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ORIGINAL RESEARCH

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Hematocytological, biochemical, and hemostasis parameters' role in predicting the possibility of the various forms of the COVID-19 course in hospitalized Ukrainian patients: A cross-sectional study

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Abstract

Background and Aims: The main objective of this study is to establish the characteristics of blood laboratory parameters in hospitalized coronavirus disease 2019 (COVID-19) Ukrainian patients and the significance of the above-mentioned parameters for predicting the course of the disease.

Methods: Hematocytological, biochemical, and hemostasis methods of research have been used. Groups of patients with different forms of the coronavirus disease course have been analyzed (lethality - recovery, recovery with a severe and mild course).

Results and Conclusion: Age is one of the risk factors for COVID-19 mortality. Absolute values of neutrophils, neutrophil-lymphocyte ratio (NLR), systemic inflammation index, D-dimer, C-reactive protein, and soluble fibrin complex can be used by clinicians to effectively differentiate between two possible outcomes (lethality vs. recovery). A higher number of stab leukocytes, d-NLR, and platelets concentration have been recorded in patients with severe COVID-19 cases, compared to mild ones. The risk of adverse COVID-19 outcome (lethality) is significantly linked with D-dimer and NLR (odds ratio 1.42). The risk of a severe course of the disease was significantly associated with the count of leukocytes (odds ratio 4.96).

KEYWORDS

biochemical parameters, COVID-19, hematocytological parameters, hemostasis parameters, laboratory diagnostics, lethality, severity of the disease

1 | INTRODUCTION

In December 2019, the first case of pneumonia of unknown etiology occurred and has been registered in China (Wuhan). The researchers determined that the pathogen of unknown pneumonia belongs to a new coronavirus,[1] which differs from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV) and the Middle East respiratory syndrome virus (MERS-CoV). According to the International Committee on Taxonomy of Viruses (ICTV) data, this new coronavirus causes unknown pneumonia, and the World Health Organization (WHO) named the disease "COVID-19."[2] Since the outbreak of the epidemic, the COVID-19 infection has rapidly spread in many regions of the country and abroad.[3] So far, COVID-19 is still a threat to all humanity and affects the health care system and the global economic situation.

Covid-19 infection usually starts with flu like symptoms[4] and can be asymptomatic or may have a mild to severe course.[5] The infection is characterized with significant burden of inflammation.[6] Diagnostic stages of this disease include epidemiological anamnesis, chest X-ray, and blood laboratory tests. Real-time fluorescent polymerase chain reaction (PCR) is the gold standard for detecting SARS-CoV-2 infection.[7]

Laboratory tests' parameters of blood samples have been constantly used in clinical practice because they are fast, simple, and economical to reflect the patient's condition in vivo. Considering the obtained results is extremely important for risk stratification, patient monitoring, and prediction of the disease course.[8,9] By accurately assessing the severity of the disease, clinicians can prescribe appropriate treatment and maximize the use of limited medical resources, reducing the lethal risk.[10] In this context, it is necessary to identify effective, convenient laboratory biomarkers for distinguishing severe and mild forms of COVID-19[11]

Previous studies have found a strong correlation between old age and severe COVID-19 form.[12] An uncontrolled and severe inflammatory response is a key process in disease severity and poor prognosis of patients with COVID-19. So far, it is already known that elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), pro-inflammatory cytokines, ferritin, procalcitonin, and hypoalbuminemia are most correlated with severe disease and lethality.[13,14] CRP is significantly elevated in patients with a positive result for COVID-19.[15,16] CRP-based inflammatory markers have been reported to be associated with various inflammatory conditions such as diabetic nephropathy,[17] thyroiditis,[18] and hepatitis.[19] Moreover, a recent work found association between Covid-19 mortality and CRP-based inflammatory markers.[20] Similar features of blood have been found for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH).[21–24]

In addition, according to the conducted scientific studies, the number of neutrophils and lymphocytes, the ratio of neutrophils to lymphocytes (NLR), as well as platelets to lymphocytes (PLR) can be considered markers of systemic inflammation.[25,26] Some scientists describe the elevation of NLR as an independent risk factor of the mortality for COVID-19 patients[27,28] PLR has been introduced as a novel hemogram-derived inflammatory indice in various conditions such as liver fibrosis,[29] thyroid conditions,[30] gastrointestinal diseases,[31] cancer,[32] diabetes mellitus,[33] irritable bowel disease,[34] and Covid-19 infection.[35] NLR is another novel marker of inflammation derived from routine blood count test. Its association with inflammation has been reported in inflammatory bowel disease,[36] diabetes mellitus,[37,38] gastrointestinal conditions,[31] cardiac conditions,[39] thyroiditis,[40] and SARS CoV-2 infection.[41]

The systemic immunoinflammatory index (SII), which reflects the immune and inflammatory status of the body, is of great scientific interest.[42–44] SII is a predictor of disease severity and prognosis in patients with tumors, inflammatory diseases, obesity, pulmonary embolism, and undergoing primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction (STEMI).[45–48]

Taking into account published literature, we singled out the still unexplored issues of laboratory diagnosis of COVID-19. Also, there is no information in the scientific literature about the blood indicators of patients with COVID-19 in Ukraine (Eastern Europe), where the pandemic is still ongoing in 2022, threatening the lives and health of people. The aim of this study is to establish the characteristics of laboratory (hematocytological, biochemical, and hemostasis) blood parameters in hospitalized COVID-19 Ukrainian patients and the significance of the above-mentioned parameters for predicting the course of the disease. Following the aim of the study, we set several research objectives: (1) to analyze the peculiarities and differences in the results of laboratory tests of COVID-19 patients with various forms of severity; (2) to establish the diagnostic accuracy and informativeness of laboratory parameters for prognostic differentiation of various forms of the disease course severity; and (3) assess the risks of the occurrence of adverse forms of the coronavirus disease course using a multivariate logistic regression model.

2 | CONTINGENT AND METHODS OF THE RESEARCH

2.1 | Patients

198 women and men aged 34–96 with laboratory-confirmed COVID-19 who were receiving inpatient treatment at the Municipal Enterprise Volyn Regional Infectious Diseases Hospital of the Volyn Regional Council (Ukraine) during 2020–2021 participated in this study. All patients from the total sample have been divided into four groups: deceased (Group 0) and those who survived (Group 1). Group 1 has been divided according to the degree of severity of the course of COVID-19: recoveries with a mild (Group 2) and severe (Group 3) course of the disease. The criterion for choosing the degree of severity of the course of the disease was the referral of patients hospitalized with coronavirus disease to the diagnostic department (research group 2) and the intensive care unit (research group 3) The participants were classified according to belonging to one of the age categories: mature age I (men 22–35 years old, women 21–35 years old); mature age II (men aged 36–60, women aged 35–55); elderly (men 61–74 years old,

women 56–74 years old); old age (men and women 75–90 years old); long-lived (men and women 90 and > years old).[49] To determine the presence or absence of comorbidities in patients with COVID-19, the medical base of the Municipal Enterprise Volyn Regional Infectious Diseases Hospital has been used.

All patients provided informed consent for the use and processing of their demographic (age, sex) and medical data. The study has been performed following the provisions of the Declaration of Helsinki and in compliance with all generally accepted bioethical norms and regulations. The Bioethics Commission of the Municipal Enterprise "Volyn Regional Infectious Disease Hospital" of the Volyn Regional Council approved this study. The Bioethics Committee voted that the study does not contradict the accepted international bioethical norms for conducting clinical research with human participants. The obtained results can be used in published materials (official extract from protocol number 1 of December 22, 2022).

2.2 | Laboratory tests

The diagnosis of COVID-19 in patients has been confirmed by a positive result of real-time reverse transcription-polymerase chain reaction analysis for nasopharyngeal and oropharyngeal swab samples using the ELITenGenius automated system and reagents manufactured by ElitechGroup.

To achieve the set objectives, we conducted the following laboratory tests: general blood analysis by the Sysmex XN-350 automatic hematology analyzer using conductometry with hydrofocusing for counting erythrocytes (RBC) and platelets (PLT), as well as flow cytometry for white blood cell count (WBC) and differentiation of leukocyte formula. Microscopic evaluation of stained peripheral blood smears has been performed separately. Determining the enzyme activity (ALT, AST, LDH, and creatine phosophokinase [CPK]), whole blood lactate, and quantitative determination of CRP has been performed using the Cobaas 111 automatic analyzer and reagents manufactured by Roche. Hemostasis parameters have been assessed by clotting (prothrombin index [PI], INR, fibrinogen-activated partial thromboplastin time [aPTT]) and immunoturbidimetric (D-dimer) techniques using a Bioksel 3003 hemocoagulometer.

Several indices (based on hematological parameters) characterizing the course of pathological processes have been calculated, which could characterize the severity of the COVID-19 infection in details: SII (SII = platelet count × neutrophil count/lymphocyte count), NLR (NLR = absolute neutrophil count/absolute lymphocyte count), PLR (PLR = absolute PLT/absolute number of lymphocytes), D-dimer/fg, IGLR × 100.

2.3 | Statistical analysis of the obtained results

The value of the area under the receiver operating characteristic (ROC) curve (area under the curve [AUC]) has been interpreted in indicators of prognostic and diagnostic accuracy: 0.9–1.0 – excellent, 0.8–0.9 – very good, 0.7–0.8 – fair, 0.6–0.7 – average, 0.5–0.6 – unsatisfactory; a value of 0.5 corresponds to the inappropriateness of the model. The cut-off point (COV – cut-off value) has been calculated by the Youden index.[50] The multivariate logistic regression analysis has been used to evaluate the possibility of adverse forms of the coronavirus disease course. Odds ratios (OR) and their 95% confidence intervals (CI) have been calculated.

The use of parametric or nonparametric statistical criteria has been determined by the correspondence of the obtained numerical values to the normal distribution. The Shapiro–Wilk test has been used (at $p > 0.05$, the data distribution has been considered normal). As descriptive statistics, the values of the arithmetic mean (M) and standard deviation (SD) have been used upon the condition of a normal distribution of numerical data, as well as the median (Me) with an indication of 25%–75% percentiles [25%;75%] if the distribution did not correspond to a normal one.

To establish differences between the four study groups, the nonparametric Kruskal–Wallis test has been used followed by the Conover post hoc test).

Statistical analysis of demographic data (age) of patients of all groups has been carried out using one-way analysis of variance test and Scheffé's post hoc analysis.

To establish gender differences by age within one research group, Student's *t*-test (T) has been used.

All differences have been considered statistically significant at $p < 0.05$. Data analysis and creation of figures have been carried out using the MedCalc statistical software (version 20.113).

3 | RESEARCH RESULTS AND DISCUSSION

In the framework of this study, all patients diagnosed with COVID-19 have been divided into four study groups. Based on the outcome of the course of the disease, the examinees have been classified into a group of deceased (98 people) and those who survived (100 people: 67 women and 33 men). According to the severity of the COVID-19 course, patients have been divided into a group of those who recovered with a mild course of the disease (81 people: 56 women and 25 men) and those who recovered with a severe course (19 people: 11 women and 8 men). In the group of the deceased, the gender distribution (1/1) is represented in an equal ratio, while in the group of those who survived, the proportion of women is bigger. The age of all patients varied from 34 to 96, the average value for each of the research groups was more than 65 years (Table 1). A significant difference was found between deceased persons (71.15 ± 9.69) and those who survived (65.7 ± 12.6) in terms of age groups (Figure 1A, see Table 1). Women, who survived and had a mild course of the disease were older (Figure 1B, $p > 0.05$). While in the group with a severe course of COVID-19, the age of men was bigger than that of women ($p > 0.05$).

TABLE 1 Population information and statistical characteristics of hematological parameters of blood in COVID-19 Ukrainian patients with different forms of severity.

	Deceased total number (0)	Recovered total number (1)	Recovered, mild course (2)	Recovered, severe course (3)	*p*-Value
Patients, *N*	98	100	81	19	
Women, *n*	49	67	56	11	
Men, *n*	49	33	25	8	
Age (years), M ± SD [Min-Max]	71.15 ± 9.69,*^ [49–96]	65.7 ± 12.6* [34–90]	65.96 ± 12.96^ [34–90]	65.05 ± 11.53 [46–90]	0.01
Women (years) M ± SD [Min-Max]	71.29 ± 9.08 [56–96]	65.76 ± 12.59 [34–90]	66.63 ± 13.04 [34–90]	62.18 ± 10.40 [46–76]	>0.05
Men (years) M ± SD [Min-Max]	71.02 ± 10.36 [49–92]	65.58 ± 12.79 [35–90]	64.48 ± 12.94 [35–86]	69 ± 12.52 [56–90]	0: $p > 0.05$ 1: $p > 0.05$ 2: $p > 0.05$ 3: $p > 0.05$ >0.05
Hematological parameters	**Me (25%; 75%)**	**Me (25%; 75%)**	**Me (25%; 75%)**	**Me (25%; 75%)**	
RBC [red blood cells, 10^{12}/L]	4.54 (3.82;4.84)	4.34 (4.13; 4.69)	4.32 (4.09; 4.66)	4.67 (4.26; 4.89)	0.13
Hb [g/L]	138 (118; 149)	135 (124.25;145)	132.5 (123; 142.5)	145 (135; 155)	0.04
WBC [white blood cells, 10^9/L]	11.85 (8.82;16.63)	6.37 (4.76; 8.0)	6.27 (4.75; 7.99)	6.44 (4.85; 8.0)	<0.001
Bands#	0.43 (0.08; 1.0)	0.08 (0; 0.22)	0.07 (0; 0.17)	0.19 (0.11; 0.5)	<0.001
Neut#	10.3 (6.7; 14.5)	3.8 (2.6; 5.1)	3.8 (2.6; 5.2)	3.8 (2.53; 4.98)	<0.001
Lympho#	0.6 (0.3;0.8)	1.45 (1;1.9)	1.5 (1; 1.9)	1.4 (1.03; 1.68)	<0.001
Mono#	0.4 (0.3; 0.6)	0.5 (0.3; 0.7)	0.5 (0.3; 0.63)	0.5 (0.3; 0.8)	0.25
IG#	0.1 (0.05;0.23)	0.03 (0.01; 0.11)	0.03 (0.01; 0.09)	0.04 (0.02; 0.22)	<0.001
PLT [platelets, 10^9/L]	202.5 (165; 270)	258 (181; 343.5)	267 (204.25;358)	201.8 (167.75; 259.25)	<0.001
PLR	360.16 (241.38; 643.87)	176.63 (129.83; 242.19)	178.7 (129.94; 246.15)	173.93 (125.91; 235.61)	<0.001
NLR	16.9 (9.67; 31.33)	2.39 (1.72; 3.63)	2.35 (1.69; 3.57)	2.81 (1.82; 4.55)	<0.001
D-NLR	0.92 (0.86; 0.96)	0.83 (0.78; 0.88)	0.84 (0.8; 0.87)	0.77 (0.64; 0.87)	<0.001
IGLR×100	20 (8; 45)	2.17 (1; 6.82)	2 (0.95; 5.57)	2.5 (1.33; 23.33)	<0.001
SII	3643.6 (2035; 6840)	611.58 (400.31; 1004.41)	619.89 (443.07; 1004.272)	563.36 (272.98; 1242.16)	<0.001
ESR [erythrocyte sedimentation rate, mm/hr]	31 (20; 48)	27 (18; 38)	29 (18; 40)	25 (15.75; 30)	0.07
CRP [mg/L]	98.4 (58.6; 166.2)	35.6 (13.5; 71.5)	35.5 (15.75; 74.2)	35.9 (4.36; 66.68)	<0.001
ALT [alanine aminotransferase, U/L]	36.65 (23; 50.6)	27.25 (19.2; 39.15)	27 (18.38; 41.4)	30 (22.78; 34.43)	0.06
AST [aspartate aminotransferase, U/L]	37.5 (25; 61)	30.75 (22.9; 39.45)	31 (22.95; 39.9)	28.9 (21.7; 35.75)	0.01

TABLE 1 (Continued)

	Deceased total number (0)	Recovered total number (1)	Recovered, mild course (2)	Recovered, severe course (3)	*p*-Value
LDH [lactate dehydrogenase, U/L]	401 (219.25; 492)	166,5 (135; 200)	168 (137; 203)	159 (135; 199)	<0.001
CPK [creatine phosophokinase, U/L]	213 (190.5; 299.75)	116,5 (75; 137)	120 (79.25; 150.25)	105 (72.5; 135.5)	<0.001
Urea [mmol/L]	9.13 (6.74;14.7)	5.39 (4.02; 7.15)	5.4 (4.02; 7.49)	5.18 (4.08; 6.15)	<0.001
Creatinine [μmol/L]	99 (74.13; 132.55)	71.5 (60.25; 89)	70.9 (59.85; 88.18)	77.1 (62.83; 97.48)	<0.001
Total protein [g/L]	69 (65; 72)	70.5 (69; 73)	70.65 (69; 73)	70.5 (69; 71,25)	<0.001
Albumin [g/L]	34.5 (31.85; 38)	38 (35.85; 40.5)	38 (35.78; 41)	38 (35.5; 39.25)	<0.001
Glucose [mmol/L]	7.25 (6.3; 9.9)	5.8 (5.18; 7.27)	5.84 (5.12; 7.05)	5.6 (5.3; 7.94)	<0.001
Lactate [mmol/L]	1.9 (1.3; 2.3)	1.6 (1.2; 1.98)	1.6 (1.2; 1.9)	1.8 (1.3; 2)	0.01
PI Prothrombin index, %	94 (87; 102)	100 (91; 100)	100 (91; 100)	94 (90.25; 100)	0.34
INR [international normalized ratio]	1 (1; 1.18)	1 (1; 1.09)	1 (1; 1.05)	1 (1; 1.09)	0.002
Fibrinogen [g/L]	5.87 (4.5; 7.55)	5.3 (3.6; 6.68)	5.47 (3.77; 7.07)	4.88 (3.56; 5.6)	0.03
aPTT [activated partial thromboplastin time, s]	39 (38; 41)	35 (31; 38)	34.5 (31; 37)	36 (34; 39.25)	<0.001
D-dimer [μg/dL]	390 (301; 637)	112.5 (0; 198.5)	114 (0; 198)	111 (0; 225.25)	<0.001
D-dimer/fg	66.1 (46.1; 135.2)	19.55 (0; 38.55)	20.5 (0; 38.43)	17.8 (0; 55.5)	<0.001
SFC [soluble fibrin complex] mg/100 ml	11 (8.75;17)	0 (0; 2)	0 (0;0)	0,6 (0; 4.2)	<0.001

Abbreviations: COVID-19, coronavirus disease 2019; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SD, standard deviation; SII, systemic inflammation index.

*Statistically significant difference between groups 0–1;

^Statistically significant difference between groups 0–2.

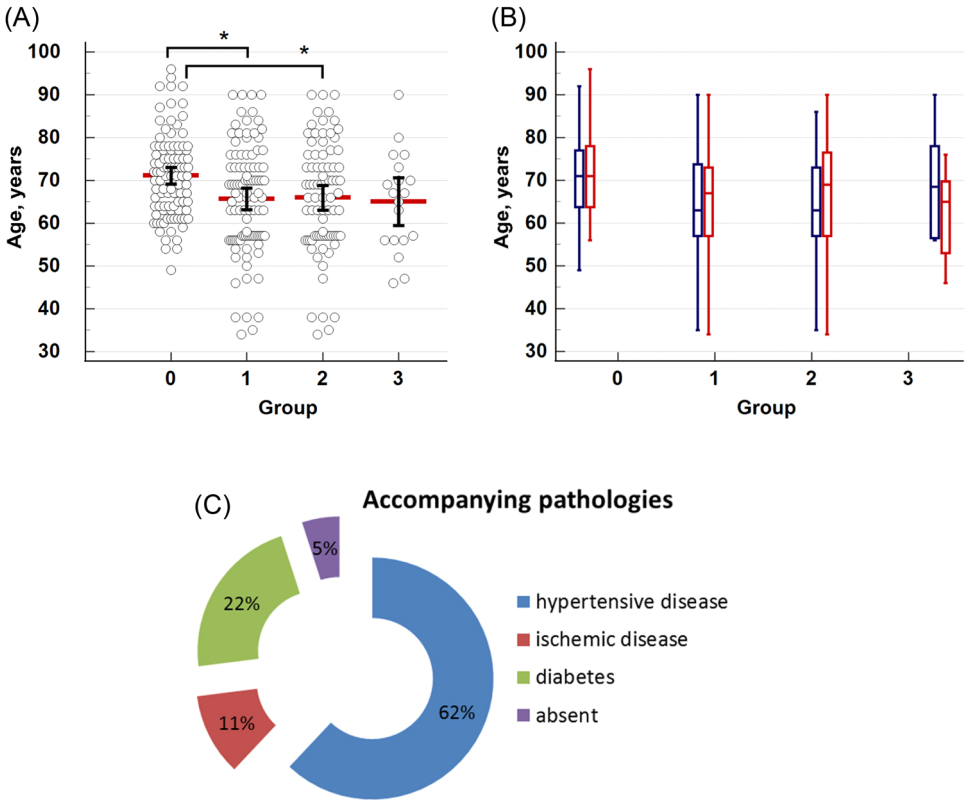

FIGURE 1 Demographic characteristics of coronavirus disease 2019 (COVID-19) patients. (A) is the age of the subjects of each research group; (B) features of gender differences by age in each group; (C) the percentage distribution of COVID-19 patients with accompanying pathologies in the anamnesis. (A, B) Arithmetic mean (horizontal line) with 95% confidence interval (vertical lines) is shown. (B) Blue color corresponds to the age of men, and red to the age of women. *Statistically significant difference.

In addition to data about the age and gender of the subjects, the presence or absence of accompanying pathologies has been also taken into account (Figure 1C).

3.1 | Analysis of patients groups with lethality and those who have recovered

The statistical analysis of hematological parameters of COVID-19 patients allowed us to establish specific general clinical and biochemical blood parameters (WBC, Bands#, Neut#, Lympho#, IG#, PLT, PLR, NLR, D-NLR, IGLR×100, SII, CRP, AST, LDH, CPK, urea, creatinine, total protein, albumin, glucose, lactate, INR, fibrinogen, aPPT, D-dimer, D-dimer/fg, and SFC), characterized by statistically significant differences in values between groups of deceased patients and those who survived (Table 1).

In general, in the group of deceased patients, higher values of the results of laboratory tests have been established ($p<0.05–0.01$), except for the level of Lympho#, PLT, total protein, and albumin. The latter had, on the contrary, smaller values in patients with a fatal outcome of the disease ($p<0.05–0.01$).

Several hematological indicators have been singled out in the course of a detailed analysis and comparison of the obtained results. The values of the above-mentioned parameters differ significantly (by times) ($p < 0.001$) in the groups of deceased patients and those who have recovered: WBC (1.86 times), Bands# (5.34 times), Neut# (2.71 times), Lympho# (2.42 times), IG# (3.3 times), PLR (2.04 times), NLR (7.07 times), IGLR×100 (9.2 times), SII (5.96 times), CRP (2.76 times), LDH (by 2.41 times), CPK (by 1.82 times), urea (1.69 times), D-dimer (3.47 times), D-dimer/fg (3.38 times), SFC (11 times) (see Table 1, Figure 2).

The next step to perform was ROC curve analysis to establish the ability of laboratory parameters (selected at the previous stage) to distinguish between two possible disease outcomes (lethality and recovery) in COVID-19 patients. When analyzing the constructed ROC curves of the studied hematological tests, their sensitivity (Se) and specificity (Sp) have been determined. To characterize the informativeness, the area under the ROC curve (AUC – Area Under the Curve) and the cut-off value (COV – cut-off value) have been determined for prognostic differentiation of the results of the disease (lethality – recovery) (Tables 2–3).

Graphs of ROC curves are shown in Figure 3. For Neut# (Se = 80.61%, Sp = 86%), the cut-off value corresponds to >5.8. Thus, values that exceed the determined value with excellent diagnostic informativeness of the parameter ($AUC = 0.91$, $p < 0.001$) may indicate a fatal outcome of the course of the disease in patients.

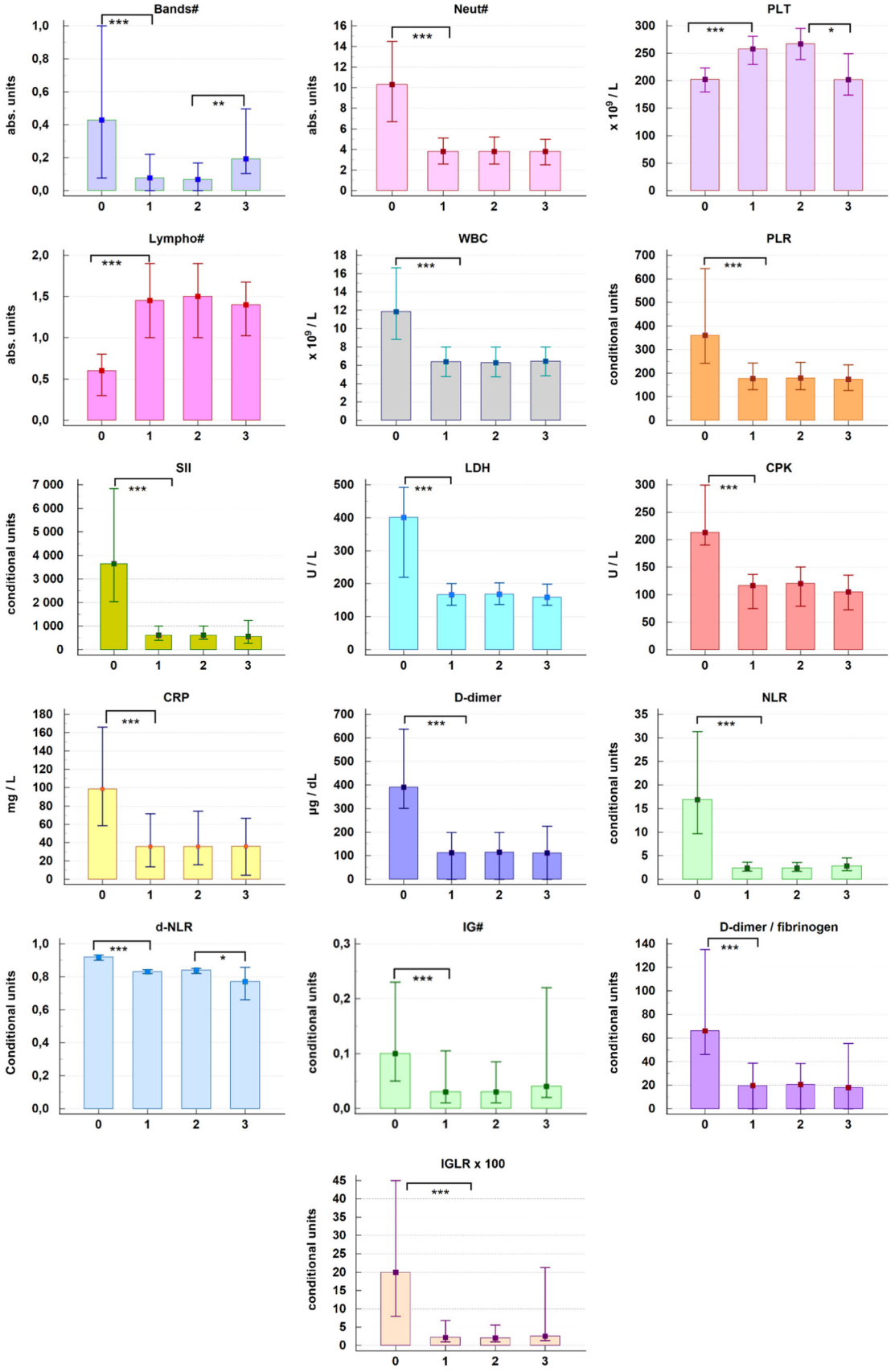

FIGURE 2 Differences in the values of hematological parameters in groups of coronavirus disease 2019 (COVID-19) patients with different outcomes and course of the disease. 0 – deceased patients; 1 – all who have survived; 2 – recovered with a mild course of the disease; 3 – recovered with a severe course of the disease. The figure shows Me (25%; 75%), as well as the level of statistically significant differences at $p < 0.05$ (*) and $p \leq 0.001$ (***).

TABLE 2 Statistical characteristics of the area under the ROC curve of various hematological parameters in COVID-19 patients with different forms of the severity of its course.

Indices	AUC	95% CI for AUC	*p*-Value	Indices	AUC	95% CI for AUC	*p*-Value
Analysis of patients' groups with lethality and recovered							
Bands#	0.7	0.63–0.76	< 0.001	CPK	0.96	0.85–1	< 0.001
Neut#	0.91	0.86–0.94	< 0.001	Urea	0.81	0.74–0.86	< 0.001
Lympho#	0.87	0.82–0.91	< 0.001	Creatinine	0.74	0.67–0.8	< 0.001
IG#	0.72	0.66–0.79	< 0.001	Total protein	0.65	0.57–0.72	<0.001
PLT	0.64	0.57–0.71	<0.001	Albumin	0.74	0.67–0.8	< 0.001
PLR	0.78	0.72–0.84	< 0.001	Glucose	0.7	0.63–0.76	< 0.001
NLR	0.95	0.91–0.98	< 0.001	Lactate	0.62	0.55–0.69	0.004
D-NLR	0.8	0.74–0.85	< 0.001	INR	0.63	0.55–0.69	0.002
IGLR×100	0.84	0.78–0.89	< 0.001	Fibrinogen	0.6	0.52–0.67	0.02
SII	0.91	0.86–0.95	< 0.001	aPTT	0.77	0.68–0.85	< 0.0001
CRP	0.81	0.75–0.86	< 0.001	D-dimer	0.95	0.9–0.97	< 0.0001
AST	0.62	0.55–0.69	0.002	D-dimer/fg	0.86	0.8–0.9	< 0.0001
LDH	0.76	0.68–0.84	< 0.001	SFC	0.99	0.96–0.99	< 0.0001
Analysis of patients' groups with mild and severe course							
Bands#	0.72	0.62–0.81	<0.001	D-NLR	0.68	0.58–0.77	0.04
PLT	0.66	0.56–0.75	0.03	SFC	0.66	0.54–0.77	0.03

Abbreviations: aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; Lymho#, lymphocyte count, abs. unit; Neut#, neutrophil count, abs. unit; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ROC, receiver operating characteristic; SFC, soluble fibrin complex; SII, systemic inflammation index.

An excellent diagnostic accuracy ($p < 0.001$) has been found for several other hematological indicators, such as NLR (Se = 85.71%; Sp = 94%; COV > 7.36), SII (Se = 88.78%; Sp = 85%; COV > 1407), CPK (Se = 89.66%; Sp = 100%; COV > 165), D-dimer (Se = 92.78%; Sp = 89%; COV > 234) and SFC (Se = 97.94%; Sp = 91.43%; COV > 4.2). However, taking into account the calculated values of the area under the ROC curve, the following blood parameters have been interpreted as very good diagnostic accuracy: Lympho# (Se = 78.57%; Sp = 85%; COV ≤ 0.8), IGLR×100 (Se = 88.66%; Sp = 68%; COV > 3.79), CRP (Se = 88.78%; Sp = 62%; COV > 44.5), urea (Se = 81.72%; Sp = 68%; COV > 6.29) and D-dimer/fg (Se = 83.67%; Sp = 79%; COV > 40.6).

The multivariate logistic regression analysis has been used to assess lethality risk factors for hospitalized COVID-19 patients. As possible risk factors to be analyzed, the age of the patients, the presence or absence of accompanying pathologies and five main hematological indicators, extracted from the previous stages of the statistical analysis, including D-dimer, D-dimer/fg, SII, NLR, IG# (Table 4) have been chosen. Mortality risk was associated with age, presence of accompanying pathologies ($p > 0.05$), D-dimer (OR = 1.02; $p < 0.001$) and NLR (OR = 1.42; $p = 0.01$).

3.2 | Analysis of patients' groups with mild and severe course

Our next task was to analyze the obtained results of laboratory hematological studies in recovered patients with a mild and severe course of the disease and to identify specific blood parameters, the values of which are statistically significantly different in both groups. We found significantly higher values of Bands# (severe: 0.19 [0.11; 0.5], light: 0.07 [0; 0.17], $p < 0.01$) and SFC ($p < 0.01$) for COVID-19 patients with a severe course, compared to those for patients with a mild course of the disease. In contrast, lower values of PLT (severe: 201.8 [167.75; 259.25], mild: 267 [204.25;358], $p < 0.05$) and D-NLR (severe: 0.77 [0.64; 0.87], mild: 0.84 [0.8; 0.87], $p < 0.05$) indicate a severe course of the disease in patients.

Good diagnostic accuracy of the Bands# indicator has been established when distinguishing the severity of the course of the disease in COVID-19 patients (AUC = 0.72; $p < 0.001$; see Table 2, Figure 4). The cut-off point is >0.10, that is, values that exceed the specified value with a diagnostic sensitivity of 83.67% and a specificity of 79% can predict a severe course of COVID-19 among patients (see Table 3).

The risk factors for logistic regression analysis were the age of the patients, the presence of accompanying pathologies and hematological

TABLE 3 Statistical parameters of the ROC-curves analysis of hematological indicators in COVID-19 patients with various forms of severity of its course.

Indices	COV	Se, %	Sp, %	+LR	95% CI	- LR	95% CI	Indices	COV	Se, %	Sp, %	+LR	95% CI	- LR	95% CI
Analysis of patients' groups with lethality and those who have recovered															
Bands#	>0.22	64.29	76	2.68	1.83–3.94	0.47	0.35–0.63	CPK	>165	89.66	100	-	-	0.1	0.04–0.3
Neut#	>5.8	80.61	86	5.76	3.51–9.45	0.23	0.15–0.34	Urea	>6.29	81.72	68	2.55	1.89–3.45	0.27	0.17–0.42
Lympho#	≤0.8	78.57	85	5.24	3.25–8.45	0.25	0.17–0.37	Creatinine	>86.2	68.04	70	2.27	1.63–3.15	0.46	0.33–0.63
IG#	>0.04	75.51	63	2.04	1.54–2.7	0.39	0.27–0.57	Total protein	≤68.9	40.91	88.42	3.53	1.92–6.5	0.67	0.55–0.81
PLT	≤228	63.27	60	1.58	1.19–2.1	0.61	0.45–0.83	Albumin	≤36	65.91	70.83	2.26	1.6–3.19	0.48	0.35–0.66
PLR	>272.18	69.39	86	4.96	3–8.2	0.36	0.26–0.48	Glucose	>6	80.61	60	2.02	1.56–2.61	0.32	0.21–0.5
NLR	>7.36	85.71	94	14.29	6.55–31.16	0.15	0.09–0.25	Lactate	>2.01	36.96	88	3.08	1.7–5.58	0.72	0.6–0.85
D-NLR	>0.91	56.12	91	6.24	3.26–11.91	0.48	0.38–0.61	INR	>1.02	59.79	72	2.14	1.5–3.04	0.56	0.43–0.73
IGLR×100	>3.79	88.66	68	2.77	2.06–3.72	0.17	0.09–0.3	Fibrinogen	>6.44	43.88	73	1.63	1.1–2.41	0.77	0.62–0.95
SII	>1407	88.78	85	5.92	3.69–9.49	0.13	0.08–0.23	aPTT	>36	83.1	69.7	2.74	1.62–4.65	0.24	0.14–0.43
CRP	>44.5	88.78	62	2.34	1.8–3.03	0.18	0.1–0.32	D-dimer	>234	92.78	89	8.43	4.82–14.77	0.08	0.04–0.17
AST	>39.9	46.94	78	2.13	1.4–3.26	0.68	0.55–0.84	D-dimer/fg	>40.6	83.67	79	3.98	2.7–5.89	0.21	0.13–0.33
LDH	>231	75.68	89.74	7.38	3.73–14.58	0.27	0.15–0.48	SFC	>4.2	97.94	91.43	11.43	5.31–24.57	0.02	0.01–0.09
Analysis of patients' groups with mild and severe course															
Bands#	>0.10	78.95	65.43	2.28	1.56–3.34	0.32	0.13–0.78	D-NLR	≤0.79	63.16	77.78	2.84	1.67–4.84	0.47	0.26–0.86
PLT	≤213	63.16	70.37	2.13	1.32–3.45	0.52	0.29–0.96	SFC	>3.4	38.89	94.23	6.74	1.95–23.34	0.65	0.45–0.94

Note: COV is the value of the cut-off point (cut-off value). Se is the sensitivity of the laboratory test; Sp – specificity of the laboratory test; + LR - positive likelihood ratio: the ratio between the probability of a positive test result in the presence of lethality and the probability of a positive result in the absence of lethality; –LR - negative likelihood ratio: the ratio between the probability of a negative test result in the presence of lethality and the probability of a negative test result in the absence of lethality.

Abbreviations: aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; Lymho#, lymphocyte count, abs. unit; Neut#, neutrophil count, abs. unit; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ROC, receiver operating characteristic; SFC, soluble fibrin complex; SII, systemic inflammation index.

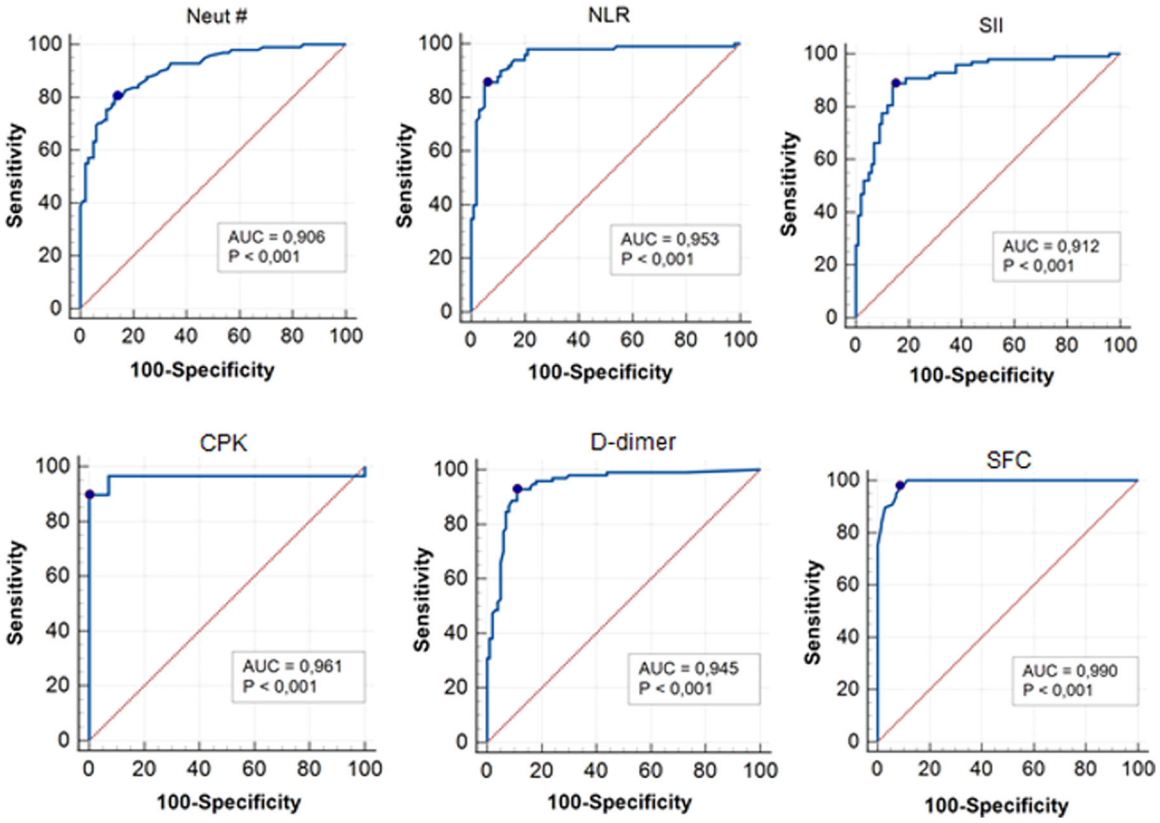

FIGURE 3 ROC curves of hematological indicators in the patients' groups with a fatal outcome of COVID-19 and those who have recovered. Note to Figures 3–4. The blue dot on the ROC curves corresponds to the Youden index. COVID-19, coronavirus disease 2019; ROC, receiver operating characteristic.

TABLE 4 Risk factors for the possibility of adverse forms of the course of the coronavirus disease in hospitalized patients.

Risk factors for the patients	Regression coefficient	Odds ratio	95% CI	*p*-Value	AUC
Analysis of patients' groups with lethality and those who have recovered					
Age (age category)	0.68	1.9730	0.68–5.69	0.20	0.98
Associated pathologies	0.11	1.1148	0.19–6.41	0.99	
D-dimer (increase per μg/dL)	0.02	1.0153	1.01–1.02	<0.001	
D-dimer/fg (decrease per)	−0.004	0.9962	0.98–1.01	0.69	
SII (decrease per)	−0.0001	0.9999	0.9986–1.001	0.82	
NLR (increase per)	0.35	1.4233	1.08–1.9	0.01	
IG# (decrease per abs. unit)	−4.13	0.0160	0.0–14.31	0.23	
Analysis of patients' groups with mild and severe course					
Age (age category)	0.14	1.1447	0.45–2.91	0.78	0.82
Associated pathologies	0.74	2.0979	0.38–11.65	0.40	
PLT (decrease per 10^9/L]	−0.008	0.9917	0.98–1	0.02	
Bands# (increase per abs. unit)	1.6	4.9640	1.24–19.88	0.02	

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil-lymphocyte ratio; SII, systemic inflammation index.

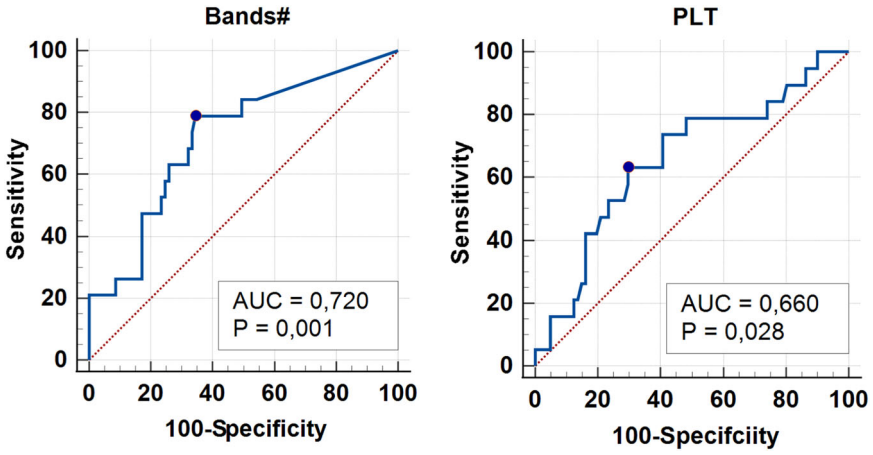

FIGURE 4 ROC curves hematological parameters in groups of recovered patients with different courses (mild-severe) of COVID-19. COVID-19, coronavirus disease 2019; PLT, platelets; ROC, receiver operating characteristic.

indicators, the values of which differ statistically significantly in the groups of patients with a mild and severe course of the disease (see Table 1): Bands#, PLT, D-NLR. The calculated regression coefficients have a clear clinical meaning, because they show the odds ratio, that is, they quantitatively characterize the probability of patients falling into one or another group. The risk of a severe course of the disease was associated with age ($p > 0.05$), the presence of accompanying pathologies (OR = 2.09, $p > 0.05$) and the level of Bands# (OR = 4.96; $p < 0.05$). Thus, if the number of Bands# increases by one, the chances of patients entering the group of patients with a severe course of COVID-19 increase by 4.96 times (see Table 4).

4 | CONCLUSIONS

Thus, our specification of general clinical, biochemical, and hemostasiological blood parameters and their values can be used by clinicians as a prognostic risk stratification of COVID-19 patients and help optimize the allocation of limited human and technical resources during the ongoing pandemic. Age is one of the risk factors for dying from COVID-19. We have established that the age of deceased patients with confirmed COVID-19 was greater than the age of those who remained alive.

Patients with a fatal outcome of the disease have been characterized by significantly higher values of hematological parameters (Bands#, Neut#, IG#, NLR, IGLR×100, SII, CRP, D-dimer, D-dimer/fg, and SFC) compared to those in patients who survived. Excellent diagnostic accuracy for the prognostic distinction between two possible outcomes (lethality-survival), taking into account the cut-off point value, has been recorded for Neut# (> 5.8), NLR (> 0.91), SII (> 1407), CPK (> 165), D-dimer (> 234), and SFC (> 4.2). Mortality risk was significantly associated with D-dimer and NLR.

More Bands#, Hb, SFC and lower D-NLR and PLT concentrations have been recorded for severe cases of COVID-19 compared to mild ones. The good diagnostic informativeness of Bands# (> 0.1) for predicting the severe form of the COVID-19 course in patients has been established. The risk of severe disease has been significantly associated with the count of Bands# and platelets.

AUTHOR CONTRIBUTIONS

Anna Yushchuk: Conceptualization; formal analysis; investigation; methodology; resources; writing—original draft; writing—review & editing. **Vasyl Pykaliuk**: Conceptualization; methodology; writing—review & editing. **Olha Korzhyk**: Conceptualization; formal analysis; visualization; writing—original draft; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Bioethics Commission of the Municipal Enterprise "Volyn Regional Infectious Disease Hospital" of the Volyn Regional Council approved this study. The Bioethics Committee voted that the study does not contradict the accepted international bioethical norms for conducting clinical research with human participants. The obtained results can be used in published materials (official extract from protocol number 1 of December 22, 2022).

TRANSPARENCY STATEMENT

The lead author Anna Yushchuk, Olha Korzhyk affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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