive to image resolution, size, and segmentation parameters [14]. Moreover, the derived fractal characteristics primarily reflect the degree of space filling by bone tissue rather than the complexity of its surface configuration [22]. It has been established that with the intensification of resorption and bone remodeling, the micro-relief of trabecular surfaces and the endosteal contour changes, becoming more tortuous and complex [23]. Therefore, the quantitative assessment of bone surface configuration is essential for detecting morphological signs of remodeling, a task that traditional fractal algorithms cannot fully realize.

Given this, a need arises to develop a modified fractal analysis methodology focused on assessing the complexity of the bone tissue surface rather than solely its volumetric filling. In our study, we developed an original algorithm for investigating mandibular bone architecture on CT images based on the contour smoothing method, which we previously developed for the fractal analysis of the pial surface configuration of the cerebral cortex [24].

The **aim** of the study was to develop an original modification of the contour smoothing method for investigating mandibular bone architecture on computed tomography images. The specific objective of this research stage is to calibrate the method and determine the optimal algorithm parameters for fractal analysis, rather than to perform clinical diagnostics on a population.

Material and Methods

To develop and calibrate the fractal analysis methodology, digital cone-beam computed tomography images of the mandible of a healthy volunteer (34 years old, female) were used.

Axial tomographic images were selected (*Fig. 1, A*). The apices of the tooth roots served as anatomical landmarks: the tomographic slices were located immediately below the deepest points of the tooth roots in the mandibular bone. Digital images were selected using the Ez3D2009 software (E-WOO Technology Co., Ltd., Yongin, Republic of Korea).

Further image segmentation and analysis were performed using the Adobe Photoshop CS5 graphics editor (Adobe Systems Inc., San Jose, CA, USA). Selected digital images in DICOM format were transferred to a pre-created "blank" JPEG image with dimensions of 720×720 pixels and a resolution of 72 pixels per inch. The absolute scale was 1 mm = 7.5 pixels.

Next, image segmentation was performed: using the "Threshold" tool, the image was converted to binary format (*Fig. 1, B*). An empirical pixel brightness threshold value of 110 was used: all pixels with a brightness value greater than the threshold were colored white (brightness value 255), and pixels with a brightness value less than the threshold were colored black (brightness value 0).

The threshold value of 110 was selected based on the histogram analysis of the grayscale image, corresponding to the valley between the peaks of soft tissues/marrow and calcified bone tissue. A global threshold was selected for segmentation. As a result of this binarization, bone tissue (including the compact substance of the cortical plate and the cancellous substance inside the mandible) was colored white, while surrounding structures and cavities between bone trabeculae were colored black (*Fig. 1, B*). Following binarization, color inversion was performed, resulting in bone structures becoming black, and the background and cavities within the bone becoming white (*Fig. 1, C*).

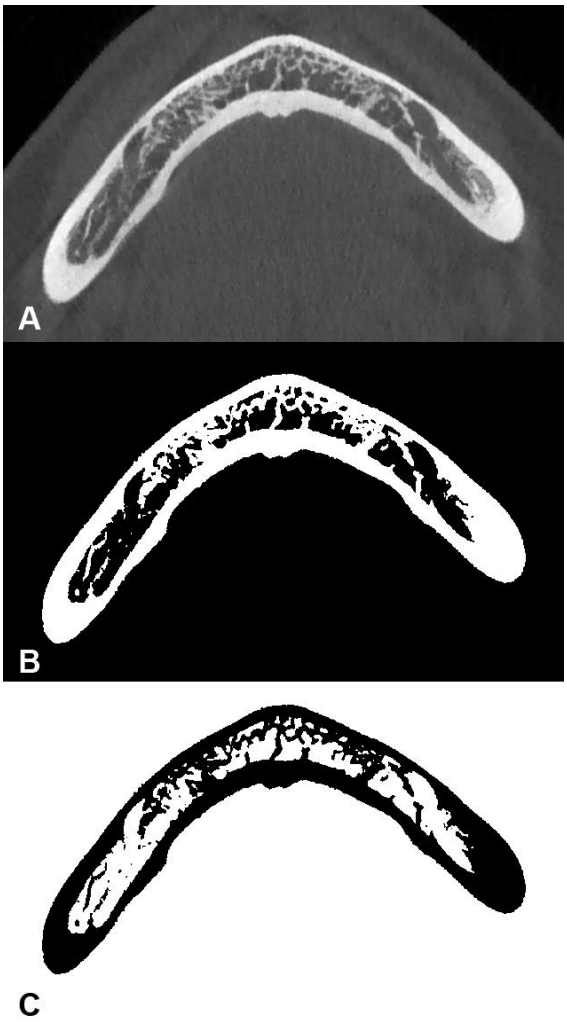

Fig. 1. Computed tomography image of the mandible and its segmentation:
A – original CT image,
B – segmentation (binarization) using the "Threshold" tool,
C – inversion of the binary image.

Subsequently, the actual fractal analysis was performed using the contour smoothing method. Since this technique was previously employed by the authors to investigate the external surfaces of anatomical structures, it was modified for the study of bone (and internal surfaces – contours of cavities within it). To outline the external and internal surfaces of the mandibular bone tissue, the "Selection" tool of the graphics editor was used; all black pixels were automatically selected, creating a closed selection area corresponding to the silhouette of the bone tissue in the image. The contour of the selected area corresponded to the external and internal surfaces of the bone (*Fig. 2, A*).

To develop the methodology for bone tissue investigation, six stages of Fractal Analysis (FA) were initially used, consistent with the original methodology. At the *first FA stage*, no contour smoothing was performed. After outlining the contour, its length (perimeter, P1) was determined. Starting from the *second FA stage*, the contour smoothing procedure was performed: at the second stage, the contour smoothing radius (R2) was 2 pixels; at the third (R3) – 4 pixels; fourth (R4) – 8 pixels; fifth (R5) – 16 pixels; and sixth (R6) – 32 pixels. Considering that no smoothing was performed at the first stage, the smoothing radius for the first FA stage (R1) was taken as unity (1) for further calculations.

The smoothing procedure stepwise removes protrusions or invaginations from the contour with a radius of curvature smaller than the smoothing radius. Thus, at the initial stages, the contours of small bone trabeculae and small protrusions on them are removed; subsequently, the contours of larger bone trabeculae are removed (*Fig. 2, A–C*). As a result, at the *fourth FA stage*, the contours of the cortical plates remain, while the contours of cancellous bone trabeculae are mostly absent, persisting only in areas of their dense arrangement (*Fig. 2, D*). At the *fifth FA stage*, smoothing led to partial removal of cortical plate contours (since their thickness was less than the set smoothing radius – 16 pixels) (*Fig. 2, E*), and at the sixth FA stage, the contour was represented by only a few areas where the bone as a whole had a thickness slightly greater than the set smoothing radius – 32 pixels (*Fig. 2, F*).

At each FA stage, the contour length P (P1–P6) was measured, and the data were recorded (*Table 1*). Mathematical modeling and statistical processing were performed using Excel 2016 (Microsoft Corp., Redmond, WA, USA). For the analysis, two values were calculated: the natural logarithm

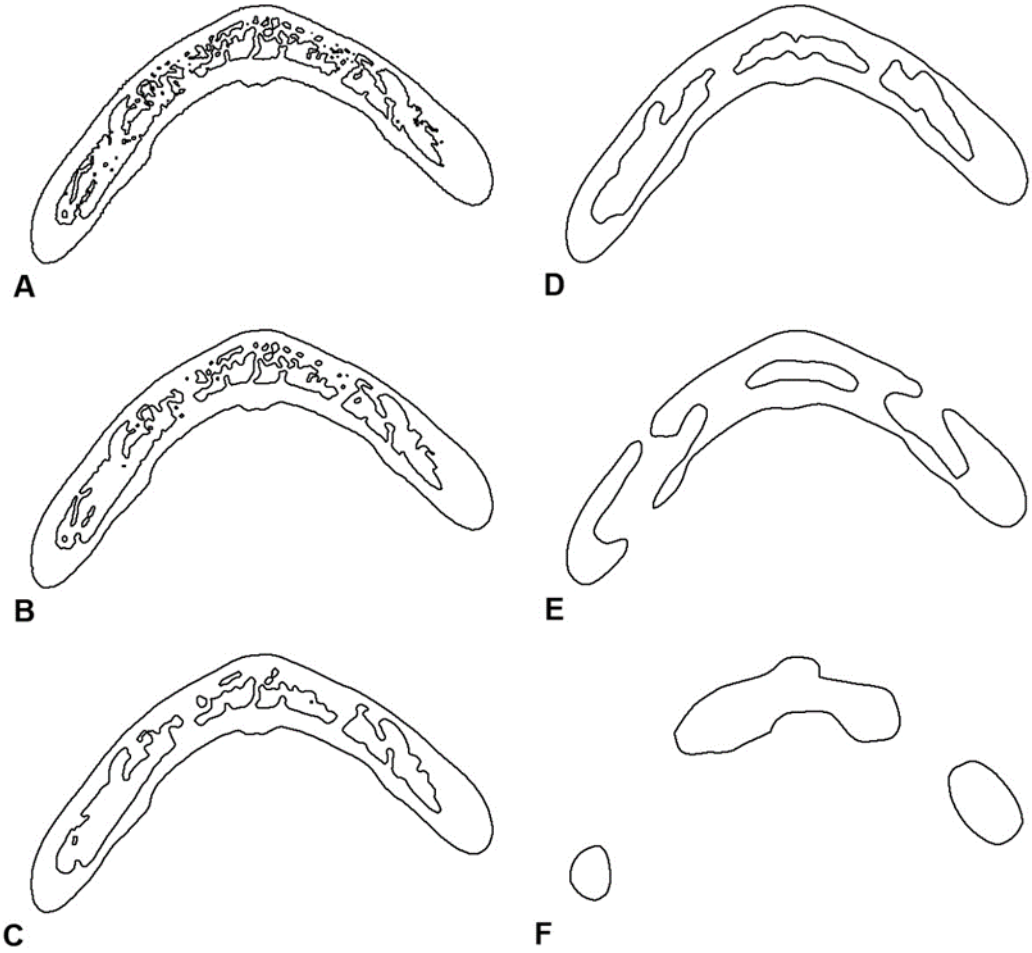

Fig. 2. Fractal analysis (FA) of mandibular bone tissue contours using the contour smoothing method; the contour is outlined in black for clarity.

A – 1st FA stage, contour without smoothing;
B – 2nd FA stage, contour smoothing with a radius of 2 pixels;
C – 3rd FA stage, contour smoothing with a radius of 4 pixels;
D – 4th FA stage, contour smoothing with a radius of 8 pixels;
E – 5th FA stage, contour smoothing with a radius of 16 pixels;
F – 6th FA stage, contour smoothing with a radius of 32 pixels

of the reciprocal of the smoothing radius, *ln(1/R)*, and *ln(P/R)*. Based on these values, linear regression analysis was performed using the least squares method to derive the equation $y = bx + a$. In this equation, the independent variable x corresponds to *ln(1/R)*, the dependent variable y corresponds to *ln(P/R)*, a is the intercept coefficient, and b is the slope coefficient (*Fig. 3*). The fractal dimension of the investigated structure is defined as the slope coefficient b.

The quality of the linear model fit was evaluated using the coefficient of determination (R2). The linearity of the relationship was considered sufficient at R2 values close to 1.0 (R2 > 0.99), which served as the criterion for selecting the optimal range of smoothing scales demonstrating monofractal properties.

Research Ethics

The research protocol was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University (Protocol No.5 dated February 01, 2023). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later

Table 1. Fractal analysis using the contour smoothing method: data for fractal dimension calculation

FA stage	Smoothing radius, R	1/R	ln(1/R)	The contour length (perimeter, P)	P/R	ln(P/R)
1	1*	1.0000	0.000	1981	1981.0	7.591
2	2	0.5000	–0.693	1747	873.5	6.773
3	4	0.2500	–1.386	1606	401.5	5.995
4	8	0.1250	–2.079	1564	195.5	5.276
5	16	0.0625	–2.773	2167	135.4	4.909
6	32	0.0313	–3.466	1184	37.0	3.611

Note: * – since no contour smoothing is performed at the first stage, the value of R1 is taken as unity for calculations.

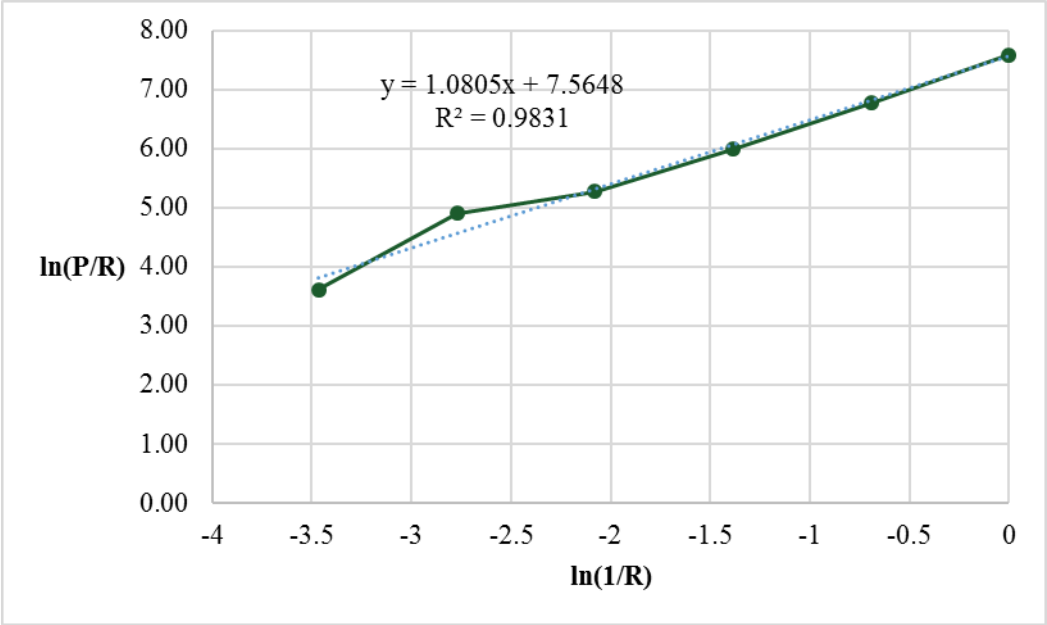

Fig. 3. Calculation of the linear regression equation characterizing the dependence of ln(P/R) on ln(1/R): six FA stages

amendments. Written informed consent was obtained from the patient for the use of their medical data (computed tomography images) for scientific purposes. All data were anonymized prior to analysis to ensure confidentiality.

Results

A critical step in FA is selecting the range of scales used to calculate the fractal dimension. It is necessary to determine the range where the investigated object exhibits fractal properties, which manifests as a linear dependence between the scaling coefficient (in this case, *ln(1/R)*) and the quantitative parameter characterizing the structure's size at different FA stages (*ln(P/R)*).

As shown in the graph in *Fig. 3*, from the first to the fourth stage of fractal analysis, the dependence of *ln(P/R)* on *ln(1/R)* is linear. This indicates the invariance of the bone structural organization across different scales and a consistent change in the configuration of bone trabeculae during contour smoothing. Such a property is characteristic of monofractal structures; precisely within this

range of FA stages, the bone trabeculae demonstrate fractal properties.

However, at the 5th and 6th FA stages, the linearity of the relationship between the two variables is disrupted. Furthermore, the smoothing process at these stages leads to the disappearance of cortical plate contours (*5th FA stage, Fig. 2, E*) and entire fragments of the mandible (*Fig. 2, F*).

To evaluate how well the calculated linear regression equation fits the graph characterizing the dependence of the two variables *ln(P/R)* and *ln(1/R)*, the coefficient of determination (R2) was used. When using all six FA stages, the R2 value is 0.9831 (*Fig. 3*), which is lowered due to the violation of linearity at the 5th and 6th stages. Consequently, it is advisable to exclude these stages when studying the mandibular bone and to retain only those stages where the structures demonstrate a monofractal character of organization. This corresponds to the linearity of the relationship between the variables – specifically, the first four stages of FA (*Fig. 4*).

When using data from the first four FA stages for calculations (*Fig. 4*), the R2 value is 0.9992, indicating a practically functional linear relationship between the two investigated variables, *ln(P/R)* and *ln(1/R)*.

Thus, the range of FA stages to be used for determining the fractal dimension includes the first through fourth stages. These stages utilize small smoothing radius values (2–8 pixels), which allows for the stepwise removal of bone trabeculae contours without removing the contours of cortical plates and the bone as a whole, as occurs at the 5th and 6th FA stages when using large smoothing radii (16 and 32 pixels). This range covers the stages where the surface configuration of the mandibular bone exhibits a monofractal character; these precise stages allow for the accurate determination of the fractal dimension of the investigated structure. The linear regression equation in *Fig. 4*, calculated based on the results of four FA stages, is $y = 1.1144x + 7.5674$. Therefore, the fractal dimension of the mandibular bone surface contours (Hausdorff dimension) in this example equals 1.1144.

Discussion

When performing fractal analysis of bone tissue and other natural structures, various FA methods can be employed, determining different types of fractal dimensions. The most common method used in morphological studies is the box-counting method [25] and its variants, such as the tile-counting method, which is used for investigating bone trabeculae [14; 19]. This method determines the Minkowski dimension, which primarily characterizes the capacitive properties and the degree of space filling by the investigated object.

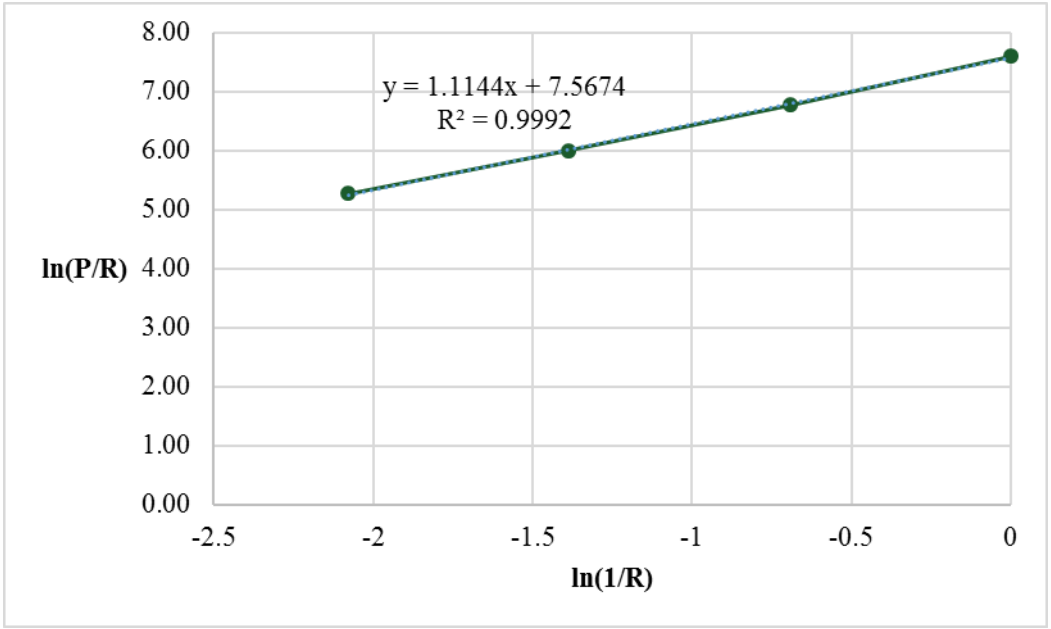

Fig. 4. Calculation of the linear regression equation characterizing the dependence of ln(P/R) on ln(1/R): four FA stages.
The fractal dimension equals 1.1144.

In histomorphometric studies of bone trabeculae, methods such as box-counting (used to determine the Kolmogorov dimension), dilation (for the Minkowski-Bouligand dimension), and sandbox (for the "mass-radius" dimension) have been utilized [22]. In their classical variations, these techniques predominantly characterize the space filling by trabeculae rather than surface characteristics.

To characterize the surface properties of bone trabeculae, modifications of the box-counting method with specific image preprocessing have been previously used. For instance, a modification of the tile-counting method additionally employed contour outlining, allowing for the determination of its Minkowski dimension [14]. The box-counting method with contour outlining has also been used to assess implant surface roughness to predict osseointegration [26]. However, the use of the Minkowski dimension determined via box-counting (and its variants) with pre-outlined structure contours has limitations: such algorithms are dependent on image resolution and size, the thickness of the outline used, and the segmentation algorithm [27].

In view of this, the Hausdorff dimension, determined via the contour smoothing method, is a more appropriate parameter for assessing surface contour configuration. In our previous research, we established that this dimension is independent of image scale, size, resolution, and contour thickness [27]. Therefore, the use of the contour smoothing method for investigating bone tissue surfaces may be more informative and technically robust compared to existing methods. We previously used this FA method to assess the configuration of external contours of anatomical structures and artificial fractals [24; 27]. In the present work, this method demonstrated its capability to determine the fractal dimension of internal structure contours – specifically, the contours of the endosteum lining the bone cavities. We hypothesize that in healthy bone, the trabecular network is dense and complex, resulting in a higher fractal dimension. In osteoporosis, the loss of trabeculae simplifies the contour, likely leading to a decrease in the Hausdorff dimension.

Another challenge in bone fractal analysis is the selection of ROI. Typically, small square areas corresponding to the cancellous bone are analyzed rather than the bone as a whole. Fractal dimension values can vary depending on both the size of the digital image area used for analysis and its localization [14; 21]. Performing fractal analysis on the entire mandibular tomographic slice, as implemented in our algorithm, allows for the assessment of the whole bone state and mitigates errors caused by ROI selection bias.

The main limitations of the proposed methodology include the ability to investigate only closed contours, which may restrict the use of this algorithm when studying cropped image fragments of bone tissue. Another important factor is the selection of the FA stage range (the range of smoothing radii where the *ln(P/R)* vs. *ln(1/R)* dependence is strictly linear) when using CT images with different scales and resolutions. Future studies should address the influence of metal artifacts on contour extraction.

The proposed algorithm for fractal analysis of mandibular bone architecture using the modified contour smoothing method can be used to assess bone remodeling and resorption activity during healing after implant placement, fracture healing, or following mandibular surgery. Additionally, this technique can be employed to evaluate the complexity of bone architecture for assessing changes in osteoporosis and predicting implant integration into the mandible.

Conclusions

1. The original fractal analysis algorithm using the contour smoothing method, described in this study, allows for the quantitative assessment of the configuration complexity of internal endosteal surface contours within the mandibular bone.

2. The surface contours of the mandibular bone tissue demonstrate monofractal properties within a smoothing radius range of 2 to 8 pixels; consequently, the fractal analysis algorithm was modified and restricted to four stages with small smoothing radius values.

3. The advantages of the proposed algorithm include the ability to analyze mandibular bone slices in their entirety, independence from the size and location of a selected ROI, and independence from image size and resolution.

4. The proposed fractal analysis algorithm can be used for diagnostic purposes to assess the activity of remodeling and resorption of mandibular bone tissue on computed tomography images.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Stepanenko O.Yu.	+	+		+	+	+
Maryenko N.I.	+	+	+		+	+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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SYMPTOMATIC TREATMENT OF DYSOSMIA IN RHINOLOGICAL PATHOLOGY OF FUNCTIONAL AND VIRAL (SARS-CoV-2) ORIGIN

Shushliapina N.O., Kalashnyk-Vakulenko Y.M., Bondarenko Y.D.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Olfactory disorders are widespread and are of considerable socio-medical importance. However, effective evidence-based approaches to the symptomatic treatment of dysosmia – both in common rhinological diseases and post-viral conditions, particularly COVID-19-associated olfactory dysfunction – remain insufficiently defined.

Aim. To evaluate the effectiveness of symptomatic conservative therapy in the treatment of patients with respiratory dysosmia of functional and viral (SARS-CoV-2) origin, including assessment of olfactory function.

Materials & Methods. The study included 183 patients, aged 18 to 60, with olfactory dysfunction resulting from rhinological pathology of functional and post-viral origin. The patients were divided into four groups and received traditional symptomatic treatment. Data collection involved the SNOT-22 questionnaire, rhinomanometry, and olfactometry, conducted both before and after treatment. Statistical analysis was performed using descriptive statistics and Student's t-test with Excel 2022 (Microsoft, USA).

Research Ethics. The study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki (1964–2024). All study participants provided informed consent.

Results. The symptomatic treatment demonstrated significant effectiveness across the groups according to the questionnaire results ($p<0.001$), showing a reduction in subjective symptoms. Rhinomanometry findings also showed significant improvement in indicators across all groups ($p<0.05$); however, a moderate degree of severity persisted in patients with functional dysosmia. Following treatment, olfactometry findings demonstrated no significant improvement in olfaction among patients with viral dysosmia ($p=0.33$). In the remaining groups, the degree of olfactory impairment remained at the level of hyposmia, although the indicators were higher post-treatment ($p<0.005$).

Conclusions. The choice of treatment method for patients with olfactory dysfunction should be considered based on the disease origin, with particular focus on the mechanical-obstructive and sensorineural mechanisms of its development.

Keywords: *otolaryngology, olfactory dysfunction, rhinomanometry, COVID-19, rhinosinusitis, nasal obstruction.*

Introduction

Dysosmia, including anosmia, hyposmia, parosmia, and other olfactory disorders, represent a heterogeneous group of clinical conditions with multifactorial etiology and a complex pathophysiological architecture, posing a substantial challenge in modern rhinological practice and significantly determining patients' quality of life [1; 2]. Despite the high prevalence and socio-medical significance of olfactory disorders, current clinical practice is characterized by a limited evidence base regarding effective therapeutic strategies for the symptomatic treatment of dysosmias – both in classic rhinological diseases and in post-viral conditions, including COVID-19-associated dysfunction (COronaVIrus Disease-2019) [3; 4]. In the context of modern pharmacotherapy in otorhinolaryngology, local and systemic corticosteroids traditionally constitute the cornerstone of anti-inflammatory therapy for acute and chronic rhinosinusitis, allergic rhinitis, and associated inflammatory diseases of the middle ear [5]. At the same time, clinical observations indicate their inconsis-

Corresponding Author:
Shushliapina Nataliia O. – Candidate of Medical Sciences, Associate Professor of the Department of Otorhinolaryngology of the Kharkiv National Medical University, Ukraine.
✉ 4, Nauky Ave., Kharkiv, 61022, Ukraine.
E-mail: no.shushliapina@knmu.edu.ua

tent and often unsatisfactory effectiveness in cases of virus-induced olfactory dysfunction, necessitating a critical reappraisal of the pathophysiological rationale for their use [6]. Thus, post-viral perceptual (sensorineural) dysosmia arises as a result of damage to the olfactory epithelium or central olfactory pathways in the absence of significant nasal obstruction [7]. In contrast to conductive forms, perceptual dysosmia does not respond to surgical or anti-inflammatory treatment [8; 9].

Alongside inflammatory processes, anatomical and functional abnormalities of the nasal cavity play a significant role in the development of olfactory dysfunction, as they determine pathological airflow aerodynamics and impaired transport of odorants to the olfactory region, which likewise require an appropriate therapeutic strategy. Architectural impairments, such as nasal septal deviation, concha bullosa (pneumatization of the middle turbinate), paradoxical curvature of the middle turbinate, hypertrophy of the inferior turbinates, and other structural anomalies of the nasal architecture, create mechanical obstructions to normal airflow reaching the olfactory cleft in the superior nasal meatus and the olfactory zone at the level of the superior turbinate [10; 11]. These variations in anatomical structure lead to airflow turbulence, a reduction in its laminar component within the upper regions of the nasal cavity, and a decrease in the effective delivery of odorant molecules to the olfactory epithelium [12]. In such cases, surgical correction of anatomical deformities may become the only viable option to restore aerodynamics and improve olfaction in patients with conductive impairments [13]. Specifically, techniques such as septoplasty, conchoplasty, reduction of hypertrophied inferior turbinates, polypectomy, and endoscopic treatment of chronic rhinosinusitis are used [14]. Therefore, our objective is to analyze two pathogenetically independent cascades of olfactory dysfunction with fundamentally different structural and functional substrates, clinical presentations, and therapeutic responses.

The **aim** of the study was to evaluate the effectiveness of symptomatic conservative therapy in the treatment of patients with respiratory dysosmia of functional and viral (SARS-CoV-2) origin, including assessment of olfactory function.

Material and Methods

The study included 183 patients (115 men and 68 women) aged 18 to 60 years who were hospitalized in the Head and Neck Surgery Department of the Municipal Nonprofit Enterprise of Kharkiv Regional Council "Regional Clinical Hospital",

The participants were divided into four groups based on the disease origin. Group1consisted of 38 patients with acute post-viral rhinosinusitis caused by COVID-19, with duration of up to 12 weeks. COVID-19 diagnosis was confirmed based on a documented positive polymerase chain reaction test findings. Group 2 included 53 patients with impaired nasal breathing and structural changes in the nasal cavity architecture lasting for 3–5 years. Group 3 comprised 48 patients with impaired nasal breathing and structural changes in the intranasal structures with duration of up to 6 months. Group 4 consisted of 44 patients with impaired nasal breathing and structural changes in the nasal architecture lasting up to 1 month.

All patients received traditional therapy, which included topical decongestants (xylometolazine 0.1% 2 drops in each nostril three times daily) and irrigation therapy (isotonic saline solution, 1 spray in each nostril three times daily) for 10 days.

The patients with acute rhinosinusitis; history of COVID-19 within the previous 12 weeks; presence of impaired nasal breathing and olfactory dysfunction associated with pathology of the intranasal structures; patient age between 18 and 60 years; signed informed consent were included. Exclusion criteria were age under 18 or over 60 years; chronic rhinosinusitis (with or without nasal polyps); olfactory dysfunction of traumatic origin; pregnancy; and oncologic diseases.

Clinical examination included the symptom assessment using the validated Ukrainian version of the SNOT-22 questionnaire (Sino-Nasal Outcome Test-22) [15; 16] consisting of 22 items designed to assess the severity of nasal symptoms. Each symptom was rated on a scale from 0 (absence of symptoms) to 5 (very severe). The total score ranged from 0 to 110, with higher values indicating a greater negative impact of symptoms on quality of life. An ENT examination included nasal endoscopy. Nasal breathing was evaluated by measuring aerodynamic nasal resistance using posterior active rhinomanometry with a computerized rhinomanometer. Olfactory function was assessed using the Sniffin' Sticks test (Burghart®, Germany) and a method for processing respiratory test signals in response to various types of odorants [17; 18]. The results of olfactometry were evaluated in accordance with the provided data of the test system as anosmia (1 point), hyposmia (2–6 points) and normosmia (7–16 points) according to the threshold test. The identification test data, depending on the number of correctly identified markers with an odorant, had a value of 0–6 points

for anosmia, 7–10 points for hyposmia, 11–12 points – normosmia.

To determine treatment effectiveness in the examined patients, subjective and objective parameters were recorded before and after therapy. The effectiveness of the prescribed symptomatic conservative treatment was evaluated based on the changes in subjective rhinological symptoms including reduction of nasal obstruction, restoration of nasal breathing, decreased nasal secretion, and improvement of olfactory function, as well as objective measures – rhinomanometry and olfactometry results.

Statistical analysis of the obtained results was performed using biometric methods within Microsoft Excel 2022 (Microsoft, USA). In the descriptive analysis, continuous variables were presented as [mean ± standard deviation], while categorical variables were expressed as frequencies and percentages. The Shapiro Wilk test was used to assess the distribution of variables. To compare indicators before and after treatment within each group, the paired Student's t-test was utilized. The results were considered statistically significant at $p<0.05$.

Research Ethics

The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (1964–2024), Directive 86/609 of the European Community on the participation of humans in biomedical research, and Order No.690 of the Ministry of Health of Ukraine dated September 23, 2009. Written informed consent for participation in the study was obtained from all participants after they were provided with clear, comprehensive, and accessible information regarding the study purpose, design, and methodology, as well as its potential risks, expected benefits, possible alternatives, and the voluntary nature of participation.

Results

During the initial examination, the most common complaints in the subjective status of all evaluated patients included impaired nasal breathing and nasal congestion. In Group 1, according to the questionnaire results, the mean score was [61.4± ±2.2]. The most prevalent complaints included nasal congestion (63.1%), post-nasal drip (34.2%), rhinorrhea (21.1%) and facial pain/pressure (13.2%). In most cases, the severity of these symptoms ranged from 1 to 3 points, corresponding to a moderate impact on quality of life. All patients reported olfactory impairment, of which 31.6% rated it at 5 points, 52.6% at 4 points, and 15.8 % at 3 points, indicating a significant impact on quality of life.

According to the questionnaire results, the mean SNOT-22 score for patients in Group 2 was [74.8±2.4]. The most prevalent complaints were nasal congestion (100.0%), nasal discharge (64.1%), post-nasal drip (26.4%), and facial pain/pressure (15.1%), with the severity of these symptoms ranging from 3 to 5 points. Olfactory impairment was reported by all patients, with severity scores varying between 3 and 4 points, corresponding to a moderate impact on quality of life.

In Group 3, the mean SNOT-22 score was [68.6±1.9] points. All patients reported nasal congestion, while 52.1% of individuals experienced nasal discharge, 33.3% had post-nasal drip, and 10.4% reported facial pain/pressure. The severity of these symptoms ranged from 2 to 4 points, indicating a moderate impact on quality of life. The majority of patients rated their olfactory impairment at 2 points (62.5 %), while 37.5 % rated it at 3 points.

In Group 4, the mean score according to the questionnaire was [81.3±2.7]. The most prevalent complaints included nasal congestion (100.0%), nasal discharge (72.7%), post-nasal drip (31.8%), and facial pain/pressure (18.2%), with the severity of these symptoms ranging from 3 to 5 points. Olfactory impairment was observed in all patients, with severity scores varying from 3 to 5 points.

Endoscopic examination of the nasal cavity revealed hyperemia and edema of the nasal mucosa, along with minor mucous discharge. Obstruction of the olfactory cleft was observed in 2 patients (5.3%) in Group 1 (partial obstruction), 19 patients (35.8%) in Group 2, 13 patients (27.0%) in Group 3, and 15 patients (34.1%) in Group 4. In cases where endoscopic visualization of the olfactory cleft was not possible, computed tomography was performed.

Rhinomanometry results revealed an increase in aerodynamic nasal resistance across all patients. In Group 1, the mean aerodynamic resistance coefficient was [1.9±0.4] kPa·s/L. In Group 2, the aerodynamic resistance was in the range of [3.1± ±0.4] kPa·s/L. In Group 3, the value was [2.2±0.4] kPa·s/L, while in the fourth Group, the aerodynamic resistance was in the range of [3.6±0.5] kPa·s/L.

According to the olfactometric assessment in Group 1 following COVID-19, anosmia was identified in 12 patients (31.6 %) based on both the threshold test (mean score [0.9±0.5]) and the identification test (mean score [5.0±1.2]). Hyposmia

was observed in 26 patients (68.4 %), with mean threshold test scores of [4.1±0.9] points and identification test scores of [8.2±1.3] points.

All patients in Group 2 demonstrated hyposmia at a level of [4.1±1.3] points according to olfactometric threshold testing. The identification test revealed hyposmia in 48.3 % of patients, with a mean score of [10.3±1.3] points, while normosmia was observed in 51.7% of patients with a mean score of [11.8±1.7] points.

Olfactometric examination of patients in Group 3 revealed a mild degree of olfactory impairment on the threshold test in all patients, with a mean score of [5.6±2.2]. On the identification test, the majority of patients (81.3%) demonstrated normosmia, while hyposmia was observed in 18.7% of individuals, with a mean score of [10.2±1.2] points.

Olfactometry results for Group 4 revealed hyposmia according to the threshold test, with a mean score of [3.4±2.4] points. The identification test showed moderate hyposmia in 62.7 % of patients, with a score of [9.3±1.4] points, while normosmia was observed in 37.2 % of individuals.

The treatment effectiveness in the study groups was evaluated based on follow-up instrumental examinations and the assessment of subjective symptoms using the SNOT-22 questionnaire (*Table*).

in all patients and were rated at 5 points in 31.6%, at 4 points in 50.0%, and at 3 points in 18.4%. These findings were confirmed by objective assessments. Specifically, rhinomanometry demonstrated a statistically significant reduction in the nasal resistance coefficient, which decreased to [0.8±0.6] kPa·s/L. In contrast, no statistically significant difference was observed between pre- and post-treatment olfactometric results (p=0.33), and a severe degree of olfactory loss persisted in the form of anosmia and hyposmia.

Patients in Group 2 also demonstrated a positive therapeutic effect. According to the questionnaire findings, the majority of patients reported improvement in nasal breathing (69.8%) and a reduction in nasal discharge (88.6%). Overall, symptom severity was rated at 3 points. Complaints of olfactory impairment persisted in all patients; however, 43.3 % reported some degree of improvement. The mean SNOT-22 score was [45.4±1.8] points. Rhinomanometric findings indicated a statistically significant reduction in the nasal resistance coefficient to [2.1±0.6] kPa·s/L, although it remained moderately elevated. Olfactometric assessment demonstrated a significant improvement in olfactory function, particularly on the identification test, which reached normal values ([11.1±2.4] points). Nevertheless, hyposmia

Table. Comparison of examination results before and after treatment in the studied groups

Parameter	Group 1		Group 2		Group 3		Group 4	
	Before	After	Before	After	Before	After	Before	After
SNOT-22	61.4±2.2	34.5±2.3	74.8±2.4	45.4±1.8	68.6±1.9	37.3±1.5	81,3±2.7	49.6±1.7
	p<0.001		p<0.001		p<0.001		p<0.001	
Rhinomanometry	1.9±0.4	0.8± 0.6	3.1±0.4	2.1±0.6	2.2±0.4	1.9±0.4	3.6±0.5	2.4±0.7
	p<0.05		p<0.05		p<0.05		p<0.05	
Olfactometry	0.9±0.5* 5.0±1.2**	1.0±0.8* 5.5±1.4**	4.1±1.3* 10.3±1.3**	5.3±1.6* 11.1±2.4**	5.6± 2.2* 10.2±1.2**	6.4±2.1* 11.0±2.2**	3.4± 2.4* 9.3±1.4**	4.7± 0.9* 10.7±1.7**
	p=0.33		p=0.001		p<0.005		p<0.001	

*Notes: * – threshold test; ** – identification test.*

After the course of symptomatic therapy the patients in Group 1 demonstrated a positive dynamics according to questionnaire results, with a mean score of [34.5±2.3] points. The patients reported a reduction in both the number and severity of symptoms. Nasal obstruction persisted in 7 individuals (18.4%) and was rated at 2 points. However, complaints of olfactory impairment persisted

persisted on the threshold test in the majority of patients ([5.3±1.6] points).

In patients of group 3, SNOT-22 scores improved significantly, primarily due to a reduction in nasal obstruction and nasal discharge. Overall, symptoms were rated by patients at 2 (43.7%) or 3 points (56.3%). Olfactory function was assessed at 2 points in 71.7% of patients and at 3 points in

28.3%. The mean SNOT-22 score was [37.3±1.5] points.

Rhinomanometric evaluation demonstrated a statistically significant decrease in the nasal resistance coefficient to [1.9±0.4] kPa·s/L, although it remained moderately elevated. Olfactometric testing also showed a significant improvement in both the threshold test ([6.4±2.1] points) and the identification test ([11.0±2.2] points), indicating a mild degree of dysosmia.

Treatment effectiveness was also observed in patients of Group 4. Questionnaire findings indicated a reduction in the severity of subjective complaints, particularly nasal obstruction (70.5%) and nasal discharge (79.5%), which was generally rated at 4 points. Complaints of olfactory impairment persisted; however, the severity of their impact decreased and was rated at 3 to 4 points. The mean SNOT-22 score was [49.6±1.7] points. Rhinomanometric assessment showed that the nasal resistance coefficient remained moderately elevated at [2.4±0.7] kPa·s/L, but a statistically significant improvement after treatment was observed ($p<0.05$). Olfactometric evaluation demonstrated a significant improvement in olfactory parameters; however, values remained reduced on both the threshold test ([4.7±0.9] points) and the identification test ([10.7±1.7] points).

Discussion

The administered symptomatic treatment aimed at reducing mucosal edema demonstrated effectiveness across all study groups. This is confirmed by a reduction in subjective symptoms by more than 1.6 times and 1.5 times decrease in nasal resistance within the examined groups. It should be noted that, despite the significant improvement, patients in groups 2, 3, and 4 maintained a relatively high nasal resistance coefficient, which is attributed to impaired nasal cavity architectonics. In the majority of patients, olfactory impairment was more pronounced in the threshold test than in the identification test, which may further indicate the presence of mechanical obstructions preventing odorant vectors from binding to olfactory receptors. However, patients in group 1 continued to exhibit significant olfactory loss in the form of anosmia and hyposmia, suggesting a perceptual (sensorineural) mechanism of olfactory dysfunction caused by COVID-19.

The study demonstrated that the development of olfactory dysfunction depends on the etiology of the disease. Furthermore, the research proves that dysosmias of various etiologies should not be considered a single pathophysiological phenomenon, but rather the result of two fundamentally different mechanisms: conductive (mechanical-obstructive) and sensorineural (neuroepithelial-destructive), each of which requires a specific strategy in the choice of treatment. In the conductive type of dysosmia, the olfactory epithelium remains morphologically intact and functionally preserved; the pathology lies in the creation of a barrier preventing odorant access to the receptor zone due to edema, hypersecretion, or anatomical abnormalities. In such cases, anti-inflammatory therapy aimed at resolving the obstruction is pathogenetically justified and highly effective; however, structural changes in the architectonics of intranasal structures necessitate the use of methods alternative to therapeutic intervention. In this regard, surgical planning utilizing computerized virtual analysis of aerodynamic changes in the nasal cavity and paranasal sinuses would be the most appropriate approach [19]. In contrast, in the sensorineural type characteristic of virus-induced dysosmias, the primary lesion is localized directly within the olfactory apparatus at the level of cellular destruction of sustentacular cells and impairment of the regenerative potential of basal cells. This renders anti-inflammatory therapy pathophysiologically insufficient, as irrigation and corticosteroids lack regenerative properties and are unable to restore the damaged epithelium [20]. In such cases, a fundamentally different strategy, namely neurorehabilitation through olfactory training aimed at stimulating epithelial regeneration and central neuroplasticity, is required. Accordingly, the mismatch between the underlying pathophysiological mechanism and the therapeutic approach explains the high rate of treatment failure observed with conventional anti-inflammatory therapies in post-viral dysosmias and underscores the necessity of mandatory clinical phenotyping of dysosmias prior to therapy selection.

Conclusions

1. The choice of treatment method for patients with olfactory dysfunction should be considered based on the disease origin, with particular focus on the mechanical-obstructive and sensorineural mechanisms of its development.

2. Conservative therapy contributed to a more rapid regression of both subjective and objective manifestations of the inflammatory response, which was accompanied by a reduction in mucosal edema and improvement in aerodynamic parameters across all studied clinical groups. Therefore, the outcomes of conservative symptomatic treatment may be regarded as highly favorable. Ho-

wever, in patients of clinical groups 2, 3, and 4, elevated olfactory perception thresholds persisted despite subjective and objective reduction of edema. This likely indicates the need for additional therapeutic approaches, including surgical correction of intranasal structures.

3. In patients of group 1, a mixed type of olfactory dysfunction was observed; therefore, complete recovery of olfactory function after resolution of mucosal edema cannot be expected. Consequently, further management in these patients should include therapeutic approaches aimed at restoring receptor mechanisms of olfaction, in particular neurorehabilitation through olfactory training.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Shushliapina N.O.	+	+	+		+	+
Kalashnyk-Vakulenko Y.M.	+	+	+		+	+
Bondarenko Y.D.				+	+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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EFFICACY OF MINIMALLY INVASIVE POSTERIOR INTERBODY STABILIZATION WITH DISTRACTION CAGES IN LUMBAR SPONDYLOLISTHESIS

Stognii A., Piatykop V.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Degenerative Lumbar Spondylolisthesis (DLS) is a prevalent cause of neurogenic symptoms in older adults and is frequently managed surgically when conservative therapy fails. Comparative effectiveness of decompression and fusion strategies in DLS remain debated in contemporary evidence.

Aim. To evaluate the clinical efficacy and biomechanical rationale of the proprietary MIS-PLIF technique using distraction cages in patients with degenerative lumbar spondylolisthesis.

Materials and Methods. Pre-clinical FEA was provided in a detailed three-dimensional lumbosacral model (L3–S1). Clinical study was as a prospective, controlled, single-center interventional enrolling 24 patients with symptomatic DLS (median age 56 years; 18 females and 6 males; median body mass index 32 kg/m²). Patients of the main group were treated with the proprietary MIS-PLIF distraction-cage method, of comparison group – with standard MIS-PLIF using static cages, and a control group managed with alternative interbody fusion strategies. Non-parametric statistical testing was used at $p<0.05$. The research was conducted as a private initiative of the authors, did not receive funding from grant programs.

Research Ethics. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the institutional ethics committee (Protocol No.7 of October 10, 2017).

Results. In the clinical stage, the main group (n=5) treated with the proprietary MIS-PLIF technique exhibited significantly lower operative trauma: median blood loss was 100 mL compared to 500 mL in the control group ($p<0.05$). Operative time was reduced by half, reaching 180 min versus 360 min in open surgical approaches ($p<0.05$). Early clinical outcomes in the main group included a more pronounced reduction in pain intensity (VAS median decrease of 4 points) and improved functional status (ODI median improvement of 10 points). Radiographic assessment confirmed the method's superiority in restoring intervertebral disc height (median +10 mm) and effective correction of sagittal alignment parameters (SVA, PT, SS), facilitating accelerated patient recovery.

Conclusions. The tested MIS-PLIF technique using an expandable distraction cage appears feasible and clinically advantageous in early outcomes, providing a coherent biomechanical and medical rationale.

Keywords: *segmental lordosis restoration, spinal-pelvic balance, distraction cage biomechanics, sagittal alignment correction, postoperative neurological recovery, minimally invasive posterior lumbar interbody fusion clinical outcomes.*

Introduction

Degenerative Lumbar Spondylolisthesis (DLS) is one of the most urgent and complex problems of modern spinal surgery [1–5]. In cases of ineffective conservative treatment, extensive open surgical interventions have traditionally been used [6; 7]. However, in recent years, there has been a significant breakthrough due to the introduction of minimally invasive technologies that have radically changed approaches to the treatment of DLS, allowing for shorter hospitalization times and improved patient recovery [8–15].

Among minimally invasive interventions, special attention is paid to Minimally Invasive Surgery Posterior Lumbar Interbody Fusion (MIS-PLIF), in particular with the use of distraction cages, a promising approach that ensures minimal invasiveness and preservation of anatomical structures [16–20].

Corresponding Author:
Stognii Artem V. – Assistant of the Department of Neurology with a Course in Neurosurgery of the Kharkiv National Medical University, Ukraine.
✉ 4, Nauky Ave., Kharkiv, 61022, Ukraine.
E-mail: astognii@gmail.com

The need for further development of such techniques has increased significantly in the context of a full-scale war in Ukraine and other global crises, which, in addition to DLS of degenerative etiology, increase the frequency and severity of spinal injuries, including DLS [21–28].

Complicated logistical conditions, limited access to medical devices, and the need for operational efficiency necessitate the choice of technologies that allow achieving a therapeutic result with less resource use. In this context, the development and implementation of effective minimally invasive techniques, such as posterior interbody stabilization with distraction cages, is of not only medical but also socioeconomic strategic importance.

Today, surgeons from different countries are actively working to improve the methods of interbody stabilization for PS, in particular, posterior minimally invasive fixation [29]. Despite the good results of traditional and minimally invasive posterior approaches in achieving fusion, as well as a low complication rate, they are limited by the risks of iatrogenic damage to nerve structures and paravertebral muscles. Alternative options – anterior and lateral approaches – have their own anatomical and clinical advantages, but are associated with the risk of complications from the blood vessels, abdominal cavity or nerve plexuses [30].

Thus, the search for existing methods and implementation of new, more effective options for surgical treatment of DLS, in particular, using MIS-PLIF with distraction cages, is an urgent and reasonable task of modern medicine.

The present study is a continuation of our previous efforts [31, 32]. The previous stages of the study included the investigation of spinal biometric parameters and the dynamics of neurological disorders before and after surgical treatment with the traditional method; the study of restoration of spinal biometric parameters using distraction cages using a biomechanical model; analysis of the stress-strain system "transpedicular structure – spinal motor segment – distraction cage"; development of our own MIS-PLIF with distraction cages [31; 32].

Our pre-clinical study [31], conducted at Sytenko Institute of Spine and Joint Pathology, utilized a highly detailed 3D model of the lumbosacral spine (L3–S1) anchored to the pelvis. The choice of the L3–S1 segment is mechanically significant. The L5–S1 junction represents the "keystone" of the spine, transitioning load from the flexible lumbar column to the rigid sacral base. In spondylolisthesis, this segment is subjected to extreme anterior shear forces. The model incorporated vertebral geometry (differentiating between the stiff cortical shell with Young's Modulus E=12,000 MPa and the spongy cancellous core, E=100 MPa); intervertebral discs (modeled as composite structures, E=4.2 MPa); fixation hardware (modeling transpedicular screws and rods made of medical-grade steel, E=210,000 MPa).

A Finite Element Analysis (FEA) simulated a posterior spondylodesis at the L4–S1 level (fusion) under a vertical load of 422 N applied to L3, representing the weight of the upper body in a standing 700 N individual. Two distinct implant scenarios were subsequently compared. Scenario A (control) – L5–S1 interbody fusion using a standard PEEK cage (E=2,200 MPa), PEEK is currently the industry standard due to its radiolucency and modulus of elasticity similar to bone. Scenario B (experimental) – L5–S1 interbody fusion using the new distraction cage; this device is metallic, possessing a much higher stiffness and expansion capability.

The results of the FEA provided a critical biomechanical rationale for the distraction cage, challenging the conventional opinion regarding implant stiffness.

In the intact (normal) model, the stress on the inferior surface of the L5 vertebra was approximately 14.8 MPa. Following instrumentation, both the PEEK and Distraction Cage models saw this stress spike to ~40 MPa (40.2 MPa vs. 40.7 MPa). This finding confirms that rigid fixation inevitably concentrates stress at the fused level, necessitating robust endplates to prevent subsidence. The similarity between the two groups suggests that the *cage material* does not significantly alter the axial load seen by the vertebral body itself; rather, the *fixation construct* dictates this.

However, the stress distribution above the fusion (L3, L4) remained near normal levels (4.9–6.6 MPa) for both groups. This indicates that, in the short term (static loading), neither construct immediately alters the biomechanics of the adjacent segments, a positive finding for the prevention of Adjacent Segment Disease (ASD).

The most clinically relevant finding emerged at the S1 screw-bone interface. S1 pedicle screws are prone to loosening because the sacral alae are cancellous and the lever arm from the lumbar spine is long. High stress at the screw entry point is a primary predictor of toggle and pullout. In PEEK model the stress at the S1 screw entry was 27.3 MPa. In new distraction cage model the stress was reduced to 17.8 MPa.

The PEEK cage, being relatively compliant (E=2,200 MPa), deforms under the 422 N load. This deformation forces the rigid posterior rods and screws to carry a larger proportion of the load to maintain stability. The screws effectively become the primary load-bearing elements, leading to high interface stress.

In contrast, the new distraction cage is stiff and does not deform significantly. It acts as a rigid anterior column pillar, absorbing the compressive load directly. By preventing anterior column settling, it partially absorbs the excessive toggle forces on the posterior screws. The hypothesis of load transfer is confirmed by comparing the internal stresses of the cages themselves: PEEK cage stress 35.7 MPa; distraction cage stress 113.3 MPa.

The distraction cage carries more load than the PEEK cage. While 113.3 MPa is a high stress value, it is well within the yield strength of titanium alloys (typically >800 MPa) or surgical steel. By bearing this massive load, the distraction cage relieves force load on the posterior hardware – specifically the S1 screws (58.0 MPa in PEEK vs. 49.0 MPa in new distraction cage) and the L5 rods (80.8 MPa in PEEK vs. 72.2 MPa in new distraction cage).

The FEA study substantiates the mechanical superiority of the distraction cage for posterior stabilization. This can be a modification factor in spondylolisthesis patients, who often have compromised bone quality, which could cause screw long-term stability failure.

Previous finite element modeling and earlier radiographic observations related to the developed distraction-cage technique were published separately and are cited here as methodological background [31, 32]. The present manuscript reports the clinical comparative stage of testing the method and does not present those previously published findings as new primary results.

Aim of the study was to evaluate the clinical efficacy and biomechanical rationale of the proprietary MIS-PLIF technique using distraction cages in patients with degenerative lumbar spondylolisthesis.

Material and Methods

The study enrolled 24 patients, of them 18 females (75%) and 6 males (25%), diagnosed with degenerative lumbar spondylolisthesis. The demographic profile of the cohort was stated accordingly: main group 4 to 1 female to male ratio, comparison group – 8 to 3, and 6 to 2 ratio for control group. This skew reflects the known epidemiology of DLS, where hormonal factors and pelvic geometry predispose women to L4–L5 slips. Median age was 56 years. The inclusion of younger patients (32 years) represents some cases of isthmic spondylolisthesis or early-onset degeneration, though the focus remained on degenerative pathology. Body Mass Index (BMI) median was 32 kg/m². Obesity increases the anterior shear force on the lumbar spine, exacerbating the slip and increasing the mechanical demand on any surgical implant.

Selection criteria were applied to ensure internal validity: inclusion – symptomatic DLS with neurogenic claudication, radiculopathy (paresis grade [3–4]), or segmental sensory deficit; failure of conservative therapy; age [32–68]; exclusion – age >75 years (due to poor bone quality confounding screw fixation), severe somatic comorbidity, complete plegia (requiring different urgency), or minimal symptoms not warranting fusion.

To isolate the effect of the distraction cage method, the patients were divided into three groups. Main group (n=5) included the patients treated with the author's proposed method of MIS-PLIF using distraction cages. Comparison group (n=11) consisted of the patients treated with standard PLIF method with reduction using conventional static cages (PEEK or titanium). The controls (n=8) were the patients treated with the method, which included non-minimally-invasive posterior fusion with decompression but without reduction of spondylolisthesis, also serving as a baseline for surgical trauma comparison. The main group was small (n=5), reflecting the "probation" of a new medical device trial; the comparison against a larger pool of controls (n=19 total) allowed for statistically valid non-parametric analysis ($p<0.05$).

The main outcomes of the present clinical stage were operative time, intraoperative blood loss, postoperative pain intensity, disability dynamics, duration of hospitalization, and time to completion of rehabilitation. Completion of rehabilitation was defined as the patient’s ability to return to work and to the level of functioning present before the disease.

Pain intensity by VAS and disability by ODI were assessed in the postoperative period on day 3. These measures were recorded during joint assessment by the patient and the operating surgeon. Independent blinded assessment was not used. Paraspinal muscle atrophy had been assessed by MRI at 6 months.

Statistical analysis. The normality of data distribution was assessed by the Shapiro-Wilk test.

Since the data distribution in most parameters and groups differed from normal, nonparametric methods of statistical analysis were used. The main tendency was described using the median (Me), the variability – with the definition of the lower (LQ) and upper (UQ) quartiles. The median values of study groups were compared using the Kruskal-Wallis test. The reliability of paired intergroup differences was assessed using the post-hoc Mann-Whitney test with Bonferroni adjustment. Comparison of indicators frequency (absolute and relative) was carried out using the Fisher exact method.

Research Ethics

The study adhered to the World Medical Association Declaration of Helsinki (1964–2024) and was approved by the Ethics and Bioethics Commission of Kharkiv National Medical University (Protocol No.7 dated October 10, 2017). All patients signed informed consent for surgical treatment and for participation in the study, including the use of anonymized clinical data.

Results

Using a distraction cage and MIS PLIF approach [32] integrates this device into a strict MIS protocol. The patients were placed in a prone position on a radiolucent table. Paramedian incisions (Wiltse approach) were used. Retraction was achieved by installation of tubular retractors. Crucially, this approach *splits* the muscle fibers rather than detaching them from the spinous processes. Decompression – unilateral facetectomy and hemilaminectomy to access the disc and decompress the nerve root. Preparation – radical discectomy and endplate preparation to expose bleeding bone (essential for fusion). Stabilization – insertion of the distraction cage and activation of the expansion mechanism under fluoroscopic guidance. To decompress nerve root, unilateral facetectomy was performed, with subsequent discectomy and endplate preparation to expose bleeding bone (essential for fusion). Then interbody cage was inserted and *in situ* distraction performed. This was followed by transtubular pedicle screw fixation.

This technique differed from the control group (open PLIF), which required midline incision and extensive subperiosteal muscle stripping, and formed the comparison group, where significant part of the vertebral canal was exposed.

The intraoperative data provides compelling evidence for the efficiency of the new method (*Table 1*).

The main group's operative time, 180 minutes (min.) was half that of the control group (360 [240; 480] min).

Blood loss in the main group was about 100 ml [100]. Compared to the 500 [400; 600] ml loss in the control group, thus reducing the modifying factors which can influence on the risks of the need for transfusions and postoperative hematoma.

The safety profile of the distraction cage method was adequate regarding soft tissue preservation (*Table 2*).

The study evaluated the "functional state" of the spine through biomechanical parameters. Disc height restoration in main group was +10 [9; 11] mm; in comparison group: +8 [5; 9] mm; in control group +9 [7; 10] mm. The distraction cage achieved the greater median height restoration.

Patient-Reported Outcome Measures (PROMs) were as follows. By Visual Analogue Scale (VAS) in pain evaluation the main group saw a median reduction of 4 points (e.g., from 8 to 4); comparison group dropped by 3 points; control group by 2 points. The difference was statistically significant ($p<0.05$).

As for the disability data, Oswestry Disability Index (ODI) in the main group improved by 10 points (median), while the control group showed a larger raw change (18 points), this is likely an artifact of higher baseline disability in the open surgery group. The main group achieved excellent absolute outcomes.

Table 1. Operative parameters in patients with lumbar spondylolisthesis

Parameter	Main group (n=5)	Comparison group (n=11)	Control group (n=8)	Statistical significance
Operation time (minutes)	180 [180; 180]	180 [160; 210]	360 [240; 480]	p<0.05 (main vs control)
Blood loss (ml)	100 [100; 100]	200 [200; 300]	500 [400; 600]	p<0.05 (main vs all)
Hospital stay (days)	13 [11; 18]	9 [7; 12]	11 [6; 22]	–

Table 2. Postoperative complications in patients with lumbar spondylolisthesis

Complication	Main group (n=5)	Comparison group (n=11)	Control group (n=8)	Insight
Muscle Atrophy	–	11/11 (100%)	4/8 (50%)	Complete preservation of paraspinal muscles in main group
Hemorrhage	–	3/11 (27%)	1/8 (13%)	Superior hemostasis with new method
Cerebrospinal fluid leak	–	1/11 (9%)	–	Safe dural handling
Radiculitis	1/5 (20%)	3/11 (27%)	1/8 (13%)	Comparable nerve irritation rates

In sagittal balance, the study noted effective restoration of segmental lordosis, pelvic tilt (PT), and sacral slope (SS). Correction of these spinopelvic parameters is essential for energy-efficient standing and walking. The reduction of the sagittal vertical axis (SVA) indicates an improvement in global spinal alignment.

Discussion

The FEA shows that in a posterior fixation construct, a soft cage transfers stress to the screws (58 MPa at S1). By using a stiff, expandable metal cage, the implant takes the load (113 MPa), sparing the screws (17 MPa). The distraction cage forms anterior load column, while the screws act as a posterior fixation line.

The distraction cage, inserted collapsed, requires a smaller footprint and less manipulation time (180 min operation time). Preserving the muscle envelope reduces postoperative pain (VAS – 4) and maintains the spine's dynamic stabilizers, potentially reducing the rate of Adjacent Segment Pathology (ASP) in the long term.

Based on the current evidence, MIS posterior interbody fusion with expandable cages represents a viable and feasible treatment option for appropriately selected patients with lumbar spondylolisthesis. It offers improvement in clinical symptoms and propones restoration of disc and foraminal height.

The research initiated by us on the proprietary MIS-PLIF method using distraction cages was situated within evolving landscape. The approach, incorporating upfront biomechanical modeling to address key parameters such as sagittal alignment and stress distribution, is desirable given the need for long term observation and retrospective studies. Future validation through larger, rigorous clinical trials comparing established standard-of-care MIS procedures and MIS PLIF with expandable cages is essential to demonstrate any tangible benefits in efficacy, safety, and alignment maintenance.

A statistically significant reduction in pain was achieved in the main group: by 4 points on the VAS scale, which is a statistically significant result compared to 3 points in the comparison group and 2 points in the control group. Similar results were reported by Lu V.M. et al. (2017) [10], who noted that patients after MIS-TLIF had significantly lower pain intensity in the early postoperative period. Also, Arts M.P. et al. (2017) [8] showed that, compared to open interventions, MIS techniques contribute to an accelerated reduction in pain.

The peculiarities of functional recovery according to the ODI were revealed: patients in the main group showed a decrease of 10 points, which exceeded similar indicators in other groups. According to Hammad A. et al. (2019) [9], a similar decrease of [8–10] ODI points after MIS-TLIF correlates with a significant improvement in patients' daily activities.

The key parameter of postoperative stability was the intervertebral space. In the group with distraction cages, its restoration was 10 mm, which is higher than the value in the comparison group (8 mm) and is fully consistent with the results of Wu Y. et al. (2024) [15], which noted that adequate expansion of the intervertebral space significantly reduces the risk of secondary neurocompression.

The sagittal balance assessment showed that the proposed technique allows optimizing the parameters of sacral and pelvic tilt and Sagittal Vertical Axis (SVA) index, bringing them closer to physiological norms. This corresponds to the data of simulations conducted at Sytenko Institute of Spine and Joint Pathology, which demonstrated an

improvement in balance due to the use of distraction cages with the possibility of intraoperative reduction [31].

In addition to clinical advantages, the proposed technique showed a reduction in the duration of the operation (180 minutes) compared to 360 minutes in the control group ($p<0.05$). Similar time savings were noted in the publications of Yang Y. et al. (2018) [12], which indicated that MIS-TLIF halved the duration of the intervention compared to open methods. The reduction in operative time is directly related to less blood loss, which in this study was only 100 ml versus [200–500] ml in other groups. According to Lu V.M. et al. (2017) [10], the amount of blood loss is a determining factor in the prognosis of the postoperative course.

The absence of complications in patients of the main group, in particular, atrophy of paravertebral muscles, cerebrospinal fluid leaks, and infections, is an extremely important indicator of the safety of the technique. Comparing this with the literature data (Mobbs R.J. et al. (2015) [30]), it can be argued that the proposed method reduces the incidence of the most common postoperative complications. Thus, the incidence of radiculitis with root dysfunction in the main group was only 25%, while in the comparison group – 30%, and in the control group – 50%.

Thus, the clinical testing of the Expandable MIS-PLIF method using distraction cages showed desirable clinical outcomes in both the short and medium term. In combination with the data from the world literature, our findings confirm the feasibility of further implementation of this method in surgical practice, especially in the context of increased requirements for the effectiveness and safety of surgical interventions.

Limitations. Sample Size (n=5 in the main group) is small, suitable for a "probation" study but requiring expansion for high-power statistical certainty and low statistical representability. As there was no single blinded assessment, thus the study has higher bias risks. Follow-up, long-term data (2+ years) on fusion rates and potential late subsidence, is needed, although the FEA predicts low subsidence risk due to load distribution.

Conclusions

1. Clinical testing of the proprietary MIS-PLIF technique with distraction cages confirmed its capability for effective listhesis reduction and restoration of intervertebral height (median +10 mm, $p<0.05$), facilitating the correction of sagittal alignment parameters (SVA, PT, SS) toward physiological values.

2. The use of a minimally invasive approach combined with expandable implants significantly reduces surgical trauma: intraoperative blood loss is limited to 100 mL (compared to 500 mL in open surgery), and operative time is reduced to 180 min ($p<0.05$), ensuring a favorable safety profile and minimal postoperative complications.

3. Preliminary outcomes indicate high functional efficiency of the method, with a 4-point reduction in VAS pain scores and a 10-point improvement in the ODI index. These findings support the feasibility of the technique for wider clinical application, especially in resource-constrained healthcare environments.

Prospects for further research are to continue the study of the clinical effectiveness of the developed method of minimally invasive posterior interbody fusion of the lumbar spine using distraction cages in patients with lumbar spondylolisthesis.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Stognii A.	+	+	+	+		+
Piatykop V.	+				+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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PECULIARITIES OF IMMUNOLOGICAL DISORDERS AND THE DEVELOPMENT OF COMPLICATIONS IN PATIENTS WITH UVEITIS OF TUBERCULOUS ETIOLOGY

Panchenko M.V., Honchar O.M., Panchenko H.Y., Kitchenko I.V.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Tuberculosis is an infectious disease that can severely affect the visual system, presenting with a broad spectrum of clinical manifestations, including various forms of uveitis. The role of the immune response in tuberculous uveitis is currently receiving increased attention regarding its diagnostic, therapeutic implications, and contribution to the development of ocular complications.

Aim. To investigate the peculiarities of immunological disorders and the development of complications in patients with uveitis of tuberculous etiology.

Materials and Methods. We studied clinical features, disease progression, and immunological parameters in 39 patients (60 eyes; aged [28–87] years; 13 men, 26 women) with relapsing tuberculous uveitis and pulmonary tuberculosis (disease duration [3–32] years). Standard ophthalmological and immunological examinations (first- and second-level tests) were performed. The control groups included 61 patients (98 eyes) with non-tuberculous uveitis and 35 healthy individuals.

Research Ethics. The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (1964–2024) and was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University (Protocol No.5 of May 07, 2025). All patients provided written informed consent prior to participation.

Results. Complicated forms of tuberculous uveitis were identified in 49 eyes (81.7%). These were most frequently observed in generalized (100.0%) and anterior (95.2%) uveitis, while posterior uveitis was complicated in 58.3% of cases. The most common complications were uveal cataract (61.7%) and corneal involvement (46.6%). Immunological assessment revealed an immunodeficiency syndrome with a significant decrease in the number of T-lymphocytes, T-helper cells, and the helper/suppressor ratio ($p<0.05$) compared to the non-tuberculous group. Suppression of humoral immunity was also observed, manifested by a significantly greater decrease in the number of B-lymphocytes and immunoglobulin G concentration ($p<0.05$).

Conclusions. Tuberculous uveitis, compared to non-tuberculous etiology, is significantly more often complicated by uveal cataract, keratitis, and uveal glaucoma. Patients with tuberculous uveitis exhibit a significantly more pronounced decline in both cellular and humoral immunity parameters, demonstrating that endogenous immunosuppression plays a major role in the progression of complicated forms of uveitis.

Keywords: *ophtalmology, complicated forms of uveitis, T-lymphocytes, humoral immunity, ocular complications.*

Introduction

Tuberculosis remains a major global health threat; according to the World Health Organization, approximately 10.6 million people worldwide were living with this infectious disease in 2021 [2]. Caused by Mycobacterium tuberculosis [1], the infection can also severely affect the visual system. The proportion of uveitis cases attributed to tuberculosis varies widely depending on the region, ranging from [0.7–2.0] % up to 10.1% [3; 4].

Ocular involvement presents with a broad spectrum of clinical manifestations, including, but not limited to, anterior uveitis, intermediate uveitis, retinal vasculitis, posterior uveitis, scleritis, and optic neuropathy [5–8]. Despite advances in diagnostics, identifying and managing tuberculous uveitis remains challenging due to the varia-

Corresponding Author:
Panchenko Mykola V. – MD, Professor, DMedSc, Professor at the Department of Ophthalmology, Kharkiv National Medical University, Ukraine.
✉ 4, Nauky Ave., Kharkiv, 61022, Ukraine.
E-mail: panchenko0802@gmail.com

bility of the host's immune response. Currently, increasing attention is being paid to the immune response in tuberculous uveitis [9], both in terms of its diagnostic and therapeutic implications, as well as its role in the development of disease complications [10]. It is hypothesized that systemic depletion of immune resources, caused by the underlying tuberculous process, creates a foundation for the development of secondary immunodeficiency, which may significantly aggravate the course of uveitis. However, the exact patterns of cellular and humoral immunosuppression in these patients and their direct impact on ocular outcomes remain insufficiently studied.

The **aim** of this study was to investigate the peculiarities of immunological disorders and the development of complications in patients with uveitis of tuberculous etiology.

Materials and Methods

A prospective study was conducted involving a total of 135 individuals, who were divided into three distinct groups. Main Group (tuberculous uveitis) consisted of 39 patients (60 eyes) with uveitis of tuberculous etiology and concurrent pulmonary tuberculosis. Comparison Group (non-tuberculous uveitis) consisted of 61 patients (98 eyes) with uveitis of non-tuberculous etiology. Control Group consisted of 35 healthy individuals who provided baseline immunological values.

Main Group (tuberculous uveitis) included 13 men and 26 women aged 28 to 87 years. The duration of the disease ranged from 3 to 32 years, and all patients exhibited a relapsing course of uveitis. The etiology was established based on a comprehensive diagnostic approach that included positive intradermal and focal tuberculin tests, radiological findings of pulmonary tuberculosis, specific clinical ophthalmological signs, and a positive response to trial anti-tuberculosis therapy. Anatomically, the inflammatory process was localized in the anterior uvea in 21 eyes, in the posterior uvea in 24 eyes, and was generalized (panuveitis) in 15 eyes.

Comparison Group (non-tuberculous uveitis) was used to compare immunological disturbances and the frequency of complications. It consisted of 61 patients (98 eyes), where anterior uveitis was diagnosed in 41 eyes, posterior uveitis in 35 eyes, and generalized uveitis in 22 eyes. No statistically significant differences in anatomical distribution were observed between the main and comparison groups ($p>0.05$).

Healthy Control Group consisted of 35 healthy individuals matched for age and sex to provide reference ranges for the immunological parameters evaluated in the study.

Exclusion criteria were applied to ensure the accuracy of immunological data. Patients with systemic autoimmune diseases, HIV infection, other primary or secondary immunodeficiency states unrelated to tuberculosis, or those receiving systemic immunosuppressive therapy at the time of sampling were excluded.

Materials and Methods

All patients underwent standard ophthalmological examinations. Immunological evaluation involved first- and second-level diagnostic tests. The absolute and relative numbers of T and B lymphocytes, as well as T-lymphocyte subpopulations, were determined using indirect immunofluorescence with monoclonal antibodies [11; 12]. Quantitative determination of serum immunoglobulins (IgA, IgM, IgG) was performed by the Mancini G. (1965) radial immunodiffusion method [13], as modified by Fahey J.L. (1965) [14] and McKelvey E.M. (1973) [15].

Statistical processing of the results was performed using parametric statistics. The normality of data distribution for quantitative variables was assessed using the Shapiro-Wilk test. Because the data were normally distributed, parametric methods were chosen for further analysis. Descriptive statistics for quantitative data are presented as the mean and standard deviation (M±SD). To compare the mean values of quantitative parameters among three or more independent groups, a one-way analysis of variance (One-Way ANOVA) was applied. Post-hoc group comparisons were conducted using Tukey's Honestly Significant Difference (HSD) test. Differences were considered statistically significant at a level of $p<0.05$. Statistical analysis was carried out using the SPSS Statistics 27 (IBM, USA).

Research Ethics

The study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (1964–2024) and was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University (Protocol No.5 of May 07, 2025). All patients provided written informed consent prior to participation.

Results

To investigate the role of endogenous immunosuppression in the development of complicated forms of uveitis, we analyzed immune system disturbances and the frequency of complications of tuberculous uveitis (*Fig. 1*), occurring against the background of pulmonary tuberculosis.

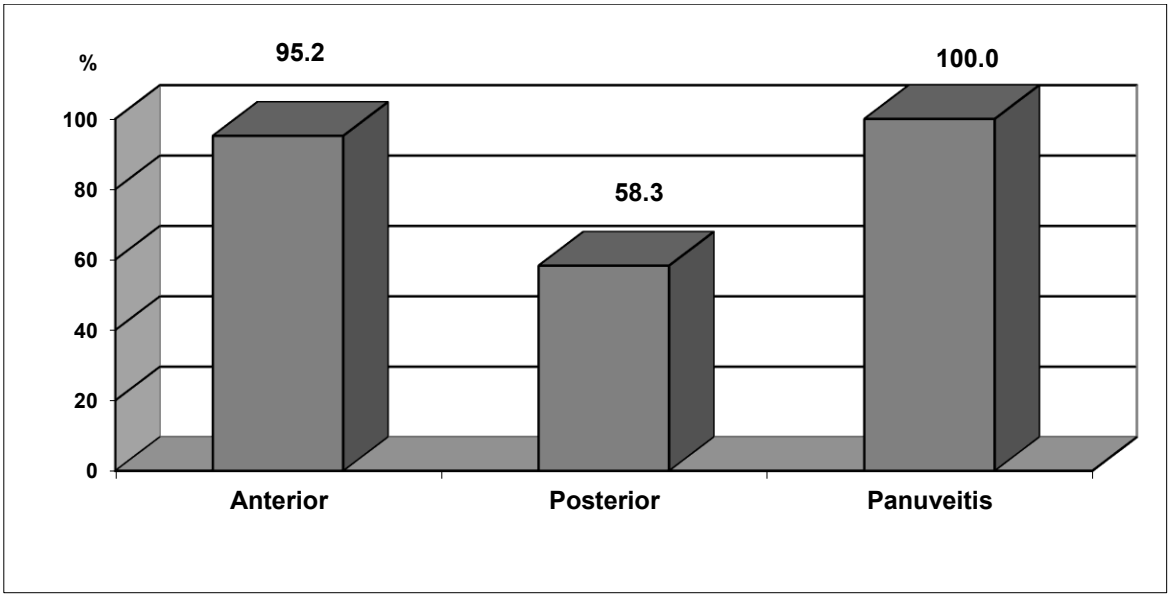

Fig. 1. Frequency of complicated forms of tuberculous uveitis depending on the anatomical localization of the inflammatory process.

Complicated forms of uveitis were identified in 49 eyes (81.7%). These were most frequently observed in generalized (100.0%) and anterior (95.2%) uveitis. In patients with posterior uveitis of tuberculous etiology, complications were noted in 58.3% of cases.

The most common complication of tuberculous uveitis was uveal cataract (61.7%). The disease presented as keratouveitis in 38.3% of cases, in 5 eyes (8.3%) the disease was complicated by corneal degeneration. Post-uveitic chorioretinal dystrophies were present in 17 eyes (28.3%), secondary uveal glaucoma in 13.3%, and iris atrophy in 13 eyes (21.7%). Uveitis was complicated by optic neuritis in 6 eyes (10%), by partial optic atrophy in 5 eyes (8.3%). Marked vitreous destruction and opacification were observed in 23 eyes (38.3%), while vitreous strands were noted in 4 eyes (6.7%).

Tuberculous uveitis was complicated by macular edema in 3 eyes (5%) and by subatrophy of the eyeball in 2 eyes (3.3%). Retinal detachment, ocular hypotony, central retinal vein thrombosis, and secondary strabismus were identified as rare complications, with one case (1.7%) reported for each.

In comparison with non-tuberculous uveitis (*Fig. 2*), tuberculous uveitis was significantly more often associated with uveal cataract (61.7% vs. 19.3%; $p<0.05$), keratitis (38.3% vs. 8.0%; $p<0.05$), and uveal glaucoma (13.3% vs. 2.4%; $p<0.05$).

The indicators of cellular and humoral immunity are presented in *Table 1* and *Table 2*.

It was established that patients with uveitis of tuberculous etiology exhibited a significantly more pronounced reduction in the number of T lymphocytes ($p<0.05$), T helper cells ($p<0.05$), and the helper/suppressor ratio ($p<0.05$).

In addition to cellular immunodeficiency, suppression of the humoral component of the immune system was also observed in these patients (Table 2), which manifested as a significantly greater decrease in the number of B lymphocytes ($p<0.05$) and in the concentration of immunoglobulin G ($p<0.05$).

Thus, the conducted research demonstrated that endogenous immunosuppression plays a significant role in the onset and progression of complicated forms of uveitis.

Discussion

The findings of our study highlight the complex clinical profile of tuberculous uveitis, particularly regarding its anatomical distribution and the high rate of associated complications. In our cohort, the posterior segment was the predominant site of inflammation (40%). This observation is consistent with the findings of numerous other researchers, who reported the proportion of posterior uveitis ranging from 38.89% to 83.3% [16–19].

However, literature data suggest that the anatomical localization of tuberculous uveitis varies significantly across different geographic regions and patient populations. For example, in a study

Table 1. Indicators of Cellular Immunity in Patients with Uveitis of Tuberculous and Non-Tuberculous Etiology

Study Groups		T-lymphocytes, cells/μL	T-helpers, cells/μL	T-suppressors, cells/μL	Immunoregulatory index
I. Tuberculous uveitis (n=39)		702±47	413±33	292±26	1.64±0.25
II. Non-tuberculous uveitis (n=61)		882±72	594±65	285±27	2.49±0.17
III. Healthy individuals (n=35)		1301±78	989±73	311±38	3.22±0.18
Significance of Differences, p	I–II	<0.05	<0.05	>0.05	<0.05
	II–III	<0.05	<0.05	>0.05	<0.05
	I–III	<0.05	<0.05	>0.05	<0.05

Table 2. Indicators of Humoral Immunity in Patients with Uveitis of Tuberculous and Non-Tuberculous Etiology

Study Groups		B-lymphocytes, cells/μL	Immunoglobulins, g/L		
			A	M	G
I. Tuberculous uveitis (n=39)		137.00±22.00	1.32±0.18	1.07±0.14	7.62±0.58
II. Non-tuberculous uveitis (n=61)		211.00±27.00	1.55±0.16	1.27±0.09	9.37±0.61
III. Healthy individuals (n=35)		218.00±32.00	1.58±0.13	1.21±0.10	9.31±0.53
Significance of Differences, p	I–II	>0.05	>0.05	>0.05	>0.05
	II–III	>0.05	>0.05	>0.05	>0.05
	I–III	<0.05	>0.05	>0.05	<0.05

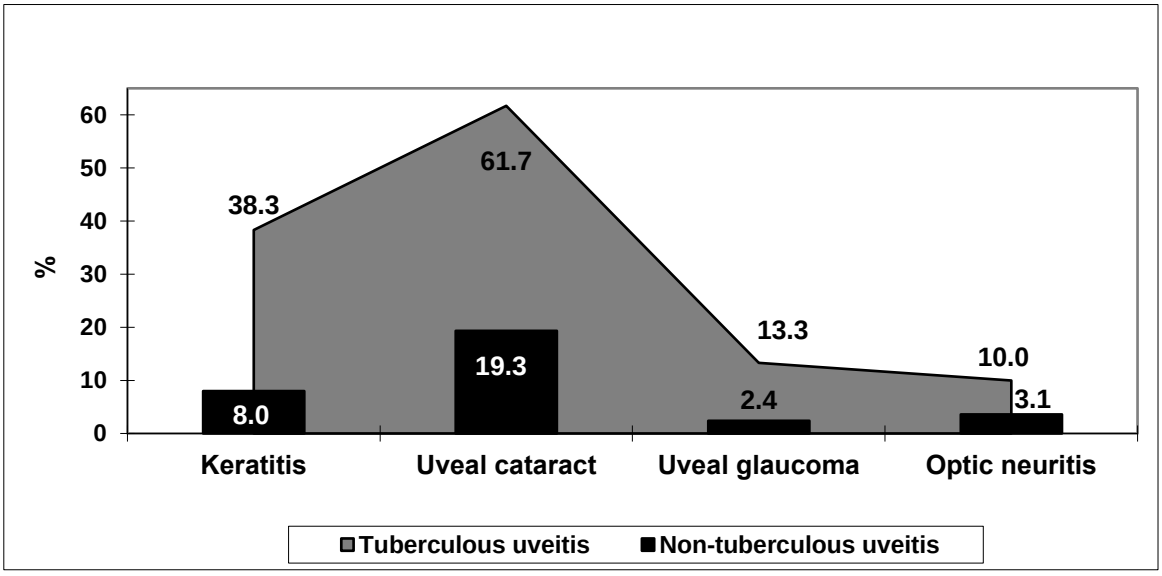

Fig. 2. Frequency of complications in tuberculous uveitis.

by Xie J. et al. (2023) [16], posterior segment involvement was the most common presentation among 84 eyes (83.3%), while anterior uveitis accounted for only 4.7% of cases, and panuveitis was observed in 11.9%. Similarly, Rahman H. et al. (2022) [21] reported that among patients with concurrent pulmonary tuberculosis, posterior uveitis was present in 69% of eyes, anterior uveitis in 23%, and panuveitis in 7%. Conversely, in a case series described by Tsui J.K. et al. (2023) [22], anterior uveitis was the predominant manifestation (50%). This variability underscores the heteroge-

neous nature of ocular tuberculosis, which may be influenced by systemic disease severity, host immune status, or regional strain differences.

A major clinical challenge in the management of tuberculous uveitis is the severe structural damage it inflicts on the eye. According to our findings, complications were observed in 81.7% of cases, which is in close agreement with the results of Tsui J.K. et al. (2023) [22], who reported uveitis-related complications in 70% of patients. Current literature indicates a wide variability in the frequency and types of tuberculous uveitis complications, including: macular edema – 8.2% to 44.1% [16; 18; 20; 23–26]; retinal ischemia – 36.9% [16]; cataract – 14.2% to 20.1% [20; 24–26]; subretinal neovascular membrane – 1.7% to 36.3% [16; 18; 20; 24; 26]; ocular hypertension and glaucoma – 3.3% to 30% [16; 20; 24–26]; vitreous hemorrhage – 16.3% to 21.3% [18; 25]; tractional retinal detachment – 3.3% to 15.5% [16; 25]; epiretinal membrane – 3.3% to 7.9% [24; 25]; retinal vein occlusion – 3.7% [24]; and optic nerve atrophy – 4.9% [25].

In our patient cohort, the most frequent complications were uveal cataract (61.7%) and corneal involvement (46.6%). Notably, the rate of uveal cataract in our study substantially exceeds the standard ranges reported in the literature [20; 24–26]. We hypothesize that this elevated frequency is intrinsically linked to the profound endogenous immunosuppression identified in our results. The inability of the compromised cellular and humoral immune systems to effectively clear the infection likely leads to a chronic, relapsing inflammatory state, resulting in severe collateral tissue damage. The destructive potential of this prolonged inflammation is further evidenced by the occurrence of severe, end-stage complications, such as subatrophy of the eyeball, which was noted in 3.3% of our cases.

Ultimately, the extensive anatomical damage and high complication rates associated with tuberculous uveitis indicate a critical need for improved early diagnosis and more targeted treatment strategies. Managing these patients requires addressing not only the infectious agent but also the underlying immune dysregulation.

A ***limitation*** of this study is the relatively small number of patients examined, highlighting the need for future large-scale studies to validate these mechanisms.

Conclusions

1. Uveal cataract (61.7%) and corneal involvement (46.6%) were identified as the most frequent and sight-threatening complications in patients with tuberculous uveitis.

2. Tuberculous etiology is a major risk factor for severe structural ocular damage; compared to non-tuberculous uveitis, it is significantly more likely to result in the development of uveal cataract, keratitis, and secondary uveal glaucoma.

3. Patients with tuberculous uveitis exhibit a profound secondary immunodeficiency, characterized by a significantly more pronounced depletion in both cellular (T-lymphocytes, T-helper cells) and humoral (B-lymphocytes, IgG) immunity parameters.

4. Endogenous immunosuppression plays a pivotal pathophysiological role in the onset and progression of complicated forms of tuberculous uveitis, indicating that effective management requires addressing not only the infectious agent but also the underlying systemic immune dysregulation.

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Declarations

Conflict of interest is absent.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Panchenko M.V.	+	+			+	+
Honchar O.M.			+	+		+
Panchenko H.Y.				+		+
Kitchenko I.V.			+		+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data; E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

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SUICIDAL RISK IN PEOPLE LIVING WITH HIV IN UKRAINE: THE ROLE OF DEPRESSION, ANXIETY, AND PSYCHOSOCIAL FACTORS

Cherevko O.[1], Kozhyna H.[2]

[1]Sumy State University, Sumy, Ukraine
[2]Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Suicidality remains a critical public health concern among People Living With Human immunodeficiency virus (PLWH). Psychological distress, including depression and anxiety, has been identified as a major predictor, but data from Eastern Europe remain limited.

Aim. To assess the relationship between depression, state anxiety, and suicidal risk among PLWH.

Materials and Methods. A cross-sectional study included 132 adult patients with confirmed human immunodeficiency virus infection who attended Sumy Regional Clinical Medical Center for Socially Dangerous Diseases. Exclusion criteria were pregnancy, active substance use disorder, current opioid substitution therapy, severe somatic condition, or inability to provide informed consent. Participants completed the Luban–Plozza Suicide Risk Scale, Beck Depression Inventory, State-Trait Anxiety Inventory – State Subscale, and Symptom Checklist-90-Revised. Demographic and clinical data, including CD4 count and clinical stage, were collected. The study was performed within the approved PhD dissertation topic "Anxiety-depressive disorders in PLWH: clinical-psychopathological features, psychosocial determinants, and therapeutic approaches". Statistical analysis was performed in R software 2025.05.1 (R Foundation for Statistical Computing, Austria). Normality was assessed using the Shapiro–Wilk test; Spearman correlation, non-parametric group comparisons, and multiple linear regression were used. Regression coefficients are reported as unstandardized coefficients (B).

Research Ethics. The study was approved by the Bioethics Committee of Sumy State University. All participants provided informed consent.

Results. The mean Luban–Plozza score was 3.02, standard deviation – 2.4 points, with a median of 2 points and an observed range of [0÷10] points out of 16 possible points. Elevated suicidal risk was defined by the 75th percentile threshold, ≥4 points. Depressive symptoms (B=0.098, p<0.001) and state anxiety (B=0.054, p=0.002) were the only statistically significant independent predictors. The model explained 42.4% of the variance. Age, sex, CD4 count, clinical stage, socioeconomic status, marital status, employment, number of children, and alcohol use were not significant predictors.

Conclusions. Depression and state anxiety are key determinants of suicidal risk in PLWH. Mental health screening should be integrated into HIV care regardless of demographic or clinical profile. Early identification and intervention may reduce suicidality and improve HIV-related outcomes.

Keywords: *psychiatry, PLWH, suicidality, psychosocial determinants, Luban–Plozza scale, mental health.*

Introduction

Human Immunodeficiency Virus (HIV) and Acquired ImmunoDeficiency Syndrome (AIDS) remain major global public health concerns, with a disease burden that cannot be overlooked. In 2024, the Joint United Nations Program on HIV/AIDS (UNAIDS) reported 1.3 million new HIV infections and an estimated 40.8 million People Living With HIV (PLWH) worldwide [1]. Beyond virological and immunological challenges, psychiatric illnesses represent a critical health issue for PLWH, with depression being the most prevalent neuropsychiatric complication. Estimates suggest that the prevalence of depression among PLWH ranges from 22% to 71% [2], and social discrimination and HIV-related stigma are frequently cited as key contributing factors.

Corresponding Author:
Oksana Cherevko – PhD student of the Department of Neurosurgery and Neurology, Medical Research and Educational Institute of Sumy State University, Ukraine.
✉ rm. 405, 22, Bilopilskyi Shlyakh, Sumy, 40009, Ukraine.
E-mail: o.cherevko@med.sumdu.edu.ua

The burden of suicidality among PLWH is profound. A systematic review suggested that suicide mortality in this group could be up to 100-fold higher than in the general population [3], although subsequent re-analyses have challenged this magnitude, estimating a more conservative fourfold increase [4]. Suicide risk also shows subgroup variation: in one meta-analysis, men exhibited higher suicide mortality than women, while sexual minorities, such as Men who have Sex with Men (MSM) and transgender women, were disproportionately affected [3; 5]. Sexual minority status itself is an independent risk factor for suicidal ideation and attempts [6].

Age plays an additional role in shaping suicidality. A nationwide Korean cohort study (2025) reported that PLWH over the age of 40 faced significantly higher suicide mortality [7], while in individuals under 50, suicide emerged as the leading cause of death, accounting for 17% of deaths among men and 25% among women [8]. Across studies, approximately 21% of PLWH report suicidal ideation [9], around 5% report a past-year suicide attempt, and [1÷2]% eventually die by suicide [10; 11]. This highlights suicide as both a psychiatric and a mortality outcome of central concern in HIV care.

While the introduction of AntiRetroviral Therapy (ART) has substantially reduced overall HIV-related mortality, ART does not eliminate the virus and may itself introduce psychiatric complications. Certain regimens, particularly efavirenz, have been associated with increased suicidality [12]. Moreover, psychiatric comorbidities such as depression, anxiety, and Post-Traumatic Stress Disorder (PTSD) are frequently underdiagnosed in HIV care settings, limiting opportunities for referral and intervention [11]. Effective diagnosis, documentation, and evidence-based psychiatric treatment could reduce suicide risk in PLWH.

Suicide is a global public health challenge. Each completed suicide is estimated to correspond to 20 attempts, and suicide accounts for more than one in every 100 deaths worldwide [13]. In the general population, men outnumber women in suicide mortality nearly 4:1, with the highest male suicide rates observed among those aged 75 years and older (37.97 per 100,000), and the highest female rates among those aged [40÷50] years (7.53 per 100,000) [13]. Although suicide rates historically increased linearly with age, recent data suggest a more complex age distribution [14].

Among PLWH, psychosocial determinants such as marital status and social support significantly affect suicide risk. Married individuals and women with sufficient social support exhibit lower suicide rates [15]. Conversely, socioeconomic adversity – including poverty, unemployment, unstable housing, and exposure to violence – acts as a structural driver of suicidality [16]. HIV-related stigma and mental health comorbidities are consistently identified as major contributors to suicide risk in this population [16]. Encouragingly, more recent studies have reported relatively lower suicide rates, possibly reflecting reduced stigma and growing awareness of mental health [17; 18]. Access to ART and stigma reduction have been identified as protective factors [18].

Depression is the leading psychiatric comorbidity among PLWH and a key predictor of suicidality [19–21]. Multiple studies demonstrate higher prevalence of depression in PLWH compared to HIV-negative peers [22–25], with meta-analyses estimating an overall prevalence of around 30% [26]. For comparison, the World Health Organization (WHO) reports a global prevalence of depression of 3.8% in the general population, including 5% of adults and 5.7% of those aged over 60 years [27]. Among PLWH, women are more likely to experience severe depression, while men more often report moderate symptoms [28]. Younger adults newly diagnosed with HIV exhibit higher depression rates than those with chronic infection, while in older adults, depression is more common among those with long-standing HIV compared to HIV-negative peers [19; 29].

Anxiety disorders follow similar patterns, with younger PLWH experiencing higher rates shortly after diagnosis [19; 30].

Exposure to trauma is also elevated among PLWH, with reported rates of child abuse, sexual assault, or physical violence ranging from 40% to 90%. Correspondingly, PTSD prevalence in PLWH ranges from 30% to 74%, with two-thirds attributing their symptoms directly to HIV diagnosis [22]. Lifetime prevalence of PTSD among PLWH approaches 50%, compared with 7% in the general population [32]. PTSD frequently co-occurs with substance use and depression, further amplifying suicide risk and accelerating HIV progression [22; 31].

The mid-1990s marked a turning point in HIV care with the introduction of combination ART. Since then, thresholds for initiating therapy (200, 350, 500 CD4 cells/mm³) have evolved, although CD4 count remains a critical biomarker for monitoring disease progression and treatment response [25; 32]. Psychiatric factors, however, increasing-

ly emerge as equally important determinants of health outcomes in PLWH.

Globally, suicide ranks as the 17th leading cause of death and the fourth leading cause among individuals aged [15÷29] years [33]. Despite these figures, suicide remains underreported due to stigma, misclassification, and weak surveillance systems [34]. Among adolescents, recent meta-analyses estimate global suicide rates at 3.77 per 100,000 people, with substantially higher rates among older adolescents [35].

Evidence consistently shows elevated suicide risk among PLWH compared to the general population [3; 36; 37]. Notably, a systematic review found that women living with HIV were more likely to report suicidal ideation and attempts, even though suicide mortality rates were equivalent between sexes – an unusual deviation from general population trends [5; 18]. However, critical reappraisals have demonstrated that earlier estimates of a 100-fold increased risk were inflated due to methodological flaws, including inappropriate statistical comparisons and reliance on global rather than region-specific suicide baselines [4].

The heightened risk of suicide in PLWH is also shaped by intersecting demographic and behavioral vulnerabilities. In high-income regions, HIV disproportionately affects MSM and people who inject drugs, groups already at increased baseline risk of suicide independent of HIV status [38; 39]. In these populations, prevalence estimates indicate that [30÷70]% of PLWH identify as MSM [40; 41]. Within this subgroup, gay and bisexual men living with HIV report elevated suicidal ideation and attempts, with HIV-related stigma playing a central role in suicidality [18].

Taken together, the evidence highlights suicide as a major yet underrecognized component of HIV disease burden. Discrepancies in reported risk magnitudes underscore the need for methodological rigor in epidemiological studies, while subgroup analyses reveal that suicide risk is disproportionately concentrated among older PLWH, sexual minorities, and individuals with intersecting vulnerabilities such as trauma and substance use. Addressing suicidality in PLWH therefore requires accurate surveillance, culturally tailored prevention strategies, and integration of mental health services into HIV care.

The **aim** of study was to assess the association between depression, anxiety, and suicidal risk among people living with HIV in Ukraine, and to identify key psychological predictors of suicidality independent of demographic and clinical characteristics.

Materials and Methods

This study employed a cross-sectional design, which is appropriate for obtaining a single-time-point assessment of psychological status and suicidal risk in PLWH. Such a design allows for the identification of associations between variables, such as depression, anxiety, and suicidality, without implying causality, and is efficient for assessing clinically relevant mental health factors in a defined population. Participants were recruited from an outpatient HIV clinic. Inclusion criteria were a confirmed HIV diagnosis verified via medical records, age ≥18 years, a stable somatic condition sufficient to participate in research procedures, and not receiving opioid substitution therapy. Exclusion criteria included pregnancy, severe or decompensated somatic illness, and current active substance use disorder. Although the presence of psychological complaints was not a formal inclusion criterion, patients reporting such complaints demonstrated greater willingness to participate, reflecting a common recruitment dynamic in clinical research and a potential source of selection bias.

Suicidal risk was assessed using the Luban–Plozza Suicide Risk Scale, a structured screening tool for suicidal ideation and behavior previously applied in European clinical and psychiatric studies. The scale provides a theoretical total score ranging from 0 to 16, with higher scores indicating greater suicidal risk. In the present sample, observed scores ranged from 0 to 10. Since no validated clinical cut-off for the Luban–Plozza scale has been established for PLWH, suicidal risk was categorized using a distribution-based approach. The 75th percentile of the Luban–Plozza score distribution was used as the threshold for elevated suicidal risk; in this cohort, it corresponded to 4 points. Therefore, scores of [0÷3] were classified as low risk, while scores ≥4 were classified as elevated suicidal risk. For descriptive visualization, elevated risk was further subdivided into moderate elevated risk ([4÷6] points) and high elevated risk within the observed sample range ([7÷10] points).

Compared with internationally established instruments such as the Columbia-Suicide Severity Rating Scale (C-SSRS) [42] and the suicide-related item of the Patient Health Questionnaire-9 (PHQ-9) [43], the Luban–Plozza scale has a more limited international validation base and has been used mainly in Eastern European and German-

speaking clinical contexts. To our knowledge, no direct head-to-head studies have established the sensitivity or specificity of the Luban–Plozza scale against C-SSRS or PHQ-9 in people living with HIV. Therefore, in the present study, the Luban–Plozza scale was used as a regional screening instrument for suicidal risk rather than as a diagnostic standard, and categorical thresholds were defined using a distribution-based approach. Depressive symptoms were evaluated using the Beck Depression Inventory (BDI), one of the most widely used and psychometrically validated self-report questionnaires in psychiatry and clinical psychology, with robust reliability data in Eastern European populations. The BDI allowed for dimensional assessment of symptom severity and categorical differentiation of clinical depression thresholds. Anxiety was measured using the State-Trait Anxiety Inventory – State Subscale (STAI-S), which captures current situational anxiety rather than stable trait anxiety. This subscale was selected because the study focused on the patients' current psychological distress and its association with suicidal risk at the time of assessment. Broader psychological symptomatology was captured using the Symptom Checklist-90-Revised (SCL-90-R), which evaluates nine primary dimensions of psychopathology – somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism – alongside indices of global distress. Collectively, these instruments provided both specificity and breadth: the Luban–Plozza scale directly assessed suicidal risk, the BDI and STAI-S measured prevalent psychiatric syndromes associated with suicidality, and the SCL-90-R offered a multidimensional view of overall psychological burden.

All statistical analyses were conducted using R software 2025.05.1 (R Foundation for Statistical Computing, Austria). Descriptive statistics included means, standard deviations, medians, and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Normality of continuous variables was assessed using the Shapiro–Wilk test and visual inspection of histograms and Q-Q plots. As the Luban–Plozza total score was not normally distributed, non-parametric tests were used where appropriate. In the analyses, B denotes an unstandardized regression coefficient, ρ denotes Spearman's rank correlation coefficient, χ^2 denotes the chi-square statistic, R^2 denotes explained variance, adjusted R^2 denotes variance explained after correction for the number of predictors, F denotes the regression model statistic, and p denotes the probability value. Bivariate analyses were performed using χ^2 tests for associations between categorical variables (e.g., sex, marital status) and suicidal risk categories, independent samples t-tests or one-way ANOVA for normally distributed continuous variables, and Mann–Whitney U or Kruskal–Wallis tests for non-normally distributed variables. Pearson or Spearman correlations were used to examine relationships between continuous variables, such as BDI scores and Luban–Plozza scores. Multivariate analyses included multiple linear regression to identify independent predictors of suicidal risk, with the total Luban–Plozza score as the dependent variable. Independent variables included age, sex, HIV clinical stage, absolute CD4 count, depressive symptoms (BDI), state anxiety (STAI-S), socioeconomic status, marital status, employment status, and number of children. Regression coefficients are reported as unstandardized coefficients (B) with corresponding p-values. Regression models were checked for multicollinearity, heteroscedasticity, and normality of residuals. A p-value <0.05 was considered statistically significant, while values between 0.05 and 0.10 were reported as trends or marginally significant. All tests were two-tailed. This statistical approach was justified given the cross-sectional design: methods focused on assessing associations rather than causation, regression analysis controlled for potential confounders, and non-parametric tests were applied when parametric assumptions were not met. Missing data were explicitly coded as NA, and no imputation was performed due to the pilot nature of the study; participants with missing values were excluded from analyses as appropriate.

Research Ethics. The study was approved by the Bioethics Committee of Sumy State University. All participants provided informed consent.

Results

This cross-sectional study included 132 people living with HIV (PLWH) recruited from the Clinical Medical Center for socially dangerous diseases, Sumy between 2021–2025 (Table). Among the participants, 55 (41.7%) were women and 77 (58.3%) were men. The age of patients ranged from 22 to 75 years, with a median of 41 years and a mean of [42.6±11.3] years. All participants were receiving antiretroviral therapy. HIV clinical stages were distributed as follows: stage 1 – 48 patients (36.4%), stage 2 – 18 (13.6%), stage 3 – 30 (22.7%), and stage 4 – 36 (27.3%). Socioeconomic status, assessed subjectively, was rated as

Table. Descriptive and psychometric characteristics of the study sample

Variable	n	Mean ± SD	Median (Range)	Notes	Clinical interpretation
Suicidal risk (Luban-total)	132	3.02±2.4	2 (0–10)	Low / moderate elevated / high elevated: 89 / 30 / 13*	Higher scores indicate greater suicidal risk; elevated risk is defined as ≥4 points
BDI (Depression)	132	18.6±9.7	17 (2–42)	Mild/absence of depressive symptoms: 52, Moderate: 55, Severe: 25 (*Fig. 4*)	Higher scores indicate more severe depressive symptoms
STAI-S (State Anxiety)	132	42.8±10.5	43 (20–65)	–	Reflects current situational anxiety
Correlation (Suicide risk vs BDI)	–	ρ=0.56	p<0.001	Significant	Moderate positive association
Correlation (Suicide risk vs STAI-S)	–	ρ=0.59	p<0.001	Significant	Moderate positive association
Correlation (Suicide risk vs Age)	–	ρ=–0.06	p=0.48	Not significant	No meaningful association
Correlation (Suicide risk vs CD4)	–	ρ=–0.003	p=0.97	Not significant	No meaningful association

Notes: distribution-based categories: low risk = [0÷3] points (n=89), moderate elevated risk = [4÷6] points (n=30), and high elevated risk within the observed range = [7÷10] points (n=13). Elevated suicidal risk was defined as ≥4 points, corresponding to the 75th percentile.

satisfactory by 75 participants (56.8%), good by 48 participants (36.4%), and unsatisfactory by 9 participants (6.8%). Other sociodemographic characteristics included marital status, employment, and number of children, with distributions reflecting a diverse clinical population.

In the present sample, observed scores ranged from 0 to 10, with a mean total score of [3.02±2.4] and a median of 2 (*Fig. 1*). The 75th percentile corresponded to 4 points; therefore, participants scoring [0÷3] points were classified as having low suicidal risk, whereas those scoring ≥4 points were classified as having elevated suicidal risk.

For descriptive purposes, the elevated-risk group was further subdivided into moderate elevated risk ([4÷6] points) and high elevated risk within the observed sample range ([7÷10] points) (*Fig. 2*). According to this classification, 89 participants were classified as low risk (35 women, 54 men), 30 as moderate elevated risk (14 women, 16 men), and 13 as high elevated risk (6 women, 7 men).

The distribution of suicidal risk scores by sex is shown in *Fig. 3*. No statistically significant difference in Luban–Plozza scores was observed between women and men (Wilcoxon rank-sum test, p=0.114).

The Symptom Checklist-90-Revised (SCL-90-R) was used to assess a broad spectrum of psychological symptoms across nine domains, including somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. In addition, the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory – State Subscale (STAI-S) were administered to evaluate depressive and state anxiety symptoms, respectively. Both instruments served as covariates in analyses and allowed triangulation of findings with SCL-90-R results. Significant positive correlations were observed between Luban–Plozza total scores and BDI (ρ=0.56, p<0.001) and STAI-S scores (ρ=0.59, p<0.001).

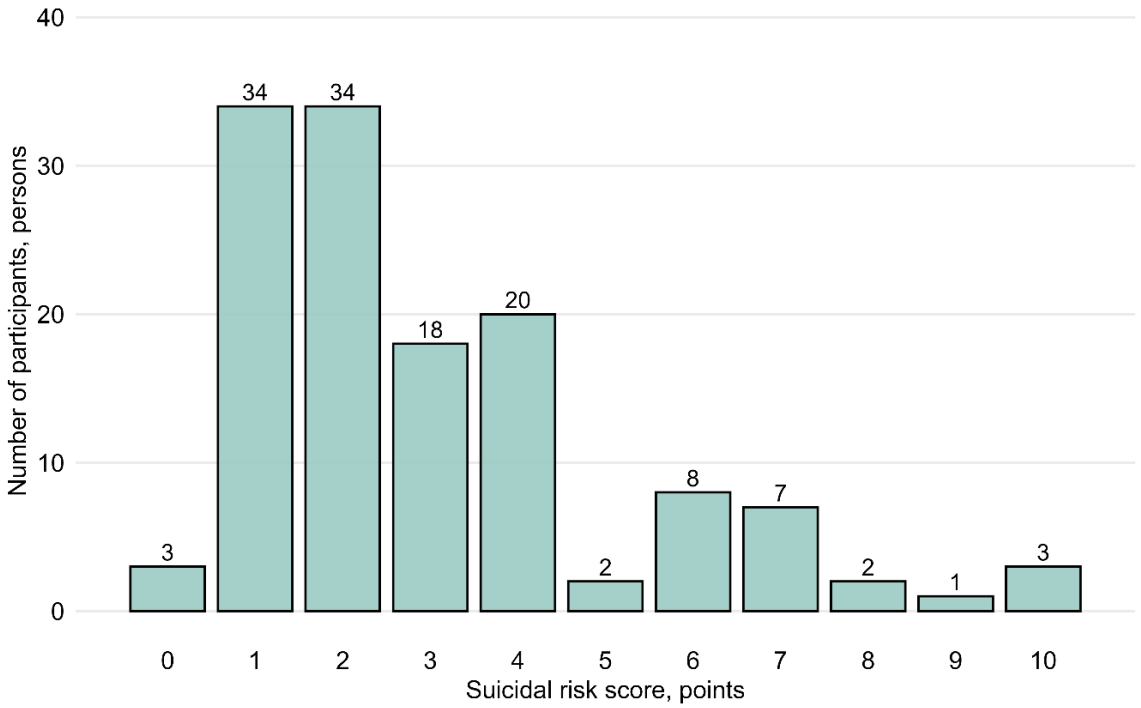

Fig. 1. Distribution of suicidal risk scores according to the Luban–Plozza scale.

Notes: the theoretical score range is [0÷16] points; observed scores in this sample ranged from 0 to 10 points.

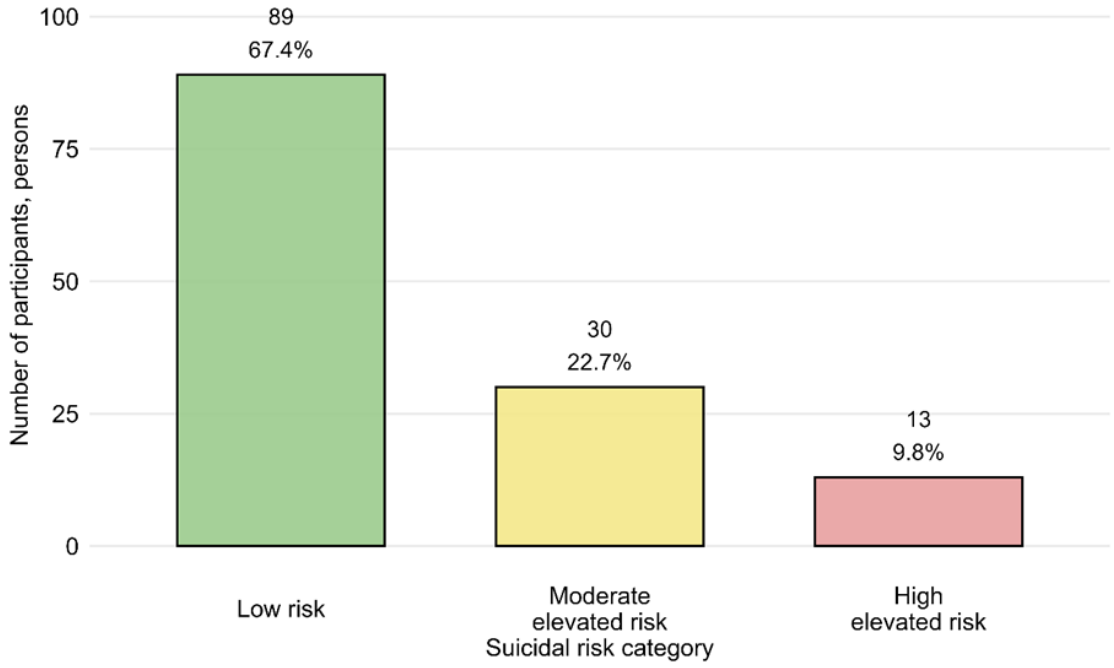

Fig. 2. Distribution-based categories of suicidal risk according to the Luban–Plozza scale.

Notes: low risk was defined as [0÷3] points. Elevated suicidal risk began at ≥4 points, corresponding to the 75th percentile of the score distribution. For descriptive purposes, elevated risk was further divided into moderate elevated risk ([4÷6] points) and high elevated risk within the observed sample range ([7÷10] points).

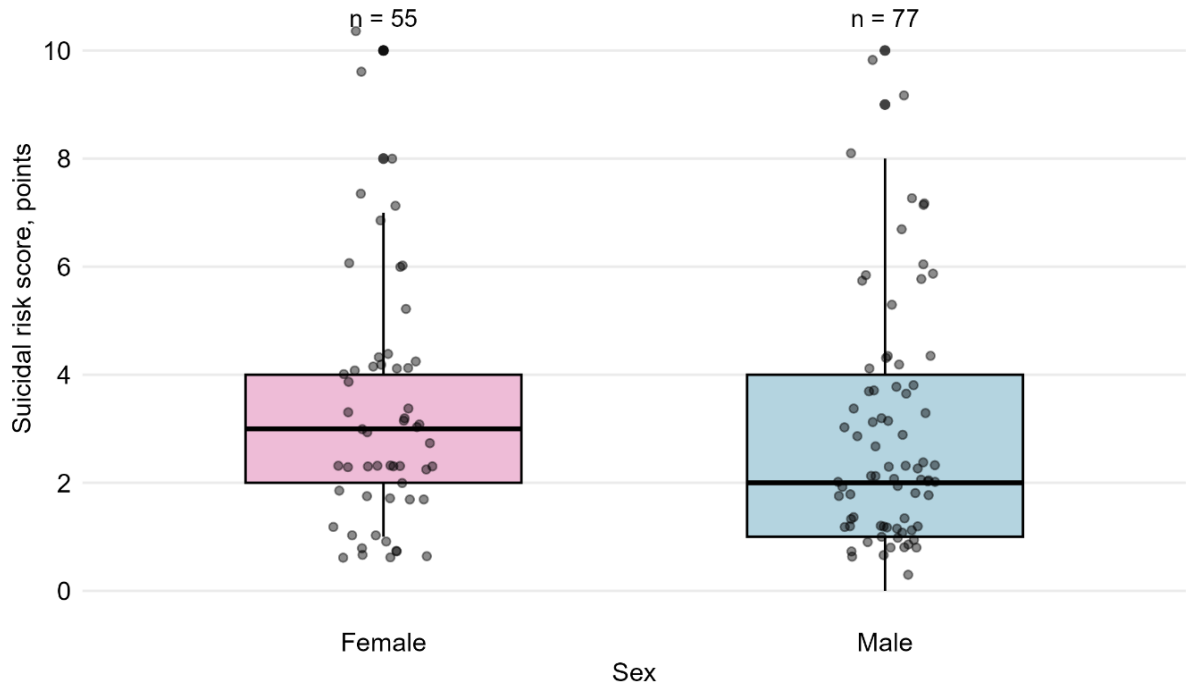

Fig. 3. Distribution of suicidal risk scores by sex.

Notes: boxplots show the median, interquartile range, and individual Luban–Plozza scores. No statistically significant difference in suicidal risk scores was observed between female and male participants.

Among SCL-90-R domains, somatization (ρ=0.38), depression (ρ=0.47), and anxiety (ρ=0.54) were significantly associated with suicidal risk, indicating that higher psychological di stress corresponded to greater Luban–Plozza scores. The distribution of suicidal risk scores across BDI depression severity categories is shown in *Fig. 4*.

Immunological status was evaluated using absolute CD4+ T-cell counts (cells/μL), which ranged from 17 to 1477 in the sample (median = 398.5; mean = [430.8±268.3]). CD4 counts were categorized into three clinically relevant groups: <200 cells/μL (advanced HIV disease), [200÷349] cells/μL (moderate immunodeficiency), and ≥350 cells/μL (satisfactory immune status). No significant associations were observed between CD4 categories and Luban–Plozza scores, suggesting that suicidal risk was independent of immune status in this cohort.

Multiple linear regression was conducted to identify independent predictors of suicidal risk, with the total Luban–Plozza score as the dependent variable. Independent variables included age, sex, HIV clinical stage, absolute CD4 count, depressive symptoms (BDI), state anxiety (STAI-S), socioeconomic status, marital status, employment status, and number of children. Regression coefficients are reported as unstandardized coefficients (B). The model was statistically significant ($F(19, 112) = 4.34$, $p<0.001$) and explained 42.4% of the variance in Luban–Plozza scores ($R^2=0.424$; adjusted $R^2=0.326$). Depressive symptoms (B=0.098, $p<0.001$) and state anxiety (B=0.054, p=0.002) were the only statistically significant independent predictors of suicidal risk. Age, sex, HIV clinical stage, CD4 count, socioeconomic status, marital status, employment status, and number of children were not statistically significant predictors.

Patients reporting psychological complaints were more likely to engage in the study, suggesting potential selection bias. This recruitment pattern should be considered when interpreting the generalizability of findings to the broader population of PLWH.

Discussion

Our findings indicate that psychological factors, particularly depressive symptoms and state anxiety, were the only statistically significant independent predictors of suicidal risk among peop-

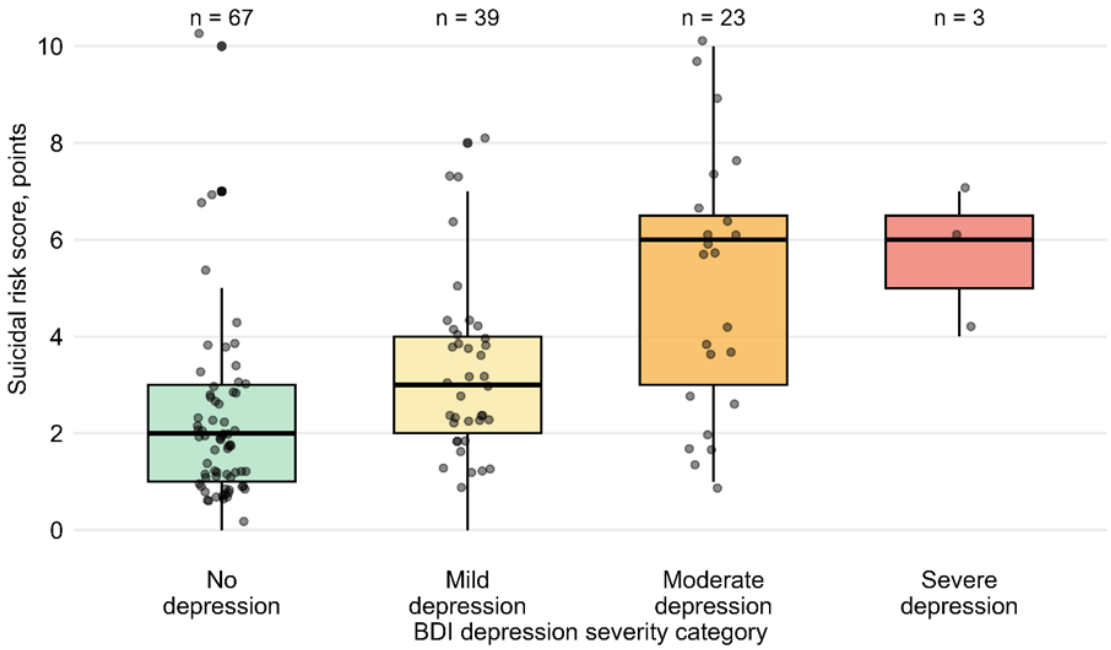

Fig. 4. Distribution of suicidal risk scores across depression severity categories according to the Beck Depression Inventory.

Notes: boxplots show the median, interquartile range, and individual Luban–Plozza scores. The numbers above the plots indicate the number of participants in each depression severity category.

le living with HIV (PLWH). The multivariable regression model explained 42.4% of the variance in Luban–Plozza scores, underscoring the clinical relevance of mental health assessment in this population. These results align with prior literature demonstrating that affective distress is central to suicidality in PLWH [1–3].

Spearman correlation analyses revealed significant positive associations between Luban-total scores and BDI (ρ=0.56, p<0.001) and STAI-S (ρ=0.59, p<0.001), indicating that higher depressive symptoms and state anxiety symptoms correspond to increased suicidal risk. These findings are consistent with global studies reporting elevated suicidality in PLWH with comorbid depression or anxiety [4–6]. Notably, SCL-90-R domain analysis identified somatization (ρ=0.38), depression (ρ=0.47), and anxiety (ρ=0.54) as key contributors to suicidal risk, highlighting the complex interplay between psychological and somatic symptoms.

Contrary to some previous research suggesting age, sex, and HIV clinical stage as risk modifiers [7–9], our analyses indicated negligible correlations of Luban-total scores with age (ρ=–0.062, p=0.48) and CD4 counts (ρ=–0.003, p=0.97). Additionally, categorical variables including sex, marital status, presence of children, socioeconomic status, and employment did not demonstrate statistically significant effects. These findings suggest that in the Ukrainian PLWH population, psychological distress outweighs demographic and immunological determinants as a driver of suicidal risk.

While alcohol consumption is traditionally considered a risk factor for suicidal behavior, our data did not demonstrate significant differences in Luban–Plozza scores across alcohol consumption groups (Kruskal–Wallis χ^2=4.36, p=0.225). Similarly, the Spearman correlation between alcohol consumption frequency and Luban–Plozza scores was weak and not statistically significant (ρ=0.13, p=0.139). The low prevalence of daily alcohol consumption (2.3%) may have limited statistical power, or alternatively, the effect of alcohol may operate indirectly by exacerbating depressive and anxiety symptoms rather than acting independently.

These findings emphasize the importance of integrating routine mental health screening into HIV care, with a focus on depressive and anxiety symptoms. Given that elevated suicidal risk was observed even in patients with early-stage HIV and satisfactory CD4 counts, screening should not be restricted to those with advanced disease. Early identification and management of affective symptoms could substantially reduce suicide risk and improve overall HIV care outcomes.

The prevalence and predictors of suicidality in our sample are consistent with international studies reporting higher suicidal ideation and attempts among PLWH compared to HIV-negative peers [10–12]. Importantly, our study adds novel data from Ukraine, where population-specific risk profiles and healthcare contexts may differ from high-income settings. By integrating psychometric measures (BDI, STAI-S, SCL-90-R) with clinical and demographic data, we provide a comprehensive assessment of risk determinants, demonstrating the primacy of psychological over traditional socio-demographic factors in predicting suicidal risk.

Strengths of this study include the detailed, multidimensional assessment of suicidal risk, inclusion of both psychometric and clinical variables, and the focus on a Ukrainian PLWH cohort, filling a gap in regional research. However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference and allows only the identification of associations between psychological factors and suicidal risk. Second, potential selection bias should be considered, as patients with existing mental health complaints appeared more willing to participate in the study. Third, self-report measures may be affected by response bias, particularly for sensitive topics such as suicidality and alcohol use.

An additional limitation concerns the assessment of suicidal risk. Although the Luban–Plozza scale is clinically familiar in Eastern European practice and is brief enough for use in medically burdened patients, it has a more limited international psychometric evidence base than instruments such as the Columbia-Suicide Severity Rating Scale (C-SSRS) or the suicide-related item of the Patient Health Questionnaire-9 (PHQ-9). Direct sensitivity and specificity comparisons between the Luban–Plozza scale and C-SSRS or PHQ-9 in people living with HIV are not currently available. Therefore, the present findings should be interpreted as screening-based estimates of suicidal risk rather than clinically confirmed suicidal behavior. Future studies should validate the Luban–Plozza scale against internationally established instruments, particularly the C-SSRS, in populations of people living with HIV.

Conclusions

1. Depressive symptoms and state anxiety were the only statistically significant independent predictors of suicidal risk among PLWH in Ukraine. These findings underscore the necessity of routine mental health assessment as an integral component of HIV care.

2. Age, sex, CD4 counts, clinical stage of HIV, socioeconomic status, marital status, and employment status were not significantly associated with suicidal risk in this cohort. This suggests that psychological distress may play a more important role than demographic, social, or immunological factors in determining suicidal risk among PLWH.

3. Early identification and management of depressive symptoms and anxiety symptoms are essential components of suicide prevention strategies in PLWH. Screening should be implemented regardless of HIV stage or demographic profile, with targeted interventions for those exhibiting moderate to severe psychological symptoms.

4. This study provides novel insights into suicidality among PLWH in Ukraine, integrating psychometric, clinical, and demographic data to delineate risk profiles. The findings contribute to evidence-based recommendations for mental health integration into HIV care and the development of culturally tailored prevention strategies.

Prospects for Further Research

Future studies should consider longitudinal designs to assess temporal relationships between psychological symptoms and suicidal behavior in PLWH. Investigations into the role of social support, stigma reduction interventions, and culturally adapted psychotherapeutic approaches may further inform suicide prevention strategies. Moreover, larger samples would allow exploration of subgroup differences, including sex, age, and HIV transmission risk groups.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Cherevko O.	+	+	+	+	+	+
Kozhyna H.	+	+			+	+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

The authors declare that they have no conflict of interest.

The authors state that generative AI tools were not used to perform scientific tasks related to the development of the research concept, data collection, statistical analysis, interpretation of results, or formulation of conclusions. Generative AI was used only for auxiliary editorial purposes, including language polishing, translation support, and formatting assistance. All substantive scientific work and final editing decisions were carried out by the authors, who take full responsibility for the manuscript.

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ASSESSMENT OF THE QUALITY OF LIFE IN CHILDREN WITH IRRITABLE BOWEL SYNDROME UNDER SOCIAL STRESS IN UKRAINE (PILOT STUDY)

Gonchar M.O., Omelchenko O.V., Kulikova K.T., Shestopalova D.D., Sukhorukova A.O.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. Irritable Bowel Syndrome (IBS) is diagnosed in [10÷15]% of older children, and there is a tendency for the prevalence of this condition to increase in adolescents. IBS is a long-term chronic disease that can significantly affect the quality of life of patients, causing both physical discomfort and psychological stress.

Aim. To assess the quality of life in children with irritable bowel syndrome under conditions of social stress during the hostilities in Ukraine.

Materials and Methods. We examined 30 children aged 6 to 17 years with irritable bowel syndrome. The diagnosis of IBS was made on the basis of clinical symptoms according to the Rome IV criteria (2016). For the analysis, the author's "Questionnaire for identifying risk factors affecting children's quality of life under conditions of social stress" (20 questions) was used. Responses were rated on scales of 1 to 5 points, as well as on dichotomous and graded scales ([1÷2], [1÷3], [1÷4] points depending on the content of the question). The total score ranged from 20 to 100 points. A descriptive, comparative and structural analysis of the indicators was carried out. The work was performed within the framework of the department's research project "Quality of life and the course of somatic pathology in children under social stress" (2023–2025), state registration number 0123U101768.

Research Ethics. The study was conducted in accordance with the ethical principles governing medical research involving human subjects.

Results. The average age of the examined children was [11.4±3.5] years. Depending on the clinical form of IBS: constipation-predominant IBS was observed in 17 (56.1%) children, diarrhea-predominant IBS in 13 (42.9%) children. In children of secondary school age ([12÷17] years), a higher correlation between reduced social functioning and the degree of clinical manifestations of IBS was found than in children of primary school age.

Conclusions. Changes in lifestyle, violations of diet, increased anxiety, and emotional exhaustion contribute to the exacerbation of IBS, affecting the frequency and severity of symptoms (abdominal pain, nausea, stool disorders, flatulence). Quality of life assessment should be an integral part of clinical monitoring and therapy planning in children with IBS. Effective treatment requires professional psychological support to reduce stress and develop adaptive mechanisms to respond to unfavorable environmental conditions.

Keywords: *pediatrics, gastrointestinal diseases, psychosocial factors, mental health, adolescents*.

Introduction

Irritable Bowel Syndrome (IBS), according to the Rome IV criteria, is a functional disorder of the gastrointestinal tract manifested by recurrent abdominal pain at least once a week for the last three months and associated with two or more factors: changes in the act of defecation (changes in the urge – the need to make more effort or imperative urges); changes in the frequency of bowel movements (more than four times a day or less than twice a week); changes in the shape and consistency of stool (too hard, segmented or, conversely, liquid, watery), the presence of mucus in the stool and abdominal distension [1]. The most widely used in practice and in clinical trials is the Bristol Stool Type Scale, which is ordinal and contains 7 types of stools depending on the shape and consistency, from the hardest (type 1) to the softest (type 7). Types 1 and 2 are considered ab-

Corresponding Author:
Omelchenko Olena V. – MD, PhD, Docent, Associated Professor of the Department of Pediatrics No.1 and Neonatology, Kharkiv National Medical University, Ukraine.
✉ 4, Nauky Ave., Kharkiv, 61022, Ukraine.
E-mail: ov.omelchenko@knmu.edu.ua

normally hard stools (and in combination with other symptoms indicate constipation). Types 6 and 7, vice versa, are considered abnormally loose stools (and in combination with other symptoms indicate diarrhea). Types 3–5 are considered the most "normal" stools [2]. The diagnosis of IBS is made when there are no anatomical or physiological abnormalities during clinical examination. Most often, IBS is detected in young people and middle-aged patients under the age of 50 [3]. The prevalence ranges up to 13% in Europe, and in Ukraine it is [15÷20]%. Since 2022, the number of patients with IBS has been increasing. IBS with diarrhea occurs in 35% of patients, with constipation in 25%, with a mixed subtype in 20%, and unclassified IBS is observed in 20% [4].

Among children with functional digestive disorders, this syndrome is diagnosed in a quarter of cases, and there is a tendency for the prevalence of this condition to increase in adolescents. IBS is a long-term chronic condition that can significantly affect the quality of life of patients, including both physical discomfort and psychological stress [5].

Not one, but several etiologic factors and pathophysiologic mechanisms play a role in the development of the disease. In each specific clinical case, the combination of etiopathogenetic mechanisms is individual. Among them, the socioeconomic status of the family, genetic predisposition, psychological aspects, visceral hypersensitivity, gastrointestinal motility disorders, changes in the neuroendocrine system (brain-gut axis), somatoform autonomic dysfunction, the concept of postinfectious IBS, microbiota imbalance, and, finally, certain nutritional factors are of particular relevance [6; 7]. Social stress factors can increase the probability of occurrence and affect the course of IBS. The full-scale outbreak of hostilities has led to dramatic changes in the lives of civilians. The shelling of residential buildings and other infrastructure has significantly worsened people's living conditions. Constant exposure to stress, changes in lifestyle, and nutrition have contributed to the increase in the incidence of diseases among the population. Quality of Life (QoL) examines the impact of the disease on physical, mental, and social aspects of a patient's life. Assessment of QoL plays a key role in improving the effectiveness of treatment. To evaluate the effectiveness of treatment, the list of necessary criteria should include Quality of Life indicators [8; 9].

The **aim** of study was to assess the quality of life in children with irritable bowel syndrome under conditions of social stress during the hostilities in Ukraine.

Materials and Methods

The study involved 30 children aged 6 to 17 years with IBS, including 16 girls and 14 boys, who were treated in the gastroenterology department of the Regional Children's Clinical Hospital in 2022–2024. All children were living in the frontline zone (Kharkiv region, Kharkiv) for 2 years. The diagnosis was made on the basis of clinical, laboratory, and instrumental examination of the sick children, according to the Rome criteria IV (2016). To assess the quality of life, the authors' 20-question survey was used to identify risk factors in the context of social stress [10]. The respondents evaluated the answers on a point scale. The average age of the examined children was [11.4±3.5] years, including 36.6% of patients of primary school age (6 to 11 years) and 63.4% of patients of secondary school age (12 to 17 years).\

The diagnosis was made on the basis of clinical symptoms in accordance with the Rome IV criteria (2016). According to the way the assessed issues were allocated, parametric (mean value, standard deviation) and nonparametric statistical methods were used. Quantitative attributes with a normal distribution are represented as [M±m], where M is the mean value, and m is the standard error of the mean (SEM). Characteristics whose distribution differed from the normal ones are represented as Me (Q1; Q3), where Me is the median, Q1 is the first quartile (25th percentile), Q3 is the third quartile (75th percentile), and the level of statistical significance (p). The normality of the distribution in the samples was determined using the Shapiro-Wilk method. The critical value of the significance level (p) was taken as ≤5% (p≤0.05).

Research Ethics

The study was approved by the Commission on Biomedical Ethics for Compliance with Moral and Legal Norms of Medical Research of Kharkiv National Medical University. It was confirmed that the conducted study does not contradict the basic bioethical norms and complies with the provisions of Good Clinical Practice (1996), the Council of Europe Convention on Human Rights and Biomedicine (April 04, 1997), the World Medical Association Helsinki Declaration (1964–2024), as well as the Order of the Ministry of Health of Ukraine No.690 of September 23, 2009, as amended by the Order of the Ministry of Health of Ukraine No.523 of July 12, 2012.

The parents of all patients were informed about the purpose and methods of the study, after which

they signed informed consent for the children to participate in the study.

Results

The gender analysis showed that there were no statistical differences between boys and girls (there were 14 boys (46.7%) and 16 girls (53.3%) (p>0.05). The median Body Mass Index (BMI) of patients was 16.75 kg/m2 (14.16; 19.56).

Depending on the clinical form of IBS, the patients were divided into the following: IBS with predominance of constipation (type 1, 2 on the Bristol scale) was observed in 17 children (56.1%), IBS with diarrhea (type 5, 6,7 on the Bristol scale) in 13 children (42.9%), and no patients had mixed type symptoms. The main clinical manifestations were abdominal pain, which was observed in 30 children (100.0%), a feeling of early satiety in 5 (16.5%), and flatulence in 13 (42.9%). Most patients complained of nausea, with 22 patients (72.6%) noting this symptom during meals. 18 children (59.4%) reported decreased appetite and weakness.

In the vast majority of children, 25 (82.5%), abdominal pain was associated with the act of defecation. 26 (85.8%) children had a feeling of overflow after the act of defecation. The feeling of incomplete emptying was noted by 28 children (92.4%).

The structure of concomitant pathology included Protein-Energy Deficiency (PED) in 6 children (19.8%), functional disorders of the biliary tract in 10 (33.0%), and diffuse non-toxic goiter in 4 children (13.3%). Manifestations of vegetative-vascular disorders in the form of headache in 12 patients (39.6%), sleep disturbance in 27 (89.1%), and frequent mood changes in 16 (52.8%) children. Laboratory tests: clinical blood, urine, and biochemical blood tests were within the age-related norm.

Abdominal ultrasonography revealed abnormalities in the structure of the gallbladder in 10 (33%) patients, and hepatomegaly in 5 (16.5%) children. Intestinal peristalsis was slowed down in 4 (13.2%) patients, and increased in 2 (6.6%) children.

All children were interviewed to determine the degree of social stress in the context of the war in Ukraine. According to the obtained results, the majority of children, 27 (89.1%), noted a deterioration of health and exacerbation of chronic pathology. Over the past 2 years, 28 children (92.4%) noted a deterioration in the quality of sleep. The patients' diet was dominated by cereal products and flour products. Changes in the psychological state in the form of bad mood, anxiety, and despair were noted by all children, 21 (69.3%) of whom noted these symptoms very often, 9 (29.7%) – sometimes. Almost all children – 26 (85.8%) – had a connection between periods of strong emotional experience and exacerbation of the disease.

In children with IBS, impaired psycho-emotional functioning was manifested by a sense of worry, low mood, anxiety, despair, and depression [11; 12]. Children were divided into 2 groups according to the classification of childhood periods [13]. Group I – primary school age (6 to 11 years), group II – adolescents (12 to 17 years). Children in group II had a more significant decline in the quality of their lives, although the differences did not reach statistical significance (p>0.05).

Martial law has significantly affected children's quality of life, including the quality and duration of sleep [14; 15]. Most children reported difficulty falling asleep and a negative reaction to nighttime awakenings caused by alarms. Before the outbreak of hostilities, most children assessed their general condition as satisfactory. The impairment of social functioning was reflected in the deterioration of interaction with peers and parents, and also negatively affected self-esteem. In children of secondary school age (group II), there was a more significant correlation between the decline in social functioning and the severity of clinical manifestations of IBS than in children of primary school age, although the differences did not reach statistical significance (p>0.05). A comparative analysis of quality of life indicators for children with IBS in different age groups is presented in *Table*.

Table. Indicators of quality of life in children with irritable bowel syndrome in two age groups, M±m

	Younger age group (children [6÷11] years old)	Older age group (children [12÷17] years old)	Difference in indicators (p)
Psycho-emotional functioning	2.45±0.82	2,89±0.80	>0.05
Social functioning	2.09±0.83	2.42±0.76	>0.05

Discussion

Numerous studies have confirmed that IBS is a psychosomatic symptom complex that combines large intestine dysfunction and various psychopathological factors [16]. Usually, the first symptoms appear at the age of [4÷10] years, and girls are significantly more likely to be affected than boys [17; 18]. In our study, the average age of those diagnosed with IBS was [11.4±3.5] years, with no statistical differences between girls and boys. The main gastrointestinal symptoms are as follows: abdominal pain is observed in 87.9% of patients with IBS, flatulence in 25% of patients, and a feeling of incomplete emptying in 30.3% of patients [19], while in our study abdominal pain was observed in 100.0% of children, flatulence in 42.9%, and a feeling of incomplete emptying were noted by 92.4% of patients, i.e., higher than in other studies, which is probably due to the impact of hostilities on the psycho-emotional state of the children.

Analyzing the stool according to the Bristol Stool Types Scale, we obtained the following data: 56.1% of children had constipation (types 1 and 2), 42.9% of children had diarrhea (types 6 and 7). According to the studies by other authors, types 1 and 2 on the Bristol scale were typical for 61.3% of children, and types 5, 6, and 7 for 27.3% of children [20].

Among the vegetative-vascular disorders, headache was the most dominant symptom, which, according to the scientific materials, is observed in 28% of sick children [21]. According to the results of our study, headache was noted in 39.6% of patients. Functional disorder of the gallbladder was present in 65.7% of patients [22], in our study, in 33.0% of children. During the abdominal ultrasound, moderate hepatomegaly (an increase in size by [1÷2] cm from the age norm) was noted in 40.6% of children [23]. In our study, hepatomegaly was detected in 16.5% of children.

According to the studies by other authors, IBS symptoms are closely related to the child's psycho-emotional and social functioning. Impaired psycho-emotional functioning was characterized by sleep disturbance (40.9%), fatigue (66%), and mood changes (47.7%). Children had lower scores when assessing the emotional sphere [23]. According to our study, 92.4% of children had a deterioration in sleep quality, and 69.3% of patients often noted mood changes, anxiety, and despair.

In our study, particular attention was paid to the methodology for assessing patients' condition. The use of the author's questionnaire, "Questionnaire for identifying risk factors affecting children's quality of life in conditions of social stress", instead of standardised scales (such as the Pediatric Quality of Life Inventory) was due to its narrow specialisation and a number of advantages. Unlike universal tests, the questionnaire takes into account risk factors: prolonged stays in damp and cool places (shelters), living under occupation and direct exposure to hostilities; it allows changes to be objectified by comparing the child's health status "before" and "after" the onset of social stress.

The advantages of the proposed questionnaire include its comprehensiveness, contextual focus, ease of use in clinical practice, and the ability to quantitatively assess risk factors with subsequent statistical analysis. The questionnaire provides for the possibility of establishing feedback with parents for further monitoring of the patient's condition, which is critically important in an unstable social environment. Thus, the use of this particular questionnaire has enabled a more accurate identification of factors affecting children's quality of life in conditions of social stress, which would have been limited when using standard universal scales.

Conclusions

Irritable bowel syndrome in children is a multifactorial disorder that is formed under the influence of physiological, psychological, and social factors. In the context of war, psycho-emotional disorders and social stress come to the fore, significantly reducing the quality of life of patients. QoL assessment should be an integral part of clinical monitoring and therapy planning in children with IBS. To improve the condition of children with IBS, it is necessary not only to correct nutrition, treat the main symptoms, but also to assess the quality of life. Effective treatment requires a professional psychological component to reduce stress and develop adaptive mechanisms to respond to adverse environmental conditions.

Prospects for Further Research

The obtained results, in accordance with the requirements of evidence-based pediatrics, substantiate the need to create practice-oriented models of multidisciplinary care. Such models should integrate medical, psychological, and social approaches to provide timely support for children exposed to prolonged social stress and various levels of stress load.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Gonchar M.O.	+				+	+
Omelchenko O.V.		+	+	+		+
Kulikova K.T.				+		+
Shestopalova D.D.				+		+
Sukhorukova A.O.				+		+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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CARDIOVASCULAR-KIDNEY-METABOLIC SYNDROME (literature review)

Ashcheulova T.V., Herasymchuk N.M., Ambrosova T.M., Kochubiei O.A., Herasymchuk U.S.

Kharkiv National Medical University, Kharkiv, Ukraine

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ABSTRACT

Background. In recent years, the importance of the concept of cardiovascular-kidney-metabolic health has been increasingly emphasized, reflecting the close pathogenetic and clinical relationship between cardiovascular disease, renal dysfunction, and metabolic health in general. Cardiovascular and renal diseases, type 2 diabetes mellitus are key causes of high disability and mortality worldwide, and therefore impose a heavy economic burden on the health systems of all countries. The search for additional opportunities to provide more complete cardio- and nephroprotection in patients with diabetes mellitus and chronic kidney disease is a pressing issue at present.

Aim. Demonstration of the scientific and pathophysiological rationale for expanding the concept of metabolic syndrome to cardiovascular-renal-metabolic syndrome, as proposed by the American Heart Association (AHA).

Materials and Methods. This study is an analytical review of clinical and epidemiological studies from electronic databases, including PubMed and Google Scholar, mostly in the last five years, as well as official guidelines from the American Heart Association. Extensive population-based studies, including NHANES (National Health and Nutrition Examination Survey) III, were analyzed, and the pathophysiology, clinical manifestations, and treatment approaches for cardiovascular-renal-metabolic syndrome were examined. This study was conducted on the authors' own initiative and without additional funding.

Research Ethics. This work is a review of published scientific evidence and clinical guidelines and does not involve the implementation of interventions involving patients or the use of personal data, so local ethical committee approval was not required.

Results. In October 2023, the AHA for the first time officially defined what is called cardiovascular-kidney-metabolic syndrome, which is defined as a systemic disease characterized by pathophysiological interactions between metabolic risk factors, chronic kidney disease, and the cardiovascular system, leading to multiple organ dysfunction and a high level of unfavorable cardiovascular outcomes.

Conclusions. This review describes approaches to the definition, principles of staging, strategies for prevention, as well as algorithms for the treatment of cardiovascular- kidney-metabolic syndrome, presents the key provisions for the management of cardiovascular-kidney-metabolic syndrome, proposed in the indicated clinical recommendations.

Keywords: *therapy, cardiovascular diseases, chronic kidney disease, type 2 diabetes mellitus, obesity.*

Abbreviations

AASLD – American Association for the Study of Liver Diseases
ACE – Angiotensin-Converting Enzyme
AF – Atrial Fibrillation
AH – Arterial Hypertension
AHA – American Heart Association
ARBs – Angiotensin Receptor Blockers
ASCVD – Atherosclerotic CVD
BMI – Body Mass Index
BP – Blood Pressure
CaReMe – CardioREnal and MEtabolic
CHF – Chronic Heart Failure
CKD – Chronic Kidney Disease
CKM syndrome – Cardiovascular-Kidney-Metabolic Syndrome
CKMH – Cardiovascular-Kidney-Metabolic Health
CVD – CardioVascular Disease
CVM – CardioVascular Mortality
CVS – CardioVascular System

Corresponding Author:
Herasymchuk Nina M. – MD, PhD, Associate Professor of the Department of Propedeutics of Internal Medicine, Nursing and Bioethics, Kharkiv National Medical University, Ukraine.
✉ 4, Nauky ave., Kharkiv, 61022, Ukraine.
E-mail: nm.herasymchuk@knmu.edu.ua

DM – Diabetes Mellitus
DOACs – Direct Oral Anticoagulants
EASL – European Association for the Study of the Liver
GFR – Glomerular Filtration Rate
GLP-1 – Glucagon-Like Peptide 1
GLP-1Ra – Glucagon-Like Peptide 1 Receptor Agonist
HbA1c – Glycosylated Hemoglobin
HF – Heart Failure
IGT – Impaired Glucose Tolerance
KDIGO – Kidney Disease: Improving Global Outcomes
MASLD – Metabolic Dysfunction-Associated Steatotic Liver Disease
MAU – Microalbuminuria
MS – Metabolic Syndrome
NHANES – National Health and Nutrition Examination Survey
NT-proBNP – N-terminal Pro-Brain Natriuretic Peptide
RF – Risk Factors
SGLT2 – Sodium-Glucose Cotransporter 2
TG – triglyceride
T2DM – Type 2 Diabetes Mellitus

Introduction

Chronic Heart Failure (CHF), as the inevitable outcome of almost all cardiovascular diseases, occupies a leading position in the structure of total mortality and persistent disability of the population, including those of working age. Despite the impressive achievements of modern pharmacology and cardiac surgery, the prognosis of CHF remains unfavorable. Based on a number of studies, a number of comorbid conditions have been identified, which significantly influence the course and prognosis of CHF.

Until recently, the relationship between the «heart-kidney» axis and metabolic syndrome has not been discussed in detail. Cardiorenal, cardiometabolic and metabolic syndromes stood separately from each other. However, the high incidence of morbidity and mortality, in particular from cardiovascular causes, raises many questions, the answers to which have not yet been completely found. Cardiovascular-Kidney-Metabolic Health (CKMH) is a relatively new interdisciplinary concept reflecting the relationship of metabolic risk factors, CKD and the CVS, which have a serious impact on morbidity and mortality of the population [1].

According to data from the Third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994, published in 2002) [2], the combination of any two cardiovascular risk factors leads to an increase in the likelihood of developing CKD with a decrease in the glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 by 3.7 times, and with an increase in BP within 130–139/85–89 mm Hg, the likelihood of developing MAU increases by 2.13 times compared to patients with normal BP values [3].

At the same time, one of the most important risk factors determining the high incidence of both CVD and CKD is T2DM. Insufficient control of each component of the cardio-kidney-metabolic continuum leads to multisystem consequences, the most significant of which are CVD and CVM. Finding additional opportunities to provide more complete cardio- and nephroprotection in patients with DM and CKD is a pressing problem nowadays.

In view of the suboptimal CKMH, especially among individuals with unfavorable social determinants (living conditions), international professional communities emphasize the need for a clear definition of the concept of CKM syndrome, principles of staging, prediction of outcomes and a holistic approach to the treatment of patients with CKM syndrome. The introduction of unified management strategies for this syndrome will improve the effectiveness of currently used treatment methods for comorbid patients. It is also critical to address social determinants of health in care delivery models and reduce separation of care through simplified approaches to a patient-centered interdisciplinary model.

The **aim** of this review was to demonstrate how, as a result of extensive discussion and scientific evidence, citing the strong pathophysiological interactions between heart disease, kidney disease, type 2 diabetes, and obesity, the American Heart Association has for the first time formally recommended expanding the concept of metabolic syndrome to cardiovascular-kidney-metabolic syndrome and to show the principles of staging, prevention strategies, as well as treatment algorithms for this syndrome.

Materials and Methods

This study is an analytical review of contemporary clinical and epidemiological studies from the past five years, using electronic databases, including PubMed and Google Scholar, as well as official guidelines from the AHA. The data from large population-based studies, including the NHANES III registry, examining the relationship between cardiovascular risk factors, chronic kidney disease, and metabolic disorders were analy-

zed. A descriptive and comparative analysis of the pathophysiological mechanisms, clinical manifestations, and treatment approaches for cardiovascular-renal-metabolic syndrome was used.

Research Ethics

This work is a review of published scientific evidence and clinical guidelines and does not involve the implementation of interventions involving patients or the use of personal data, so local ethical committee approval was not required.

Results

Today, a bidirectional relationship between dysfunction of the cardiovascular system and kidneys, known as cardiorenal syndrome, in which dysfunction of one organ causes dysfunction of the other, is well known. There is an equally widespread understanding of cardiometabolic syndrome. Thus, in the general population of patients with AH, overt, treatment-resistant AH occurs in [7.9–13.4]% of cases, however, its frequency increases significantly in certain groups of people with obesity, metabolic syndrome, T2DM, and especially in patients with CKD, where its prevalence can reach 31% [3; 4]. Excessive and dysfunctional adipose tissue (especially visceral obesity and other ectopic fat deposits) can cause inflammation, insulin resistance, metabolic risk factors, and a variety of systemic consequences, including increased risk of CVD [5]. Although these syndromes are well known, there is a growing understanding that metabolic abnormalities play a key pathophysiological role in the bidirectional interactions of the cardiovascular system and the kidneys. In addition, kidney dysfunction is increasingly recognized as a key mediator of the relationship between metabolic risk factors and CVD, especially HF [6]. Thus, rather than viewing cardiorenal syndrome and cardiometabolic diseases as separate processes, it is becoming increasingly clear that their intersections need to be viewed as a broader concept CaReMe.

In October 2023, the AHA for the first time officially defined what is called CKM syndrome, defined as a systemic disease characterized by pathophysiological interactions between metabolic risk factors, CKD and the cardiovascular system, leading to multiple organ dysfunction and high rates of adverse cardiovascular outcomes [7; 8]. It is emphasized that CKM syndrome is a progressive condition that often begins at a relatively early age under the influence of biological, social or environmental factors [9].

The CKM syndrome includes both individuals at risk for CVD due to the presence of metabolic RF, CKD, or both, and individuals with existing CVD that are potentially associated with or complicate metabolic RF or CKD. According to experts from the AASLD and the EASL, CKM syndrome most often results from excess adipose tissue, adipose tissue dysfunction, or both. Inflammation, oxidative stress, insulin resistance and vascular dysfunction are identified as central processes leading to the development of metabolic RF, progression of kidney diseases, potentiation of cardiorenal interactions and development of CVD. Metabolic RF and CKD additionally predispose to CVD through several direct and indirect pathways, including potentiated MASLD (*Fig.*) [7; 10]. In this regard, it is very important to identify signs of CKM in the early stages in order to carry out preventive measures.

The mechanisms of vascular, cardiac, and renal injury associated with these processes can be broadly classified as hemodynamic, metabolic, inflammatory, and fibrotic. Hyperglycemia causes glomerular hyperfiltration and hypertension – hemodynamic mechanisms that have long been recognized to initiate and exacerbate renal damage. Along with obesity and systemic hypertension, glomerular hemodynamics and arterial injury are caused by overt stress and endothelial damage, which contribute to both atherosclerosis and glomerulosclerosis [11; 12].

Hypertension and obesity are also major etiological factors underlying the development of left ventricular hypertrophy and HF [12]. Hyperglycemia in T2DM initiates a series of intracellular processes that contribute to renal and vascular damage through inflammation and fibrosis [11].

Evidence of CKD, albuminuria, low glomerular filtration rate, or both are associated with a progressive increase in the risk of major atherosclerotic vascular events and cardiovascular events, as well as CVD death. Consequently, the most common causes of death in individuals with T2DM and CKD are HF and ASCVD, and only ~10% of patients with CKD survive to renal failure [10]. CKD and diabetes are more likely to cause below-knee peripheral arterial disease, which is often more difficult to revascularize and is associated with more ischemic damage. CKD also leads to anemia and disorders of bone and mineral metabolism, which worsen CVD. Decreased oxygen carrying capacity increases myocardial demand and may aggravate HF [13]. HF can reduce the glomerular filtration rate as a result of impaired cardiac output, high venous pressure, activation of the renin-angiotensin-aldosterone system and the

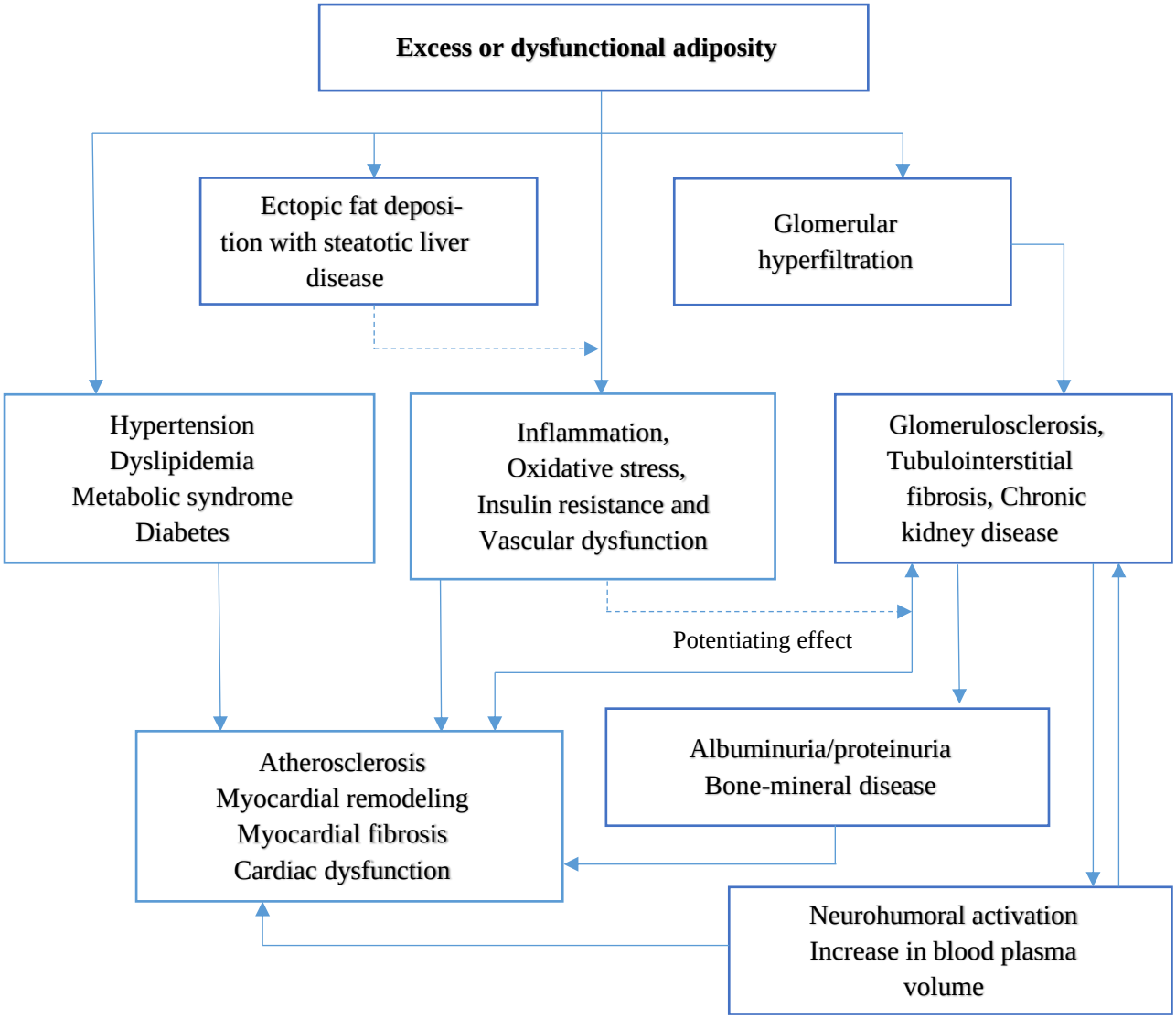

Fig. Scheme of the cardiovascular-kidney-metabolic syndrome

sympathetic nervous system [13]. Therefore, it is very important to identify the signs of CKM syndrome at early stages to carry out preventive measures.

The principles of staging and the algorithm for treating CKM syndrome reflect the pathophysiological aspects, the degree of risk and the possibilities for prevention and optimization of medical care.

The authors have identified four stages of the CKM syndrome [7].

Stage 0 is the absence of CKM risk factors with normal body mass index (BMI) and waist circumference, normotension, normoglycemia, normal lipid profile and no signs of CKD or subclinical/clinical CVD. The aim is to prevent CKM syndrome (especially unhealthy weight gain) by achieving and maintaining ideal health based on the 8 AHA Life's Essentials (diet, physical activity, smoking, BMI, fasting blood glucose, total cholesterol and BP, healthy sleep) [14]. In this case, the fight against obesity is a major aspect in the prevention of CKM syndrome due to its role in the development of T2DM, hypertension and dyslipidemia. It is also emphasized that to maintain a healthy lifestyle and prevent the development of risk factors for CKM syndrome with age, it is necessary to optimize maternal health (even before pregnancy) to reduce the likelihood of CKM syndrome in offspring, implement healthy lifestyle recommendations and use resources to prevent the development of risk factors for CKM syndrome in young patients. Adults at this stage should be examined every 3–5 years to assess lipid levels, BP and blood sugar levels.

Stage 1: excessive or dysfunctional accumulation of adipose tissue (clinically manifested as impaired glucose tolerance or prediabetes) without other metabolic RF or CVD [7]. The criteria for this stage are a BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if of Asian descent); waist circumference ≥88/102 cm in women/men (or ≥80/90 cm in women/men if of Asian descent) and/or fasting blood glucose ≥[5.5–6.8] mmol/L or HbA1c 5.7% to 6.4% [4]. Those with stage 1 also include women with a history of gestational diabetes, who are at risk of developing diabetes and should be monitored for the occurrence of impaired glucose tolerance after pregnancy [15].

Treatment includes support for healthy lifestyle changes (healthy diet and regular physical activity) with the goal of at least 5% weight loss and correction of glucose intolerance, if necessary [16]. For individuals with persistent/progressive IGT despite lifestyle modification, metformin may also be considered to prevent the development of T2DM. It is recommended to screen adults with stage 1 CKM syndrome every 2–3 years to assess BP, TG levels, cholesterol, and blood sugar [7].

Stage 2: metabolic risk factors and CKD. Stage 2 is characterized by the presence of metabolic RF (hypertriglyceridemia (≥1.5 mmol/l), AH, metabolic syndrome, T2DM), moderate or high risk CKD, or a combination of these factors with their annual screening. CKD is defined by decreased GFR or albuminuria that persists for ≥3 months [17].

The goal of treatment in the second stage is the comprehensive elimination of metabolic risk factors and CKD in order to prevent the progression of CVD to subclinical and clinical forms. Optimal reduction of cardiovascular risk in metabolic syndrome includes lifestyle changes followed by targeted pharmacotherapy to control BP, glycemia, and lipid levels. Target parameters for glycemic and BP control for most patients are: HbA1c <7%, BP <130/80 mmHg. Although thiazide-type diuretics and calcium channel blockers are equally effective, ACE inhibitors/ARBs should be a priority in patients with T2DM and albuminuria or in patients with other CKDs given their effect on preventing deterioration of renal function [18; 19].

In individuals with intermediate and high risk of ASCVD, statin therapy moderately reduces TG levels and reduces the risk of ASCVD. In individuals with TG levels ≥2.3 mmol/L and an increased risk of pancreatitis, fibrate therapy is recommended, with fenofibrate being preferred when combined with statins due to fewer side effects. In individuals with moderate hypertriglyceridemia ([1.5–5.6] mmol/L), diabetes, and associated RF, icosapent ethyl (a purified form of eicosapentaenoic acid) reduces the risk of cardiovascular events [20]. In diabetes and/or HF, SGLT2 inhibitors (empagliflozin, dapagliflozin) or a GLP-1 receptor agonist (GLP-1Ra) reduce the risk of deterioration in renal function and are probably preferred in patients with CKD [21]. GLP-1 Ra (liraglutide, semaglutide) may be preferred in individuals with severe obesity (BMI ≥35 kg/m^2), given their powerful effect on weight loss. In individuals with diabetic nephropathy and proteinuria taking ACE inhibitors/ARBs, finerenone, a highly selective non-steroidal mineralocorticoid receptor antagonist, may be considered to reduce the risk of adverse cardiovascular and renal events [22].

Stage 3: Subclinical CVD, equivalent CVD risk factors, or very high risk of CKD. Subclinical HF is defined by elevated levels of cardiac biomarkers (NT-proBNP ≥125 pg/mL, high-sensitivity troponin T ≥14 ng/L for women and ≥22 ng/L for men, high-sensitivity troponin I ≥10 ng/L for women and ≥12 ng/L for men) or echocardiographic parameters, with the combination indicating the highest risk of HF. There is a high risk of ASCVD within 10 years and a very high risk of CKD stages 4–5. The goal is to intensify efforts to prevent progression to symptomatic CVD and kidney failure. This may include increasing or changing medications and additional attention to lifestyle changes. Measurement of coronary artery calcium score in some adults is recommended to assess possible arterial narrowing when treatment decisions are unclear [7].

The addition of β-blocker therapy to ACE inhibitors in patients with asymptomatic left ventricular dysfunction is associated with lower rates of the composite endpoint of death or hospitalization for HF [23]. SGLT2 inhibitors reduce the likelihood of hospitalization for HF or CVD mortality, especially in patients with diabetes. However, combination therapy with SGLT2 inhibitors and GLP-1Ra may have a greater effect on major adverse cardiac events and HF manifestations than either drug alone [24].

Stage 4: CVD with or without renal insufficiency. Stage 4 CKM syndrome is divided into two subcategories: (4a) without renal insufficiency and (4b) with renal insufficiency. It includes clinical CVD (coronary artery disease, HF, stroke, peripheral arterial disease, atrial fibrillation) among individuals with excessive/dysfunctional obesity, other metabolic RF and CKD [7]. The aim of treatment is individualized CVD treat-

ment taking into account the conditions of CKM syndrome. Treatment of patients with HF is carried out with an emphasis on four main components of therapy: β-blockers, angiotensin/neprilysin receptor inhibitors, mineralocorticoid receptor antagonists and SGLT2 inhibitors in case of reduced left ventricular ejection fraction [25]. The use of ACE inhibitors/ARBs and mineralocorticoid receptor antagonists may be challenging in CKD due to concerns about hypotension, hyperkalemia, and worsening renal function [26]. An analysis of 6 randomized trials showed that concomitant use of SGLT2 inhibitors reduces the risk of severe hyperkalemia [27]. GLP-1Ra reduces the risk of myocardial infarction, stroke, and cardiovascular mortality in people with diabetes and causes significant weight loss ([12–18]%) [28].

Several risk factors for CKM syndrome, including AH, obesity, CKD, and dyslipidemia, are associated with a higher likelihood and severity of AF, so comprehensive RF management is recommended in such patients [29; 30]. In addition, RF CKM syndrome in DM and AH increases the risk of stroke in AF, which necessitates the use of anticoagulants for prophylaxis. When anticoagulant therapy is indicated, recent guidelines support the use of DOACs or warfarin in patients with CKM syndrome, including those with severe obesity or CKD. However, with progressive kidney disease, dose adjustment of direct oral anticoagulants is required. Weight loss, regular physical activity, and improvement of cardiorespiratory fitness are recommended to improve the course of AF. Treatment of obstructive sleep apnea, which is closely associated with obesity, may help reduce the severity of AF [29].

The risk of CVD is disproportionately increased in patients with renal failure on maintenance dialysis, with HF and atherosclerotic CVD representing the two main phenotypes in this population [31]. Although there are limited high-quality data to guide optimal treatment of HF and ACVD in renal failure, several therapies have shown beneficial effects, particularly on HF-related outcomes. Consideration should be given to frequent dialysis sessions to reduce left ventricular hypertrophy/left ventricular mass index and HF hospitalizations, and to improve quality of life [32; 33]. When using drug classes such as β-blockers or ACE inhibitors, their dialyzability and synchrony with the dialysis cycle should be considered [34]. The role of routine initiation of statins in dialysis patients without known ACVD is limited, but continuation of statins started before dialysis is reasonable [35]. Finally, given the high rates of pulmonary hypertension and right heart failure that are characteristic of renal failure and the renal replacement therapy process, an early multidisciplinary approach involving leading HF specialists is recommended [36].

There is heterogeneity in the rate and extent of progression across the stages of CKM syndrome. Progression through the stages of CKM syndrome is associated with increased relative and absolute risk of CVD, renal failure, and mortality. Factors such as genetics, behavioral factors, and environmental factors may collectively significantly influence the progression of CKM syndrome across all its stages [7].

Discussion

The most effective strategy for CKM syndrome management that ensures both multifactorial therapeutic effect and higher patient compliance is an interdisciplinary approach to providing care to such patients. It is proposed to create an interdisciplinary group for the treatment of CKM syndrome, which, together with primary care physicians, will develop protocolized recommendations for the care of patients with two or more co-occurring diseases within the framework of CKM syndrome to maintain an integrated approach to ensuring high-quality and timely access to treatment. The interdisciplinary team will be supported by a coordinator and will also include representatives of primary care, cardiologists, nephrologists, endocrinologists, pharmacy and nursing, care navigators, social workers or community health workers. At the same time, depending on the severity and associated risks, patients should be timely referred to related specialists to ensure holistic management of CKM syndrome and optimize treatment methods. It is proposed to differentiate the principles of patient management depending on the stage of CKM syndrome.

Potential thresholds for referring a patient for consultation with a specialist have been identified:

- nephrologist – in case of increased risk according to KDIGO: stages 3a (A3, especially if there is no response to ACE inhibitors/ARBs), 3b (A2/A3), 4 and 5 [37];
- endocrinologist – in case of DM with poor glycemic control (HbA1c >9%) or microvascular diseases and/or target organ damage;
- cardiologist – if CVD is present, consultation may be considered in the presence of subclinical high-risk CVD, such as markedly elevated coronary calcium (≥ 300 in non-elderly adults (men <65 years or women <75 years) and/or multiple RF

for CKM syndrome or coronary calcium ≥ 1,000) or a combination of elevated cardiac biomarker and abnormal echocardiography.

Conclusions

CKM syndrome reflects the influence of multisystem pathophysiological interactions nested within a multilevel socially and clinically determined entity, the confluence of which determines clinical outcomes. It is important that clinical trials include the full spectrum of patients with CKM syndrome, with a particular need to include patients with CKD, who have traditionally been underrepresented in cardiovascular research. Numerous knowledge gaps necessitate targeted research in key areas. In relation to the development of the CKM syndrome concept, there is an incomplete understanding of sex differences, the genetic basis and application of genetic testing, the mechanisms of vascular, myocardial and renal dysfunction, and environmental and societal RF. Strategies for the use of combination therapy, as well as evidence-based approaches to its initiation, monitoring and maintenance, are important and represent areas of future research. Improved lifelong CKM syndrome screening strategies, particularly for those at highest risk, will facilitate early intervention to avoid progression to CKM syndrome and reduce the risk of cardiovascular events and renal failure.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Ashcheulova T.V.	+	+	+	+	+	+
Herasymchuk N.M.	+	+	+	+	+	+
Ambrosova T.M.	+				+	+
Kochubiei O.A.		+			+	+
Herasymchuk U.S.	+	+	+	+	+	+

Notes: A – concept; B – design; C – data collection;
D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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THE USE OF POSITRON EMISSION TOMOGRAPHY AND COMPUTED TOMOGRAPHY WITH 18F-FLUORODEOXYGLUCOSE AS A SELECTION CRITERION FOR SURGICAL TREATMENT IN CHILDREN WITH DRUG-RESISTANT EPILEPSY (literature review)

Romanenko H.

Bogomolets National Medical University, Kyiv, Ukraine

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ABSTRACT

Background. In the contemporary context, the management of paediatric patients afflicted with drug-resistant epilepsy continues to represent a significant challenge for specialists in the field of paediatric neurology. This persistent predicament underscores the imperative for the development of precise and non-biased criteria to facilitate the selection of candidates for surgical intervention. The integration of Positron Emission Tomography with Computed Tomography with 18F-FluoroDeoxyGlucose (18F-FDG PET/CT) and high-resolution neuroimaging has the potential to facilitate a personalised approach and to identify candidates for surgical treatment.

Aim. To ascertain the diagnostic and prognostic role of positron emission tomography with 18F-fluorodeoxyglucose in combination with computed tomography in the selection of paediatric patients with drug-resistant epilepsy for surgical treatment.

Materials and Methods. The work employed a range of methodological approaches, encompassing theoretical generalisation, analysis and synthesis of results. The search for relevant works was conducted in the scientometric Scopus, Web of Science, PubMed, Google Scholar databases. The research was conducted as a private initiative of the authors, did not receive funding from grant programs, and the research topic was not officially registered in the state register.

Research Ethics. During work, studies were selected whose authors demonstrated adherence to ethical standards.

Results. The sensitivity of 18F-FDG PET/CT in localising the epileptogenic focus was found to range from 80.0% to 89.0%, with the specificity of 78.0%. The combination of PET with magnetic resonance imaging has been shown to enhance the accuracy of identifying the affected area to 85.0%. Quantitative assessment of hypometabolism using automated analysis programs (CortexID, Morphometric Analysis) has significant prognostic value for predicting postoperative outcomes. The utilisation of digital systems and algorithms of quantitative analysis serves to enhance the reliability of the results, while the absence of uniform standards continues to represent a significant limitation.

Conclusions. 18F-FDG PET/CT is a highly effective method of preoperative diagnosis, which improves the quality of selection of children for surgical treatment of drug-resistant epilepsy. Integration of PET/CT with other neuroimaging technologies, quantitative assessment of metabolism and further standardisation of protocols are promising avenues for the development of personalised diagnostics in paediatric neurology.

Keywords: *medical radiology, paediatric, treatment effectiveness, epileptogenic focus, metabolic activity*.

Corresponding Author:

Romanenko Hanna – PhD, Docent, Associate Professor of the Department of Radiology and Radiation Medicine, Bogomolets National Medical University, Ukraine.

✉ 3, Taras Shevchenko blvd., Kyiv, 01601, Ukraine.

E-mail: ganusya96@gmail.com

Introduction

Nowadays, Drug-Resistant Epilepsy (DREP) in children remains one of the most difficult problems in paediatric neurology, which necessitates the search for new approaches to accurate diagnosis and personalised treatment. Despite the achievements of drug therapy, about a third of paediatric patients do not achieve seizure control even with the combined use of antiepileptic drugs [1; 2].

In such cases, the main method of achieving stable remission is surgical intervention, the effectiveness of which directly depends on the accuracy of identifying the epileptogenic focus.

Surgical interventions in children diagnosed with DREP are planned based on various diagnostic measures, including electrophysiological testing and neuroimaging. The results of epilepsy surgery are promising, with high chances of recovery, particularly in cases of a temporal lobe epilepsy, which leads to a significantly higher absence of seizures after surgery compared to drug treatment. However, localisation of the zone of onset of seizures in DREP, and the identification of epileptogenic zones, including the determination of their boundaries, remains a challenging task [3; 4].

Whilst classical neuroimaging methods, including Magnetic Resonance Imaging (MRI), ElectroEncephaloGraphy (EEG) and video-EEG monitoring, remain fundamental tools for preoperative assessment, they do not always permit the identification of structural and functional changes in the cortex [5–7]. In this regard, the role of Positron Emission Tomography with 18F-FluoroDeoxyGlucose in combination with Computed Tomography (18F-FDG PET/CT) is increasing as a highly sensitive method capable of displaying areas of hypometabolism [3; 8; 9].

Recent years have been characterised by a significant increase in the diagnostic accuracy of PET/CT due to its integration with high-resolution neuroimaging and the introduction of quantitative data processing algorithms, in particular the CortexID and Morphometric Analysis Programme [7; 10]. This allows not only to identify lateralized hypometabolic areas of the cortex, but also to perform a semi-quantitative assessment of metabolic activity, considering individual variations in brain asymmetry [11; 12].

In most countries worldwide, the proportion of children who have access to surgical treatment of epilepsy does not exceed 1% of potential candidates. This finding suggests an underestimation of the role of preoperative neuroimaging [2]. Concurrently, the timely and accurate localisation of the epileptogenic focus enhances the efficacy of surgical intervention, mitigates the risks of cognitive disorders, reduces the duration of drug therapy and improves the quality of life of the child [11; 13; 14].

Consequently, the generalisation of modern scientific data on the use of 18F-FDG PET/CT in the preoperative diagnosis of DREP in children is an urgent and necessary task. A thorough analysis of international experience enables an evaluation of the prognostic and diagnostic capabilities of the method, and the identification of factors that affect its accuracy.

Aim and objectives

The **aim** of the study was to ascertain the diagnostic and prognostic role of positron emission tomography with 18F-fluorodeoxyglucose in combination with computed tomography in the selection of paediatric patients with drug-resistant epilepsy for surgical treatment.

The **objectives** of the study were:

1) to analyse modern literature sources on the use of 18F-FDG PET/CT in preoperative diagnosis of FRE in children, identifying the main directions of development of this technology in clinical neurology;

2) to assess the diagnostic effectiveness of 18F-FDG PET/CT in determining the localisation of the epileptogenic focus compared to other neuroimaging methods (MRI, EEG, video-EEG monitoring), considering age-related features of brain metabolism;

3) to systematise the prognostic indicators of 18F-FDG PET/CT that correlate with successful results of surgical treatment, and to outline the factors that affect the accuracy and clinical informativeness of the method.

Materials and Methods

The work used methods of theoretical generalisation, analysis and synthesis of results. The search for relevant works was conducted in the scientometric databases Scopus, Web of Science, PubMed and Google Scholar.

Research Ethics

During the work, studies were selected whose authors adhered to ethical standards.

Results

Modern epidemiological studies indicate that the frequency of DREP in children is from 20.0 to 30.0% among all cases of epilepsy, and about half of such patients have structural lesions of the cerebral cortex, which can be detected by neuroimaging [1; 2]. Early diagnosis of this pathology is of great importance, since the long-term persistence of uncontrolled seizures leads to impaired cognitive development, behavioural disorders and social maladjustment of the child. According to Beatty C.W. et al. (2021) [2], surgical treatment of paediatric epilepsy remains underutilised, despite its proven efficacy and low complication rates.

Despite the existence of a plethora of antiepileptic medications, remission remains elusive for a considerable number of paediatric patients. This

underscores the importance of surgical intervention as a viable and effective treatment option for individuals suffering from seizures. The efficacy of surgical intervention is contingent upon the precision of identifying the epileptogenic focus and the judicious selection of candidates. The purpose of complex neuroimaging with 18F-FDG PET/CT is to provide further insight into the underlying pathophysiology of the condition [13–15].

According to contemporary scientific research, the use of 18F-FDG PET/CT for diagnostic purposes offers a high degree of sensitivity in detecting metabolically inactive areas of the cortex, corresponding to epileptogenic foci. In the study by Steinbrenner M. et al. (2022) [8], the diagnostic accuracy of PET/CT was established at 85.0%, and the specificity was 78.0% in histologically confirmed forms of temporal lobe epilepsy. Furthermore, it was demonstrated that in 60.0% of patients with foci not determined by MRI, PET/CT revealed additional areas of hypometabolism, which were consistent with EEG results. Quantitative analysis of SUVmax has proven prognostic value. In the study by Steinbrenner M. et al. (2022) [8], the median SUVmax in the epileptogenic focus zone was 4.8 (IQR 3.9–5.7), which was significantly lower than in the contralateral symmetrical area ($p<0.001$). Li S. et al. (2024) [10] demonstrated that a 15% asymmetry threshold in SUVmax-based metabolism provided 82.0% sensitivity and 76.0% specificity for preoperative localization of the epileptogenic focus. Sainburg L.E. et al. (2025) [11] showed that a lateralized hypometabolism zone with a ≥20% reduction in SUVmax relative to the contralateral area was associated with a seizure-free period of two years after surgery in 84.0% of children. In addition, the high efficiency of the method was confirmed in the meta-analysis by Courtney M. et al. (2024) [4]. The presence of a clearly localised hypometabolic zone correlated with a successful surgical outcome in 72.0% of cases, while in diffuse or multifocal hypometabolism the success of the intervention decreased to 48.0%.

It has been established that in cases of MRI-negative forms, PET/CT may be the sole method that allows detecting hypometabolic areas of the cortex corresponding to foci of pathological activity [3; 6; 7]. Concurrently, it is imperative to consider age-related variations in glucose metabolism in children. The activity of glucose metabolism in the child's brain is significantly different from that of the adult. This requires the use of separate age-specific reference values for the interpretation of PET images [16].

Scientific observations of recent years confirm that integrated PET/CT and PET/MRI methods demonstrate more accurate localisation of epileptogenic foci compared to separate structural methods, especially in cases of implicit morphological changes [3; 5; 17]. Similar results were obtained in the meta-analysis of Courtney M. et al. (2024) [4], which confirmed the association between localised hypometabolism and successful seizure control after resection in 72% of cases.

Despite the high informativeness, the results of PET/CT depend primarily on the conditions of the study, including the period between attacks, the depth of sedation and correction of the child's blood glucose level. The study by Carvalho et al. (2022) [18] indicated that deviations in time from the last attack of more than 48 hours can reduce the accuracy of image interpretation by 10–15%. In addition, the type of data reconstruction and software can affect the results. The implementation of artificial intelligence and machine learning algorithms for automatic segmentation of hypometabolic areas has been actively developing in recent years [9; 19].

The use of automated analysis programmes (Morphometric Analysis Program, CortexID) facilitates the transition from subjective image assessment to quantitative characterisation of hypometabolic regions. In the study by Li S. et al. (2024) [10], it was demonstrated that the CortexID technique has sensitivity of 82.0% in detecting epileptogenic zones in temporal lobe epilepsy. Furthermore, it was found to allow for quantitatively assessment of the level of metabolic reduction in percentage relative to control areas. The utilisation of digital PET/CT systems has been demonstrated to yield favourable outcomes, characterised by enhanced image contrast, diminished scanning duration, and reduced noise [20].

The findings of contemporary studies show that indicators of hypometabolism on PET/CT can function as autonomous prognostic markers of the success of surgical intervention. In the work of Sainburg L.E. et al. (2025) [11] it has been established that lateralized zones of hypometabolism are associated with a long seizure-free period in 84.0% of children within two years after surgery. Similar data are given in the study of Wang F. et al. (2024) [12], where in patients with focal cortical dysplasia type II the positive predictive accuracy of PET/CT was 80.0%, and the lack of a clear

localisation of hypometabolism increased the risk of seizure recurrence by 2.1 times. This facilitates not only the precise determination of the lesion's localisation, but also the prediction of the outcome of surgical intervention.

Discussion

The generalisations obtained from the literature data are compelling and indicate that 18F-FDG PET/CT occupies a central place in the presurgical diagnosis of FRE in children. This method has been demonstrated to provide a high level of detection of epileptogenic zones even in the absence of structural changes on MRI. As shown by Steinbrenner M. et al. (2022) [8], Guo K. et al. (2025) [3], the sensitivity of the method exceeds 80.0%, while the specificity was 78.0%. This efficiency can be attributed to the capacity of PET/CT to reflect metabolic changes in neurons, rather than morphological changes, thereby ensuring the early detection of epileptogenic areas before the onset of macroscopic changes.

It is important to note that in childhood, when MRI-negative forms are established, PET/CT often becomes a key technique in determining surgical tactics. It was found that localised hypometabolism as evidenced by PET scanning was an independent predictor of successful surgical outcome [4]. Moreover, a decline in metabolism lateralisation has been observed to be concomitant with protracted seizure-free periods in 84.0% of children [11]. This confirms that hypometabolism is not only a marker of focal activity, but also an indicator of prognosis after surgery.

It has been found that the integration of PET data with MRI significantly increases diagnostic accuracy [3]. This indicates the feasibility of using multiparametric approaches, especially in paediatric practice, where anatomical variability and physiological changes in metabolism complicate the interpretation of results. Concurrently, disparities in PET/CT techniques, 18F-FDG dosage, and image reconstruction parameters engender variability in results between centres [9; 16; 19; 21]. This indicates the need for further standardisation of protocols. As Tian M. et al. (2021) [16] observe, the implementation of unified age-specific metabolic norms will reduce discrepancies in 20–25% of cases. In the context of predicting postoperative outcomes, most authors concur that accurate localisation of the hypometabolic area on PET/CT significantly increases the likelihood of successful resection and reduces the risk of relapse [11; 22; 23]. It was found that patients with clear metabolic lateralisation had a lower probability of recurrence compared to those with diffuse PET changes [12].

Consequently, the analysis indicates that 18F-FDG PET/CT is an indispensable component of a contemporary multidisciplinary approach to the management of children with FRE. The method has been demonstrated to serve a dual purpose; firstly, it clarifies the lesion site, and secondly, it functions as a tool for predicting the results of surgical intervention. This corresponds to modern concepts of personalised medicine.

Conclusions

18F-FDG PET/CT is a highly sensitive and specific method for presurgical diagnosis of drug-resistant epilepsy in children, which provides detection of epileptogenic zones even in the absence of structural changes on MRI. Integration of PET/CT with MRI or other neuroimaging methods increases the accuracy of localisation of the pathological focus and allows optimising surgical tactics. Quantitative assessment of hypometabolism using and automated analysis programmes (CortexID, Morphometric Analysis) has significant prognostic value for predicting postoperative outcomes.

The 18F-FDG PET/CT technique requires further standardisation of protocols for the paediatric population, considering age-related characteristics of glucose metabolism. The use of PET/CT as part of a multidisciplinary approach contributes to the timely selection of children for surgical treatment, reduces the risk of relapse of seizures, and improves cognitive prognosis.

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Declarations

Conflict of interest is absent. The author has consented to the publication of the article under the terms of the Creative Commons BY-NC-SA 4.0 International License and the public agreement with the editorial board, as well as to the processing and publication of his personal data.

The author of the manuscript states that in the process of conducting research, preparing, and editing this manuscript, no generative AI tools or services were used to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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CREUTZFELDT-JAKOB DISEASE (CLINICAL CASE)

Oros M.M., Lutz V.V., Bulecza B.A.

Uzhhorod National University, Uzhhorod, Ukraine

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ABSTRACT

Background. Creutzfeldt-Jakob Disease (CJD) is a rare neurodegenerative disorder belonging to the group of transmissible spongiform encephalopathies caused by prion agents. Despite numerous studies, early diagnosis of CJD remains challenging due to the non-specific nature of symptoms in the initial stages and their similarity to other rapidly progressive dementias and psychiatric disorders.

Aim. To present a clinical case of the sporadic form of Creutzfeldt-Jakob disease with an emphasis on diagnostic difficulties and possibilities for confirming the diagnosis.

Materials and Methods. A 47-year-old female patient with progressive cognitive impairment, cerebellar ataxia, and extrapyramidal disorders was examined. Neurological assessment included evaluation of the level of consciousness, motor functions, and coordination. Laboratory investigations comprised ElectroEncephaloGraphy (EEG), Magnetic Resonance Imaging (MRI) of the brain, and cerebrospinal fluid analysis for specific biomarkers, particularly the 14-3-3 protein, which is an important marker for confirming the diagnosis of CJD.

Research Ethics. The patient was included in the study after providing informed consent. The study was conducted in full compliance with existing international and national bioethical standards and regulations (the Nuremberg Code and the WMA Declaration of Helsinki, 1964–2024) regarding ethical principles for medical research involving human subjects.

Results. The patient demonstrated characteristic clinical manifestations, including rapidly progressive dementia complicated by pronounced cerebellar ataxia and coordination disturbances. MRI findings revealed atrophic changes in the basal ganglia and cerebellum, which are typical of CJD. EEG showed periodic sharp-wave complexes, the main diagnostic criterion for this disease. Cerebrospinal fluid analysis revealed an elevated level of 14-3-3 protein, which further confirmed the diagnosis of CJD.

Conclusions. Considering the characteristic clinical manifestations, EEG and MRI changes, and the presence of the specific 14-3-3 protein in cerebrospinal fluid, the diagnosis of CJD was confirmed *in vivo*. Identification of these changes is a key step for timely confirmation of the diagnosis and determination of further patient management strategies. Given the rapid progression of CJD and the absence of etiotropic therapy, neuro-palliative care represents an essential component of management, enabling symptom relief and improvement of the patient's quality of life during disease progression.

Keywords: *electroencephalography, magnetic resonance imaging, 14-3-3 protein, cerebrospinal fluid, neuro-palliative care.*

Introduction

Creutzfeldt-Jakob Disease (CJD) is a neurodegenerative disorder that is presumably caused by a slow infectious agent, or a prion. The main clinical manifestations of CJD include dementia, pyramidal and extrapyramidal disorders, cerebellar dysfunction, myoclonus, cognitive impairment, and loss of personal identity. The course of the disease is characterized by rapid progression: the patient's condition deteriorates to a vegetative state, with the development of coma and subsequent death within several months [1–5].

From an epidemiological perspective, the incidence of CJD is approximately 1–2 cases per million population per year [6]. At the same time, improvements in surveillance systems and increased

Corresponding Author:
Oros Mykhailo M. – DMedSc, Professor, Head of the Department of Neurology, Neurosurgery and Psychiatry, State Higher Educational Institution "Uzhhorod National University", Ukraine.
✉ 27 Andriia Novak str., Uzhhorod, 88000, Ukraine.
E-mail: kaf-neurology@uzhnu.edu.ua

awareness among healthcare professionals contribute to more timely detection of the disease. According to a recent cohort analysis in the United States, diagnostic delays, frequent misdiagnoses, and significant healthcare resource expenditures remain pressing issues, highlighting the importance of establishing specialized centers and prion disease registries [7].

One of the main difficulties is early and accurate diagnosis. Initial clinical manifestations are often non-specific and may mimic other forms of rapidly progressive dementia, parkinsonism, or psychiatric disorders. In recent years, cases have been described in which parkinsonism was the initial manifestation of sporadic CJD [1]. Although EEG and MRI remain the main diagnostic tools, their sensitivity in the early stages of the disease is limited. Recent studies emphasize the need to combine EEG data, diffusion-weighted MRI, and cerebrospinal fluid biomarkers, while simultaneously excluding potentially treatable conditions that may mimic CJD [2].

Aim of a study was to present a clinical case of Creutzfeldt-Jakob Disease, in which the diagnosis was confirmed by clinical manifestations, typical ElectroencEphaloGraphy (EEG) findings, characteristic Magnetic Resonance Imaging (MRI) features, and neuropathological signs.

Materials and Methods

The study was carried out using methods of clinical observation, laboratory and instrumental diagnostic methods, and a comparative method.

Research Ethics

The patient was included in the study after providing informed consent. The study was conducted in full compliance with existing international and national bioethical standards and regulations (the Nuremberg Code and the WMA Declaration of Helsinki, 1964–2024) regarding ethical principles for medical research involving human subjects.

Results

A 47-year-old female patient (M.) was admitted to a neurological hospital with complaints of pain in the elbow joints, which she associated with a tick bite, progressively worsening coordination disturbances, cognitive impairment, general weakness, low mood, and depressive symptoms.

From the medical history, it is known that approximately one year prior to examination the patient had been bitten by a tick. Laboratory tests revealed high titers of IgM and IgG antibodies to Borrelia burgdorferi. The patient was treated by an infectious disease specialist and completed a 28- day course of doxycycline and ceftriaxone. Despite therapy, her condition gradually worsened, with increasing cognitive impairment and ataxia. Further treatment at the place of residence was ineffective, after which the patient was referred to a neurologist for further management.

According to the life history, the patient is married, has one child, and has worked as a laboratory scientist in a clinical diagnostic laboratory of a district hospital for 24 years. She has no harmful habits.

On neurological examination, the pupils were of normal size with preserved light reaction (D=S, where D – Dexter, S – Sinister, that is, the reflex is equally pronounced on both sides); bilateral weakness of convergence was noted; horizontal low-amplitude nystagmus; flattening of the right nasolabial fold; moderate dysarthria.

Deep tendon reflexes were increased, more pronounced on the right (D>S); Babinski and Rossolimo pathological reflexes were positive bilaterally. Muscle strength and tone in the lower limbs were reduced, with preserved sensation. In the Romberg position, marked ataxia was observed; gait was ataxic; during the finger-to-nose test, bilateral dysmetria was noted.

Brain MRI revealed bilateral pathological changes in the basal ganglia and thalamus, as well as atrophic processes of the cerebral cortex and cerebellum. Differential diagnosis was recommended between a neurodegenerative process (including CJD) and metabolic disorders of the subcortical gray matter. Microangiopathy corresponded to grade 2 according to the Fazekas scale.

EEG demonstrated a pattern typical of CJD-periodic sharp-wave complexes.

Routine blood and urine analyses showed no pathological changes.

Biochemical blood analysis revealed values within physiological limits, except for increased alanine aminotransferase activity (72.6 U/L) and decreased serum ionized calcium level (1.15 mmol/L; normal range 2.15–2.5 mmol/L).

Thyroid-stimulating hormone, vitamin B12, and folic acid levels were within normal ranges.

Cerebrospinal fluid analysis showed that it was clear; protein level was 0.114 g/L, glucose 4.31 mmol/L; cytosis consisted of single neutrophils, 0–1 lymphocyte per field of view, and 1–2 erythrocytes. The cerebrospinal fluid test for 14-3-3 protein was positive.

DNA of cytomegalovirus and Epstein-Barr virus, as well as antibodies to the NMDA receptor (NR1 subunit), were not detected.

The patient received palliative care and symptomatic treatment, including sertraline and analgesics as needed.

Discussion

CJD remains one of the most severe neurodegenerative disorders due to its rapid progression, diagnostic complexity, and lack of effective therapy. Current research focuses on improving diagnostic accuracy, studying molecular heterogeneity, and integrating neuro-palliative care; however, many significant challenges remain unresolved.

During diagnosis, other causes of rapidly progressive dementia must be excluded. Alzheimer's disease, frontotemporal dementia, and dementia with Lewy bodies may clinically mimic CJD, especially in cases of atypically rapid progression. However, these disorders typically progress over months or years, and their MRI and cerebrospinal fluid biomarker profiles differ significantly. In Alzheimer's disease, amyloid and tau biomarkers (CSF Aβ42, p-tau) are informative, whereas dementia with Lewy bodies is characterized by visual hallucinations and fluctuations in attention [8; 9].

Autoimmune encephalitis is currently considered one of the most important differential diagnoses, particularly given its potential reversibility. Syndromes such as encephalitis associated with antibodies to NMDA receptors, LGI1, CASPR2, or GABA-B receptors may present with psychiatric symptoms, seizures, and movement disorders, closely resembling CJD. Unlike prion diseases, autoimmune encephalitis is characterized by inflammatory changes in cerebrospinal fluid, involvement of the medial temporal lobes on MRI, and a positive response to immunotherapy [10]. Importantly, misdiagnosis of autoimmune encephalitis as CJD has been repeatedly reported in the literature [11].

Vascular causes, including multi-infarct dementia, cerebral amyloid angiopathy, or vasculitis, may present subacutely with multifocal neurological symptoms. In such cases, MRI usually reveals ischemic or hemorrhagic lesions that do not correspond to the typical CJD pattern of cortical ribboning or basal ganglia hyperintensity [12]. Assessment of inflammatory markers and cerebral angiography help exclude primary central nervous system vasculitis.

Thus, the differential diagnosis of CJD encompasses a wide spectrum of neurodegenerative, autoimmune, and vascular pathologies. Decisive importance is attributed to characteristic MRI and EEG findings, specific cerebrospinal fluid biomarkers, and – most importantly – the potential reversibility of autoimmune and paraneoplastic processes. Therefore, a systematic and multidisciplinary diagnostic approach is essential for timely diagnosis of prion disease and exclusion of potentially treatable alternatives.

Given the inevitably fatal course, neuro-palliative care is now recognized as a key component of patient management. Recently proposed clinical guidelines emphasize the importance of early integration of palliative services to alleviate symptoms, reduce psychosocial burden, and support caregivers [3]. This is particularly relevant given the extremely rapid progression of the disease.

Therapeutic approaches remain experimental. Clinical trials involving the monoclonal antibody PRN100 have demonstrated its safety and ability to cross the blood-brain barrier; however, they have not shown a significant effect on patient survival [4]. Therefore, the mainstay of treatment remains symptomatic therapy aimed at controlling myoclonus, seizures, and agitation. There is an urgent need to develop new clinical trial design models adapted to rare, rapidly progressive diseases [5].

Conclusions

Thus, CJD remains a fatal neurodegenerative prion disorder with diverse clinical manifestations and rapid progression, creating significant diagnostic and therapeutic challenges. The presented clinical case highlights the importance of considering CJD in the differential diagnosis of rapidly progressive dementias and movement disorders, particularly when initial symptoms may mimic autoimmune, infectious, or vascular processes.

Detection of characteristic MRI and EEG changes, as well as the presence of specific cerebrospinal fluid biomarkers, particularly the 14-3-3 protein, are key criteria for confirming the diagnosis *in vivo*.

Given the absence of etiotropic treatment, early recognition of the disease is crucial not only for improving diagnostic accuracy but also for timely initiation of neuro-palliative care, genetic counseling (when indicated), and provision of psychosocial support to the patient's family.

Despite emerging molecular discoveries and promising experimental therapies, CJD remains a diagnosis of exclusion, underscoring the necessity of comprehensive evaluation to rule out potentially treatable conditions.

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Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Oros M.M.	+	+	+	+	+	+
Lutz V.V.			+			+
Bulecza B.A.			+			+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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TRADITIONAL PUBLIC COMMUNITIES IN UKRAINE (LECTURE)

Martynenko N.M.[1], Trotsenko O.V.[1], Nesterenko R.V.[2]

[1]Kharkiv National Medical University, Kharkiv, Ukraine
[2]National Academy of the National Guard of Ukraine, Kharkiv, Ukraine

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ABSTRACT

Background. The study of Ukrainian communities in the 15th–18th centuries is relevant for understanding the mechanisms of social self-organization and the formation of Ukrainian identity.

Aim. To analyze the structure, role, and interrelationships of communities to determine their influence on social and cultural processes.

Materials and Methods. Historical-cultural, comparative-historical, and system-structural methods were applied in this study. This investigation was a part of individual research work of authors. The lecture is intended for students of medical faculties.

Research Ethics. The interpretation of historical and cultural phenomena is objective, free from bias engagement. The object of the study comprises historical communities that do not involve the participation of living people; thus, consent for participation is not required.

Results. It was established that the peasant community had performed such functions as collective land ownership, mutual assistance, social support, self-governance, and justice. Guild communities regulated crafts (quality, prices, training). The Cossack community was a unique military-political formation that defended Ukrainian lands, fought for freedom, and possessed developed organs of self-governance. Brotherhoods were the communities formed for defense of Orthodoxy under conditions of confessional pressure. They founded schools, printing houses and fought for the rights of Orthodox population. Youth communities were institutions for the socialization of unmarried youth, ensuring their integration into the rural community. They possessed a regulated structure and self-governance, which governed relationships and facilitated leisure organization. The collective mutual aid was an institution of collective assistance in Ukrainian community, possessing a regulated structure of invitation, and a farewell ritual.

Conclusions. The peasant community regulated the economic life of the village, the system of social protection, and self-governance. Guild communities ensured quality control, the protection of artisans' interests, and corporate solidarity. The Cossack community combined a professional military function with developed self-governance. Brotherhoods were established for the preservation of Orthodox identity and the development of Ukrainian culture and education; they were institutions of civil society and promoted national self-organization. Youth communities were a system of learning that regulated social interaction and maintained the stability of the village. The toloka was a mechanism of social integration, collectivism and responsibility.

Keywords: *history of Ukrainian culture, peasant community, guild community, Cossack community, youth community, toloka.*

Introduction

The study of traditional communal societies in Ukraine during the Early Modern period (15th–18th centuries) remains one of the most pressing topics in Ukrainian historiography. These communities, including rural, guild, Cossack, and brotherhoods, as well as informal youth groups and so-called tolokas (communal work parties), functioned not only as economic or social units but also as key institutions that ensured the preservation of local self-governance, cultural identity, and legal pluralism under conditions of unstable national statehood or foreign administration.

The **aim** of study was a systemic analysis of the structure, role, and interrelations of these communities to determine their influence on the socio-political and cultural processes of the specified period.

Corresponding Author:
Martynenko Nataliya M. – PhD in History, Docent, Associate Professor of Public Health and Healthcare Department of the Kharkiv National Medical University, Ukraine.
✉ 4, Nauky Ave., Kharkiv, 61022, Ukraine.
E-mail: nm.martynenko@knmu.edu.ua

Materials and Methods

To systematically analyze the cultural and historical specificity of these communities, the following methods were applied: Historical and Cultural Method was used as the main approach to examine communal societies as subjects of the cultural process – carriers of the traditions, worldview, and values characteristic of Ukrainian culture during this period. Comparative Historical Method was applied to identify common features and differences in the social structure, functions, and cultural roles of various types of communities and their evolution over time. Systemic-Structural Method allows for the analysis of the internal hierarchy, rituals, and mechanisms of social control within each community, understanding them as holistic socio-cultural systems.

Research Ethics

In the study of materials related to ritual practices, religious brotherhoods, and ethnographic sources, respectful treatment is ensured towards the worldview, beliefs, and values of Ukrainian communities of past centuries. The research results aim to preserve and popularize knowledge about historical forms of self-organization, which are an integral part of the national cultural heritage. As the object of study is historical communities of the 15th–18th centuries that do not involve the participation of living individuals, informed consent is not required.

Results

Contemporary historiography, particularly over the last five years (2020–2025), demonstrates significant interest in reconsidering the resilience of these historical institutions. Research is actively moving away from simplistic sociological or economic models, focusing instead on the legal subjectivity and the capacity of these horizontal networks of self-organization to function under crisis conditions. Academic publications, such as *Ukrainian Historical Journal*, continue to be published steadily, confirming the resilience of the academic sphere and its ability to generate fundamental research results despite external challenges. This resilience allows historians to continue research that re-examines old concepts of centralized power, giving greater weight to horizontal ties in society.

The methodological framework of modern historical research on social communities necessitates a departure from the rigid division between urban, rural, and military structures. New studies emphasize social mobility and the intertwining of jurisdictions.

The most significant contribution to the study of Early Modern social structures belongs to comprehensive works published in the 2020–2025 period, which offer a synthetic view of all types of communities. Due to the high academic activity of leading researchers during this time, works have emerged that unite urban, rural, and military communities under a common methodological denominator.

These monographs introduce the concept of corporatism as a pervasive principle of societal organization. This principle extended from highly organized guilds and brotherhoods to informal youth groups (so-called, *parubocha hromada*) and even military Cossack *kurens* (camps). Researchers argue that it was this corporate nature that provided the "horizontal integration" of society, which in many cases proved to be much stronger than the vertical ties imposed by the *shlahta* (nobility) or state power.

"Corporatism, as a principle of organizing social life, permeated Ukrainian society in the 16th–18th centuries, from magnate 'clienteles' to the lowest rural 'communal associations'. This corporate nature ensured the 'horizontal integration' of society, which was much stronger than the vertical ties imposed by the authorities" [1, pp. 48–49].

This allows traditional communities to be viewed as the basis for forming a stable social structure.

Particular attention is paid to the issue of disciplinary power. It turns out that the internal disciplinary power of corporate institutions often surpassed that of the state, as it was based not so much on physical coercion as on the fear of losing social capital, exclusion from economic networks, the right to work, or religious assistance.

"The disciplinary power of institutions (guilds, brotherhoods, Cossack *kurens*) often surpassed that of the state, as it was based not on coercion, but on the fear of losing social capital and being excluded from key economic and religious networks" [2, p. 305].

The peasant *community (hromada)* in Ukraine played an exceptionally important role, performing a wide range of functions that ensured the survival and development of the rural population (*Table 1*).

The *Kopnyi Sud* (Kopa Court) (the word *kopa* denoted an assembly of people who gathered to resolve a dispute or reconcile the parties according to customary law; hence "Kopa Court") reconstruction demonstrates that rural self-governance in the 17th–18th centuries possessed broad, though

Table 1. The main goals and functions of peasant hromada

Goal/Function	Description
Land Tenure & Use	Collective land ownership, land allocation, regulation of usage, crop rotation, grazing, and forestry rules
Mutual Aid & Social Support	Assistance during hardship (illness, disaster, crop failure); organization of joint labor (*toloka*); support for widows, orphans
Self-Governance & Justice	Own self-governance bodies (village assemblies); local justice for minor offenses; maintenance of order and security
Organization of Economic Activity	Regulating agricultural work, setting planting/harvest times, organizing shared construction (mills, ponds)
Preservation of Traditions & Culture	Maintaining and transmitting traditions, customs, and cultural values; organizing feasts and rituals

unofficial, powers in regulating not only property disputes but also marital-family relations and moral norms. It functioned as the primary legal instance, effectively ensuring social control at the local level [3, p. 45].

The Rite of Admission, though sparsely documented, likely included: Community Consent (approval at village assemblies); Oaths (to be faithful to the community and its traditions); a Joint Feast (symbolizing unity); and Inclusion in Economic Life (participation in joint labor and farming). This was a crucial act of socialization.

Contemporary research (2020–2025) emphasizes the rural community's capacity for self-governance and its role as an active political actor, capable of defending its rights and conducting legal cases, moving away from viewing it merely as an object of exploitation. The use of the term "corporation of duties" highlights a methodological shift from the Marxist understanding of the community as a "class enemy" to an institutional understanding as a "corporation", reflecting the influence of Western historiography [4, pp.187–188].

Guild organizations (*tsekhovi hromady*) in the 15th–18th centuries are studied today not only as professional associations but also as important institutions that shaped the professional identity and social capital of the townsfolk (*mishchanstvo*). Their goals and functions are presented in *Table 2*.

The Rite of Admission involved a multi-stage process: Apprenticeship (learning the craft), Journeyman Status (working independently), Master Exam (demonstrating practical and theoretical knowledge), and the Admission Ceremony (oath of allegiance, joint feast, name registration, fee payment) [5, pp. 25–26].

"The statutes of craft guilds, especially after the 1650s, demonstrate strengthening of internal discipline, which was no longer limited to product quality but extended to the moral and ethical conduct of masters, effectively duplicating the functions of church and brotherhood courts" [6, p. 201].

The Cossack community (*Table 3*) was a unique phenomenon combining military, social, and political functions. Its primary goals included defense against external threats, securing liberties

Table 2. The main goals and functions of guild organization (tsekhova hromada)

Goal/Function	Description
Regulation of Craft	Establishing quality standards, controlling prices and production volumes, regulating apprenticeship and master exams
Social Protection	Aid in case of illness/accidents; organizing funerals and supporting families; fostering corporate solidarity
Self-Governance	Own governing bodies (Master Assemblies); right to establish rules and statutes; administering justice in craft-related matters
Defense of Members' Interests	Representing members before municipal authorities, participating in decisions on trade and taxation [5, p. 25–26]
Preservation of Traditions	Maintaining and transmitting craft traditions and knowledge through the apprenticeship system

Table 3. Functions of the Cossack community (Kozatska hromada)

Function	Description
Military	Professional warriors; participation in campaigns; border defense; scouting
Political	Own self-governance (Cossack Council); participation in community political life; influencing *starshyna* (officer) decisions
Social	Mutual support; development of education and culture (schools, churches)
Economic	Fishing, hunting, farming, land reclamation, trade development

and rights (self-governance, free life), and fostering social justice.

The Cossack community was open to various social strata (runaway peasants, townsfolk, petty *shlahta*), with key conditions for entry being the desire for freedom, military skills, adherence to Cossack customs, and generally, Orthodox faith.

The rite was symbolic and essential for socialization, often including: Trials (demonstration of military skills, endurance); Oath of Allegiance (on a cross or saber); Acceptance of a Cossack Name (symbolizing a break from the past); Joint Feast; and Inclusion in the Cossack Circle (gaining full rights).

Modern historiography views the Cossack community as a unique socio-political structure, distinct from the feudal formations of Eastern Europe, acting as a "corporation with variable geometry" [7, pp. 58–59]. Elite groups (*starshyna*) constantly sought to monopolize resources but were obliged to respect the "communal will" of the rank-and-file Cossacks, especially during elections. Research on the 18th century confirms that Cossack self-governance effectively resisted attempts to turn it into a mere military unit, even amidst authoritarian tendencies from moscow and the Hetmanate administration [8, pp. 15–16]. The right of veto and elective mechanisms ensured, at least formally, the preservation of democratic traditions.

The *Cossack Assembly* had the right of veto over certain decisions of the *starshyna* (officer class), and the electoral mechanisms ensured, at least formally, the observance of democratic traditions. Thus, the community remained an important institution of civil society. The democratic traditions of the Zaporizhian Sich, which stands as the most institutionalized form of the Cossack community with a pronounced *viche* (popular assembly) tradition, are studied separately.

Church Brotherhoods in Ukraine during the 14th–18th centuries played a vital role in religious, cultural, and social life. Their activities were aimed at protecting Orthodoxy, developing education and culture, and supporting the social needs of the community.

The purpose of the church brotherhoods was the protection of Orthodoxy. Amid the spread of Catholicism and Uniatism, the brotherhoods became centers for the defense of the Orthodox faith. City brotherhoods, particularly those in Kyiv, Lviv, and Lutsk, were always considered protectors of the Orthodox faith. However, contemporary research (2020–2025) is expanding their functional field, positioning them as full-fledged political subjects. The brotherhoods effectively utilized a combination of religious status and the significant economic influence of their members (many guild members and wealthy burghers) to lobby for the interests of the Orthodox burgher elite at the highest level, including the Sejm of the Polish-Lithuanian Commonwealth [9, pp. 112–113]. They fought to preserve church traditions and rites. One of the directions of the brotherhoods' activity was the development of education and culture. For this purpose, the brotherhoods founded schools and printing houses, promoting the spread of literacy and book printing in Ukrainian lands. The brotherhoods did not simply establish schools and printing houses; they transformed into a "shadow" organ of power in cities, especially where the Orthodox community resisted the Catholic or Uniate magistrate. This functional synergy between economically powerful guilds and politically active brotherhoods is a key theme of modern historiography, emphasizing the deep intertwining of jurisdictions and social networks in Early Modern cities.

Church brotherhoods supported the development of icon painting, church singing, and other forms of art. They provided aid to the poor, the sick, and families in need of social assistance. They organized charitable events and supported hospitals.

Thus, among the functions of the church brotherhoods, the religious function was primary. The brotherhoods organized divine services, church holidays, and sought to preserve Ukrainian tradi-

tional rites, upheld the purity of the Orthodox faith, and combatted heresies.

The educational function was also a priority. The brotherhoods founded brotherhood schools where children were taught literacy, theology, and other sciences. They actively published educational and religious literature.

Regarding the cultural function, the brotherhoods supported the development of art, organized theatrical performances and concerts, and collected libraries and archives.

In fulfilling the social function, the brotherhoods provided material aid to the poor, the sick, and orphans; they organized hospitals and shelters.

The political function of the brotherhoods consisted of their participation in public life, defending the rights of the Orthodox population, influencing the decisions of the city authorities, and taking part in political events.

Church brotherhoods were important centers of spiritual and cultural life in Ukraine. They contributed to the preservation of national identity and the development of Ukrainian culture.

Members of church brotherhoods in medieval Ukraine could be representatives of various social strata, but they were generally: burghers (*mishchany*) – that is, city dwellers engaged in craft, trade, and other activities, who constituted the majority of the brotherhood members; some representatives of the nobility also joined the brotherhoods, especially those interested in protecting the Orthodox faith and developing culture; occasionally, representatives of the clergy joined the brotherhoods, although their role was less significant than that of the laity. The Cossacks played a special role in the development of the brotherhoods. In 1620, Hetman Petro Sahaidachnyi with the entire Zaporizhian army joined the Kyiv Epiphany Brotherhood.

It is important to note that membership in the brotherhoods was voluntary and open to all Orthodox Christians, regardless of social status. The brotherhoods had their own statutes, which defined the rights and obligations of their members. The brotherhoods were centers where Orthodox believers could unite to protect their religious rights, develop education, and culture.

Church brotherhoods united a wide spectrum of the Orthodox population who sought to protect their faith and contribute to the development of Ukrainian culture.

The Rite of Admission to membership in a church brotherhood in Ukraine during the 16th–18th centuries was an important stage that confirmed a person's belonging to the religious community and their readiness to fulfill the duties of a brotherhood member. Although detailed descriptions of the rites could vary depending on the specific brotherhood and region, there are general features that can be highlighted. The main stages of the rite were: submitting an application, consideration of the candidacy, taking an oath, inscription in the list, a communal meal, and payment of contributions. Let us look at each of these stages in more detail. A person wishing to join the brotherhood submitted a written or oral application. The application usually indicated the motives for joining and the readiness to adhere to the statute and rules of the brotherhood. The candidacy was considered by the members of the brotherhood at a meeting. Factors such as the candidate's reputation, their confession of faith, and their readiness to perform duties were taken into account. After the candidacy was approved, the newly admitted member swore allegiance to the brotherhood and its statute. The oath could be taken on the Gospel or before an icon. Following this, the name of the newly admitted member was inscribed on the list of brotherhood members, symbolizing official acceptance into the brotherhood community. After admission to the brotherhood, a communal meal might take place, symbolizing the unity and solidarity of the brotherhood community. Acceptance into membership could also be accompanied by the payment of certain contributions.

The Rite of Admission to the brotherhood was not just a formal procedure, but also an important stage in spiritual and social life. It symbolized the acceptance of Christian values and readiness to serve God and neighbors. Church brotherhoods played a vital role in protecting the Orthodox faith, developing education, and culture.

Members of church brotherhoods in Ukraine gathered in various places, depending on the size and status of the brotherhood, as well as the available conditions. The main meeting places were church premises, brotherhood houses, premises attached to schools and printing houses, city halls or other public buildings, and, of course, private homes of brotherhood members. Let us look more closely at what these premises were. Most often, brotherhood meetings took place in the churches to which they were affiliated. These could be specially designated rooms, chapels, or even the main temple. This was especially true for large and influential brotherhoods that had their own churches or significant financial means to maintain premises.

Some brotherhoods had their own houses where meetings were held, and brotherhood archives and libraries were kept. These houses often became centers of cultural and educational life.

Many brotherhoods were engaged in educational and publishing activities, so meetings could be held in premises attached to brotherhood schools and printing houses.

In some cases, especially if the brotherhoods were actively involved in the public life of the city, meetings could be held in city halls or other public buildings.

In small brotherhoods or under conditions of limited resources, meetings could be held in the private homes of brotherhood members.

It is important to note that the meeting place could change depending on the circumstances. For example, during wartime or epidemics, meetings might be held in safer or more isolated locations.

Church brotherhoods were an important factor in preserving Orthodox identity and developing Ukrainian culture and education, successfully combining spiritual service with socio-political activism. Their broad social base and democratic model of membership provided corporate strength for the defense of religious rights and social support for vulnerable segments of the population. Thus, brotherhoods were not only religious centers but also powerful institutions of civil society and self-governance that contributed to national self-organization in cities and villages.

The study of informal community structures, such as youth (boys' and girls') communities (*parubochi* and *divochi hromady*), in 2020–2025 is marked by an intensification of anthropological and microhistorical approaches. These structures, which were previously often considered only in a folkloric or ethnographic context, are now being analyzed as full-fledged institutions of social control and regulators of the marriage market. Youth communities in Ukraine, although not as formalized as modern organizations, played an important role in social and cultural life. They had their own characteristics and functions, determined by the conditions of the time. These were traditional associations of young people organized by gender and age, operating on the basis of ethical and legal customs and norms of community life.

The purpose of youth communities was socialization and adaptation of young people to adult life, a place where youth learned traditions, customs, and behavioral norms. Youth communities acted as intermediaries between the family and the village community. At the same time, they had their own rights and interests recognized by the public. Young people united for mutual assistance in solving current social problems. Support was provided to one another within the youth communities in difficult life situations. Youth communities organized joint leisure activities, including games, dances, songs, and other entertainment. They were a place where young people could relax and have fun.

These communities consisted of unmarried youth – boys and girls who had reached majority (or were soon to reach it) and formed independent associations – boys' or girls' communities, each of which was conditionally divided into older and younger. The internal structure of the boys' and girls' communities was strictly regulated.

The age requirement for joining a youth community was not precisely defined. For boys (*parubky*), it ranged from 16–18 years. As a rule, acceptance into the boys' community was stretched over a long period, during which there were changes both in the appearance of the youngster (*pidparubok*) and in his behavior at festive entertainments and during joint work. Decisive moments proved to be physical maturity (a beard or mustache, strong physique), internal maturation, and the presence of certain personal qualities – not having a bad reputation, being lively, and sociable. Boys who could play musical instruments, sing, and tell interesting stories were held in high esteem. The youngster also had to receive some recognition from the girls' community.

Admission to the boys' community was usually timed to one of the major holidays (Christmas, New Year, Easter, or Trinity). In Podillia, this rite was called "coronation." Upon arrival, the boy bowed to the four sides. After this, he was lifted on hands while a celebratory song, "The girls sowed flax," was sung. Then everyone sat in a circle, and the new community member treated his comrades to vodka. Inclusion into the boys' community could also occur during some joint work, such as haymaking. In the Carpathians, this rite was called *vyzvolky na dobroho kosaria* (liberation into a good haymaker) or *frytsuvannia* (initiation) and resembled *vyzvolky na dobroho maistra* (liberation into a good master) that took place in guild brotherhoods. To test the abilities and endurance of the new haymaker (*fryts*), he was not allowed to rest and was forced to scythe between the best haymakers. The *fryts* was often even whipped with nettles, rubbed with a scythe sharpener on his bare stomach, tied up, etc. The rite was completed only when the newcomer arranged a treat

(*mohorych*) for the haymakers in the tavern. From then on, he gained the right to smoke a pipe, drink *horilka* (*vodka*), and visit the girls. According to custom, this was announced publicly from a high place.

The boys' communities had certain elements of self-governance. At the head was an elected leader – the otaman (*bereza*, *vaida*). He was usually characterized by such traits as energy, quick wit, and the ability to organize others. With his assistants, the otaman bore certain responsibility to the village community, organized entertainment, managed financial affairs, resolved disputes among comrades, and so on.

The girls' communities were also socially organized, although they did not have elected "*starshyna*". The path to them for all girls led first through the singing group of their neighborhood. Girls became full members of the community at 15–16 years old when they began attending evening gatherings (*vechornytsi* or *dosvitky*). Admission took place in the spring at the usual meeting place for the village youth. A girl joining the community asked one of the older members to be her friend. As a sign of agreement, they exchanged gifts (scarves, ribbons, etc.). Thus, the older girl became the patroness and mentor of the younger for life. Analogous relationships developed among the boys, but only for one season.

With entry into the boys' or girls' community, the status and self-perception of the youth changed both in the family and in the community. If previously the young man, being an adolescent, was engaged in small household chores, listened to the orders of his brothers, and worked as a hired hand, henceforth he performed traditionally male work, and his suggestions were given more weight in the family. The privileges of the new status were also manifested in the right to demonstrate it through certain attributes of clothing decoration. The greatest privilege was the right to marry and manage an independent household.

Youth communities were active especially during calendar holidays, had an internal hierarchy and performed a regulatory function. They ensured the observance of public morals, and their "courts" or "sentences," although they did not have official legal force, acted as an extremely effective form of public shaming and pressure. This confirms that the social life of the Early Modern period was regulated not only by official statutes but also by a powerful mechanism of unwritten laws and customary law. Youth communities regulated relationships among the village youth, protected the interests and honor of their members, and acted as organizers of both their own leisure and village-wide festivities. Boys and girls performed caroling and used the money they received to decorate the church; they also hired a field for cultivation for the same purpose. Youth communities had their own centers of communication and independent holidays: St. Catherine's Day (November 24, Julian Calendar) was considered a boys' affair, as it was associated with various youth rites and traditions aimed at finding a partner and future wedding. Here are some of them: fortune-telling (*vorozhinnia*) – girls told fortunes about their intended using various objects and rituals. Boys also participated in fortune-telling, trying to find out about their future wives.

In the evening before the holiday, young people gathered for evening parties (*vechornytsi*), where they sang songs, danced, and played games. During the *vechornytsi*, boys had the opportunity to meet girls and express their sympathies.

There were various rituals associated with finding a partner, such as planting cherry branches that were supposed to bloom by Christmas. Boys could participate in these rituals to attract the attention of girls.

Thus, there were several directions for the realization of the functions of youth communities, including learning and upbringing, organization of youth leisure, military training, and social interaction.

Discussion

Youth communities played an important role in teaching young people crafts, agriculture, and other necessary skills. They also contributed to the formation of moral and ethical values. Youth communities organized joint celebrations, rites, and other cultural events. They supported young people in the development of folk art and culture. Military training of youth was a necessary element of the activities of youth communities. Thus, within this training, young people participated in military exercises and drills, preparing to defend their communities. They formed self-defense detachments and participated in military campaigns. Youth communities contributed to the establishment of social connections and the formation of a network of social support. They facilitated the exchange of information and experience among young people.

The youth communities of that time performed more practical functions than similar youth organizations today, in particular, military training and assistance with agricultural work.

Youth communities played a fundamental role in traditional Ukrainian society, acting as a system

of learning and upbringing that ensured a smooth transition of young people to full membership in the community with the acquisition of all corresponding rights and obligations. "Youth communities often acted as an informal regulator of marital and family relations, ensuring the observance of public morals, especially during calendar holidays. Their 'courts' or 'sentences,' although they did not have official legal force, acted as an effective form of public shaming" [10, pp. 28–29]. Strict regulation of entry and collective initiation rites were necessary mechanisms for forming corporate solidarity, mastering ethical and legal norms, and transmitting practical skills (including military ones). Thus, these unformalized associations of youth were vitally important institutions of self-organization and self-defense that regulated social interaction and maintained cultural and social stability in the village.

There was another interesting element of traditional collective mutual assistance in the Ukrainian community – *toloka*. *Toloka* (collective unpaid labor) is a vivid example of grassroots self-organization and mutual assistance. Contemporary researchers emphasize that *toloka* was not limited only to economic efficiency, which allowed a significant amount of work (for example, building a house) to be completed in a short time.

Toloka played a key role in the socialization of youth, strengthened endogamous ties, and ensured the transmission of labor skills. "*Toloka* was not only a form of collective labor that allowed a significant amount of work (for example, building a house) to be completed in one day, but also a key tool for the socialization of youth, which strengthened endogamous ties and ensured the transmission of labor skills between generations" [11, pp. 145–146]. It also served as a platform for the synergy of various community groups: in cities, guild members could unite for joint work, and in villages, *toloka* often ended with communal entertainment, which crossed its function with youth communities. Thus, *toloka* ensured the reproduction not only of material resources but also of vitally important community ties.

It is no wonder people said: "Without *toloka*, it is like having no arm: you cannot build a house or mow hay". By its structure, it was a complex custom that included the rite of invitation, the process of collective work combined with entertainment elements, the ceremony of treating the workers, the ritual of farewell, and the holding of entertainment. This established structure of *toloka* was not fully adhered to only when it was called by the landowner: in this case, it was called a "requested" (*proshena*) *toloka* by the people. However, people understood that "request" was akin to an order, one of the varieties of corvée labor. Peasants invited to a "requested *toloka*" usually performed agricultural work: plowing the land, mowing hay, or harvesting. However, it was conditionally considered voluntary, encouraged by an obligatory feast. In the early Middle Ages, it was customary to treat them with "mead and beer," and in later times – with *horilka*. However, with the intensification of feudal-serf relations, the summoning of "requested" *tolokas* was practiced more often, and the treating – less often. The landowner, as a rule, alternated a "wet" (*horilka*) *toloka* with a "dry" one, although feeding the participants of the *toloka* was mandatory.

The classic (i.e., truly voluntary) *toloka* was much richer in content, organically combining the labor process with entertainment. It began with an invitation, and whether it was called by an individual peasant or when the decision to organize it was made by the community, the villagers went to it voluntarily. Peasants understood that by participating in the *toloka*, they secured the moral right to their own *toloka*. Moreover, it was customary to come to the *toloka* even without an invitation; this was most often practiced at youth *tolokas*, for example, when shelling corn: girls were usually invited, and boys came on their own.

The "one-day association," as *tolokas* were also called in Ukraine, was fun: with jokes, songs, and games. Often during the labor process, when it was hot, people splashed each other with water; for a laugh, they smeared each other with clay when wallowing a house; or they lined the road with corn stalks (so everyone knew there was a *toloka* here) when shelling it at one of the girls' homes.

The duration of the *toloka* varied, but it was customary to complete the entire main labor process. If the volume of work was expected to be large, the host treated the *tolokchany* (*toloka* participants) to breakfast (bread, lard, cucumbers). Upon completion of the work, he organized a feast with music and vodka, and then the *tolokchany* themselves arranged games, dances, sometimes horse riding. Peasant ethics prescribed that the host of the *toloka* be courteous to its participants, even if someone's work displeased him; he himself treated the guests, considering it an insult if someone else did it for him. The custom of treating at the *toloka* was always characterized by hospitality – not only because it was considered

a matter of honor and duty to the *tolokchany* but also because it was woven into the more general tradition of "giving and reciprocating." Peasant psychology understood this: as you treat others, so will you be treated.

Toloka was an important mechanism for survival and social integration, ensuring the completion of large volumes of work under conditions of limited resources and forming the value of collectivism and mutual responsibility. The clear ritual and ethical accompaniment of the *toloka* (invitation, joint work, treating, entertainment) confirms its significance as a social phenomenon that strengthened horizontal ties in the community. The degradation of *toloka* to the form of a "requested" duty under the pressure of the landlord reflects the direct influence of serfdom on the destruction of traditional democratic institutions of peasant self-organization.

Conclusions

The analysis confirms that the diverse traditional public communities of 15th–18th centuries Ukraine served as the foundational mechanisms of social self-organization and were indispensable to the shaping of Ukrainian identity in the early modern period.

The studied communities were not passive associations but active, organized institutions that structured the life and collective identity of the Ukrainian populace in the Early Modern era through a multifunctional system of self-regulation. First, they performed essential governance and regulatory functions, often substituting or complementing state authority. The peasant community was the primary regulator of rural economic life, managing collective land use and social security through mutual aid, while guilds controlled urban crafts, ensuring quality and protecting artisans' interests. The Cossack community uniquely combined military defense with a democratic system of self-governance, exerting significant political influence.

Second, these communities were crucial for preserving identity and culture. Brotherhoods, for example, acted as bulwarks of Orthodox identity under confessional pressure, establishing schools and printing houses and engaging in socio-political activism, thereby driving cultural and educational development and fostering national self-organization.

Third, informal communities provided mechanisms for social integration and discipline. Youth communities regulated social interaction and ensured the controlled integration of unmarried individuals, maintaining the moral stability of village life. The *toloka* (collective mutual aid) reinforced collectivism, cooperation, and mutual responsibility, serving as a fundamental tool for social cohesion.

In sum, these traditional structures provided a comprehensive, bottom-up system of self-regulation, underscoring their enduring relevance for a complete understanding of Ukrainian institutional history.

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Prospects for further research. The findings of this study, which establish the robust structure and multifaceted functions of traditional Ukrainian public communities (peasant, guild, Cossack, brotherhood, youth, and toloka) in the Early Modern period, open several promising avenues for future scientific inquiry. The next stage of research will focus on adopting micro-historical and interdisciplinary approaches to further refine our understanding of these foundational institutions.

Authors' Contributions

Contribution / Authors	A	B	C	D	E	F
Martynenko N.M.	+	+	+	+	+	+
Trotsenko O.V.	+		+			+
Nesterenko R.V.			+		+	+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.

Declarations

Conflict of interest is absent.

All authors have given their consent to the publication of the article, to the processing and publication of their personal data.

The authors of the manuscript state that in the process of conducting research, preparing, and editing this manuscript, they did not use any generative AI tools or services to perform any of the tasks listed in the Generative AI Delegation Taxonomy (GAIDeT, 2025). All stages of work (from the development of the research concept to the final editing) were carried out without the involvement of generative artificial intelligence, exclusively by the authors.

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- pediatrics and neonatology,
- phthisiology,
- physical therapy and rehabilitation,
- psychiatry,
- public health care,
- ship medicine,
- social medicine,
- sports medicine,
- surgery,
- teaching issues,
- technologies of medical diagnosis and treatment,
- theoretical medicine,
- therapy,
- urology

31.8. Authors (surnames, initials), title of the article, abstract and keywords in another language (Ukrainian or English).

31.9. "Abbreviations" ("Introduction") if there are 10 or more abbreviations in the text of the article. The list is compiled in alphabetical order.

31.10. "Introduction" should contain a description of the problem that is solved in the article; analysis of literary sources. Contradictions have been identified. References to literary sources in the "Introduction", "Results" and "Discussion" should go in the order of their mention, in turn (1, 2, 3...). Manuscripts with a violation of the citation order are returned for revision even before reviewing. The citation should be formatted, for example, as follows: [1; 3–5; 6, p. 21, 24–25]. If the source is larger than 20 pages, you must specify a page.

31.11. The "Aim" or "Aim & Objectives" (if the aim detailed) should be a logical continuation of the "Introduction" and suggest a way to solve the problem or eliminate contradictions. The section may contain a research hypothesis. The section should not contain abbreviations and references to literary sources.

31.12. "Materials & Methods" must contain a description of the design of the study, ways to obtain results, information about the number of patients or laboratory animals included in the study, their division into groups, equipment used for the study (title, model, manufacturer, country of origin), research methods, classifications, scales (with a brief description thereof or a link to a source with such description), methods of statistical processing, the software used (title, version, developer, country of origin). To describe research methods, it is allowed to refer to any (but not russian or belarusian) textbook, manual, encyclopedia, monograph, article, website.

31.13. In accordance with the principles of evidence-based medicine, materials and methods should be described in such a way that any other researcher, having reproduced the conditions of the study, experiment, could obtain the same result (the principle of reproducibility of the experiment). When resolving contradictions between authors and reviewers, the editorial board, which makes the final decision on the publication or rejection of the article, is guided by the arguments of sources with the highest evidentiary level studies, meta-analyses and systematic reviews, guidelines by Cochrane, NICE (National (UK) Institute for Health and Care Excellence), WHO (World Health Organization).

31.14. "Research Ethics" must contain information on compliance with the ethical standards of medical research involving humans and laboratory animals specified in the Nuremberg Code (1947); the Declaration of Helsinki (1964, last revised in 2013), developed by the World Medical Association; the Convention on Human Rights and Biomedicine (Oviedo, 1997); the International Recommendations of CIOMS (Council for International Organizations of Medical Sciences, Council for International Organizations of Medical Sciences) and ICH (International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)); EU Directive 2010/63/EU; Council of Europe Convention for the Protection of Laboratory Animals (ETS 123, 1986); Declaration "3R" ("Replacement, Reducetion, Refinement"), which is aimed at replacing animals in experiments with other methods, reducing their number and improving the conditions of experiments; and for research conducted in Ukraine or with the participation of Ukrainian researchers – Article 28 of the Constitution of Ukraine, Article 43 of the Law of Ukraine "Fundamentals of the Legislation of Ukraine on Health Care" (1992), Article 12 of the Law of Ukraine "On Medicines" (1996), Order of the Ministry of Health of Ukraine No.690 of September 23, 2009. It is also necessary to note the signing of informed consent of patients to participate in the study, to hospitalization, treatment, clinical trials of drugs and methods of treatment, ensuring the anonymity or confidentiality of surveys, and the availability of protocols of ethics commissions.

31.15. "Results". Your own empirical data or theoretical reasoning must be described. The results of the study can be illustrated and systematized using tables, diagrams, photographs, and must contain textual explanations.

31.16. "Discussion". It should contain a comparison of its own results with the results of similar studies. Their coincidences or differences must be explained.

31.17. "Conclusions" should explain whether the aim of the study has been achieved, whether the expected results of the research tasks have been obtained, whether the problem has been solved, whether the contradictions that were identified during the analysis of literature sources have been eliminated, whether the research hypothesis has been tested. Conclusions should not contain abbreviations and references to literary sources. The conclusions should not be a simple repetition of the results. It is necessary to minimize the amount of numerical and statistical data in the conclusions, to show only basic data. The conclusions cannot contain new data that have not been previously described in the article. They should only summarize the results.

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Contribution / Authors	A	B	C	D	E	F
Author 1 (surname, initials)						+
Author 2						+

Notes: A – concept; B – design; C – data collection; D – statistical processing and interpretation of data;
E – writing or critical editing of the article;
F – approval of the final version for publication and agreement to be responsible for all aspects of the work.
The contribution, marked as F, is mandatory for each author.
Each contribution marked with the letters A–E must be indicated for at least one author.

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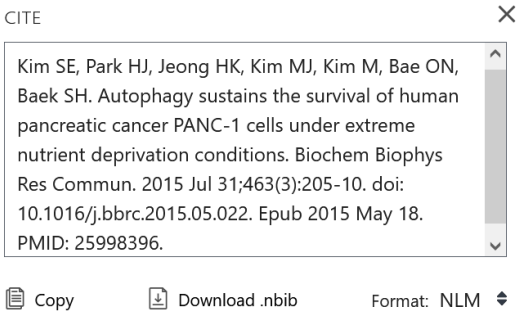

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Sahasrabuddhe NA, Huang TC, Kumar P, Yang Y, Ghosh B, Leach SD, et al. Ablation of Dicer leads to widespread perturbation of signaling pathways. Biochem Biophys Res Commun. 2015; 463(3):389-94. DOI: 10.1016/j.bbrc.2015.05.077. PMID: 26032504.

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Zaremba NI, Zimenkovsky AB. Attitude to the process of self-medication of applicants of higher medical education at pre- and postgraduate stage (according to results of the sociological survey). Pharmaceutical Review. 2018;(3):94-9. DOI: 10.11603/2312-0967.2018.3.9323. [In Ukrainian].

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Lisovy VM, Olkhovska LP, Kapustnyk VA. Fundamentals of Nursing: Textbook. 3rd edition, revised and supplemented. Kyiv: VSV "Medicine"; 2018. 912 p. Available on: https://is.gd/ssaAtO

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O'Campo P, Dunn JR, eds. Rethinking social epidemiology: towards a science of change.
Dordrecht: Springer; 2012. 348 p. Available at: https://link.springer.com/book/10.1007/978-94-007-2138-8

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Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th ed. Vols. 1, 2. Jameson JL, Longo DL, Fauci AS, eds. New York: McGraw-Hill Education; 2018.

32.8.2. The first of two volumes:

Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J. Harrison's Principles of Internal Medicine. 20th ed. Vol. 1 of 2. Jameson JL, Longo DL, Fauci AS, eds. New York: McGraw-Hill Education; 2018. 1,472 p.

32.9. *Part of the book:*

Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. Chapter 29. Endometriosis. P. 1103-33.

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O'Brien KA. The philosophical and empirical intersections of Chinese medicine and western medicine [dissertation]. Melbourne, AU; Monash University; 2006. 439 p.

32.11. *Ukrainian Dissertation:*

32.11.1. in Ukrainian for the section "Literature"

Lobas MV. Medical and social justification of the optimized functional-organizational model of medical care for the rural population of Ukraine. [Diss Cand Med Sc, spec. 14.02.03 – Social Medicine]. Kyiv: Ukrainian Institute for Strategic Studies of the Ministry of Health of Ukraine; 2018. Kharkiv: Kharkiv National Medical University; 2019. 278 p. [In Ukrainian].

Please note: the place of execution of the dissertation and the place of its defense may be indicated.

32.12. *Abstract of the Ukrainian dissertation:*

Godovanets OI. Optimization of the principles of diagnosis, treatment and prevention of dental diseases in children with concomitant thyroid pathology. [Abst Diss Doc Med Sc, spec. 14.01.22 – Dentistry]. Ivano-Frankivsk: Ivano-Frankivsk National Medical University; 2016. 30 p. [In Ukrainian].

32.13. *Conference abstracts:*

Nesterenko V, Shevchenko A, Zhuravel Ya. Prevention of neurodegenerative diseases' complications in palliative patients at home hospice: organizational principles. Proceedings of the International scientific conference "The greatest humankind achievements in healthcare and veterinary medicine" (Latvia, Riga, 7–8 Feb 2024). P. 96-9. DOI: 10.30525/978-9934-26-401-6-26. [In Ukrainian].

32.14. *Abstracts of the conference and at the same time the chapter of the book:*

Shevchenko AS, Shevchenko VV, Prus VV. Competencies in Higher Education Standards of Ukraine: Definition, Content and Requirements for the Formation Level. Chapter in: Auer ME, Cukierman UR, Vendrell Vidal E, Tovar Caro E, eds. Towards a Hybrid, Flexible and Socially Engaged Higher Education. ICL 2023. Lecture Notes in Networks and Systems, vol. 911. P. 421-8. Springer, Cham; 2024. DOI: 10.1007/978-3-031-53382-2_41.

32.15. *Ukrainian Website:*

Doctors about diabetes mellitus. Public Health Center of the Ministry of Health of Ukraine. [Internet]. Available at: https://diabetes-site.phc.org.ua/likariam [accessed 30 Jun 2025]. [In Ukrainian].

32.16. *English Website:*

Clinical Guidance for Diabetes. U.S. Department of Health & Human Services. Centers for Disease Control and Prevention, 15 May 2024. [Internet]. Available at: https://www.cdc.gov/diabetes/hcp/clinical-guidance [accessed 30 Jun 2025].

Cancer. World Health Organization, 3 Feb 2025 [Internet]. Available at: https://www.who.int/news-room/fact-sheets/detail/cancer [accessed 30 Jun 2025].

32.17. *International patent:*

International Patent "Nanoparticles for cancer treatment: compositions containing polykinase inhibitors with checkpoint inhibitors". WO 2023/283380 A1, 28 Dec 2023. International Appl. PCT/EP2022/067314, 24 Jun 2022. Inv.: Chen L [CN], Müller RH [DE], Keck CM [DE], Sarisozen C [TR], Hesse D [DE], Tiefenbacher R [DE], Fricker G [DE]. Owner: PharmaTrope GmbH. Valid in: US, EP, JP, CN, IN, CA. No confirmed grant or national-phase validation in US or EP publicly recorded as of 30 Jun 2025. Available at:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2023283380 [accessed 30 Jun 2025].

32.18. *European patent:*

European Patent "Ventilator with biofeedback monitoring and control for improving patient activity and health", reg. 18 May 2016 No. EP 2,344,791 B1. EU publ. 18 May 2016, Bull. 2016/20. Inv.: Wondka AD [US], King A [US], Cipollone J [US]. Proprietor: Breathe Technologies, Inc., Irvine, CA 92618 (US). International appl. No.PCT/US2009/059272. International publ. No.WO 2010/039989 (08.04.2010 Gazette 2010/14). Designated Contracting States: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR. Available at: https://is.gd/3vFYqJ [accessed 30 Jun 2025].

32.19. *National foreign patent:*

US Patent "Systems and methods for determining functionality of dialysis patients for assessing parameters and timing of palliative and/or hospice care", reg. No.US 2019 /031881 A1, 17 Oct 2019. Inv.: Sheetal Chaudhuri, Arlington SC [US], Usyyat L [US], Maddux DW [US], Maddux FW [US], Han H [US], Demaline JS [US], Butler KG [US]. Appl.: Fresenius Medical Care Holdings, Inc., Waltham, MA (US). Available at: https://is.gd/8YxSyn [accessed 30 Jun 2025].

Australian Patent "A system for use by a medical professional, for diagnosing a cause of a patient medical condition and for providing a patient medical condition report, including a diagnosis and treatment", registrated by Australian Patent Office on 01 Jul 2021 No.2021203679. Inv. [AU]: Dew D, Halpern S, Engler H, Steward D, Dew D, Dew D, Stratton S. Available at: https://is.gd/SsP8oh [accessed 30 Jun 2025].

32.20. *Patent of Ukraine:*

Plakida OL, Yushkovska OG, inventors. Patent of Ukraine for invention No. 123412 "Method for assessing the level of physical performance of a person". Odessa National Medical University, owner. In force from 31 Mar 2021, terminated. Ukrpatent, Bull. No.13. Available at: https://sis.ukrpatent.org/uk/search/detail/1585813 Archived on: https://kurort.gov.ua/patenty/patenty-za-2021

32.21. *Certificate of Ukraine on registration of copyright for the work:*

Nesterenko VG (author, owner). Certificate of Ukraine on registration of copyright for work No.132116 of 16 Dec 2024. Functional and organizational model of an optimized system for providing palliative and hospice care to the population of Ukraine. Kyiv: State Organization " Ukrainian National Office for Intellectual Property and Innovations". Available at: https://sis.nipo.gov.ua/uk/search/detail/1840184 [accessed 30 Jun 2025]. Published: Bulletin "Copyright and Related Rights" No.85 of 31 Jan 2025. P. 523. Available at: https://surl.li/tmvknh [accessed 30 Jun 2025]. [In Ukrainian].

32.22. *The Law of Ukraine:*

Law of Ukraine No.2801-XII of 19 Nov 1992 "Fundamentals of the Legislation of Ukraine on Health Care". Published in the Bulletin of the Verkhovna Rada of Ukraine (1993, No.4, art. 19), in force of 30 Jun 2025, with amendments and additions from 19 Nov 1992–18 Jun 2025. Verkhovna Rada (Parliament) of Ukraine. Legislation of Ukraine. [Internet]. Available at: https://zakon.rada.gov.ua/laws/show/2801-12 [in Ukrainian].

32.23. Among the sources of normative acts, the most authoritative ones have priority: the websites of the Verkhovna Rada (Parliament) of Ukraine, the Cabinet of Ministers of Ukraine (Government Portal), the President of Ukraine, the Ministries of Ukraine, the State Expert Center of the Ministry of Health of Ukraine, the Public Health Center of the Ministry of Health of Ukraine, etc.

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