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Significance of initial clinical laboratory parameters as prognostic factors in patients with COVID-19

Značaj inicijalnih kliničko-laboratorijskih parametara kao prognostičkih faktora kod bolesnika sa COVID-19

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Abstract

Background/Aim. Coronavirus disease 2019 (COVID-19) is a predominantly respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The aim of this study was to determine whether there were parameters that could predict the development of a severe clinical picture and fatal outcomes in COVID-19 patients. **Methods.** The study involved 632 patients treated at the Clinic for Infectious Diseases, University Clinical Center Kragujevac, from June 2020 to February 2021. All patients were divided into two groups according to the need for oxygen therapy (Sat 0_2 < 94 %). **Results.** Our results showed that high body mass index (BMI) was singled out as a risk factor for the development of a severe clinical picture (BMI, $OR_{adjusted}$ = 1.263; 95% CI = 1.117 – 1.427; p < 0.001). Prothrombin time ($OR_{adjusted}$ = 1.170; 95% CI = 1.004 - 1.364; p = 0.045), as well as low albumin values ($OR_{adjusted}$ = 0.878; 95% CI = 0.804 - 0.958; p = 0.003), had a predictive significance for the development of a severe clinical picture. Factors that were of predictive importance in patients with fatal outcomes were C-reactive protein (CRP) ($OR_{adjusted}$ = 1.010; 95% CI = 1.001 – 1.019; p = 0.031), lactate dehydrogenase (LDH) ($OR_{adjusted}$ = 1.004; 95% CI = 1.001 – 1.006; p = 0.002), and X-ray of the lungs ($OR_{adjusted}$ = 1.394; 95% CI = 1.170 – 1.661; p < 0.001). **Conclusion.** The study showed that routine, clinical laboratory parameters can be important in the early detection of patients with a potentially severe clinical picture and fatal outcomes. In patients with a mild clinical picture, CRP, LDH, ferritin, and serum albumin levels may timely indicate disease progression. Monitoring these parameters is of essential importance for the timely clinical assessment of patients with COVID-19 and, thus, the prompt application of adequate therapeutic protocols in the treatment of these patients.

Key words:
biomarkers; body mass index; covid-19; death; disease progression; hematologic tests; prognosis; sars-cov-2; severity of illness index; treatment outcome.

Apstrakt

Uvod/Cilj. Bolest koronavirus 2019 (COVID-19) je dominantno respiratorna bolest koju izaziva *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). Cilj rada bio je da se utvrdi postojanje parametara koji bi mogli da predvide razvoj teške kliničke slike i smrtni ishod kod obolelih od COVID-19. **Metode.** Istraživanjem su bila obuhvaćena 632 bolesnika lečena na Klinici za infektivne bolesti Univerzitetskog kliničkog centra Kragujevac, u periodu od juna 2020. godine do februara 2021. godine. Svi bolesnici su bili podeljeni u dve grupe na osnovu potrebe za kiseoničnom terapijom (Sat 0_2 < 94%) **Rezultati.** Visok indeks telesne mase izdvojio se kao faktor rizika od razvoja teške kliničke slike ($OR_{adjusted}$ = 1,263; 95% CI = 1,117 - 1,427; p < 0,001). Prognostički značaj za razvoj teške kliničke slike imalo je i protrombinsko vreme ($OR_{adjusted}$ = 1,170; 95% CI = 1,004 – 1,364; p = 0,045), kao i niske vrednosti albumina ($OR_{adjusted}$ = 0,878; 95% CI = 0,804 – 0,958; p = 0,003). Faktori koji su imali prognostički značaj kod bolesnika čija se bolest završila smrtnim ishodom bili su C-reaktivni protein (CRP) ($OR_{adjusted}$ = 1,010; 95% CI = 1,001 – 1,019; p = 0,031), laktat dehidrogenaza (LDH) ($OR_{adjusted}$ = 1,004; 95% CI = 1,001 – 1,006; p = 0,002) i radiografski nalaz pluća ($OR_{adjusted}$ = 1,394; 95% CI = 1,170 – 1,661; p < 0,001). **Zaključak.** Istraživanje je pokazalo da rutinski, kliničko-laboratorijski parametri mogu imati značaj u ranom otkrivanju obolelih sa potencijalno teškom

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kliničkom slikom i smrtnim ishodom. Kod obolelih sa lakom kliničkom slikom, CRP, LDH, feritin i nivo albumina u serumu mogu blagovremeno ukazati na progresiju bolesti. Praćenje ovih parametara je od velikog značaja za pravovremenu kliničku procenu stanja obolelih od COVID-19, a samim tim i pravovremenu primenu adekvatnih terapijskih protokola za lečenje tih bolesnika.

Ključne reči:
biološki pokazatelji; telesna masa, indeks; covid-19; smrt; bolest, progresija; hematološki testovi; prognoza; sars-cov-2; bolest, indeks težine; lečenje, ishod.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and currently presents as a dominant respiratory disease worldwide [1]. SARS-CoV-2 is considered more contagious than severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. COVID-19 is manifested by a variety of symptoms, including fever, exhaustion, loss of sense of smell and taste, croup, runny nose, cough, shortness of breath, etc. The clinical presentation is different and may include patients with asymptomatic infection, upper respiratory tract infection, and viral pneumonia [3]. Early detection of asymptomatic patients is very important in preventing the spread of the infection [4, 5]. Asymptomatic patients, by the end of clinical follow-up in most cases, remain asymptomatic with a good prognosis, without developing complications [6]. Patients with COVID-19 with pneumonia develop a secondary bacterial infection to a lesser extent than patients with influenza [7]. Severe COVID-19 occurs as a result of a systemic inflammatory response (SIRS) when other organ systems, such as the cardiovascular system, kidneys, and liver, are damaged [8, 9]. The mechanism of damage is most likely related to the expression of angiotensin-converting enzyme (ACE)-2 receptors on other organ systems, in addition to the lungs [7]. Therefore, it is extremely important to timely identify patients with risk factors of developing severe clinical manifestations, primarily pneumonia, as well as other manifestations. Patients with risk factors for the progression of the severe clinical picture should be candidates for the inclusion of adequate therapeutic protocols. The fundamental question to be asked is whether routine analyses and some clinical characteristics can exhibit predictive significance for the development of a severe clinical outcome.

The aim of the study was to determine the variables that affect the progression of the severe clinical picture of COVID-19, as well as to determine which variables may contribute to the fatal outcome of COVID-19. Moreover, one of the goals was to determine whether there were patients who switched from mild to severe patients during clinical follow-up and whether certain variables were isolated in such patients.

Methods

The study involved 632 patients treated at the Clinic for Infectious Diseases, University Clinical Center (UCC) Kragujevac in Serbia, from June 2020 to February 2021. UCC Kragujevac encompasses a region to which two million people gravitate. The study included patients who had COVID-19 confirmed by nasopharyngeal swabs [polymerase chain reaction (PCR) test or antigen (Ag) test].

All patients were divided into two groups according to the need for oxygen (O_2) therapy [with O_2 saturation (Sat O_2) < 94%]. The first group consisted of patients with Sat O_2 < 94% and the second group consisted of patients with Sat O_2 > 94%. The application of O_2 therapy implies different types of O_2 therapy depending on the degree of acute respiratory insufficiency [O_2, high flow O_2 nasal therapy (HFNO), non-invasive ventilation (NIV), mechanical ventilation (MV)]. Patients who did not use O_2 support (Sat O_2 > 94%) belonged to the group of patients with a mild form of the illness. These patients were treated in the early stages of a pandemic when hospitalization was mandatory for all people with SARS-CoV-2 positive tests. Patients aged 18 or above were included in the study. Body mass index (BMI) values were measured in all patients; therefore, values > 25 kg/m^2 were defined as overweight, while BMI values over 30 kg/m^2 were defined as obesity.

Upon admission to the hospital, all patients underwent initial laboratory analyses in the first 24 hrs, which included basic hematological analyses (complete blood count with leukocyte formula), biochemical analyses [urea, creatinine, potassium (K), sodium (Na), glycemia, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCR), ferritin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma GT, creatine kinase (CK), CK–MB, troponin, iron (Fe)]. Coagulation status [international normalized ratio (INR), activated partial thromboplastin time (aPTT), D-dimer, fibrinogen] of all patients was measured as well.

All laboratory analyses were performed in the Laboratory Diagnostics Service of the UCC Kragujevac. As a model for the analysis of radiographic lung findings, we used the scoring proposed by Italian radiologists from Brescia in May 2020 [10]. The lungs were divided into six zones: Line A – in the projection of the lower wall of the aortic arch; Line B – in the projection of the lower wall of the right pulmonary vein. The second step was to score each of the six zones according to the changes in the lungs: 0 – no changes in lungs, 1 – interstitial infiltrate, 2 – alveolar infiltrates, and 3 – interstitial and alveolar infiltrate. An X-ray found changes in the lungs were described within the range of severity from 1 to 18.

The study was approved by the Ethics Committee of UCC Kragujevac (01/20-498, on May 5, 2020). All collected data were organized into an electronic database.

Table 1

Variables monitored in patients with COVID-19 with severe and mild clinical pictures

Variable	Patients with severe clinical picture (n = 312)	Patients with mild clinical picture (n = 320)	Significance
Age (years), mean ± SD	61.64 ± 13.08	48.41 ± 15.18	t = 11.725 p < 0.001
Radiology score, mean ± SD	10.23 ± 4.11	2.61 ± 3.19	t = -25.894 p < 0.001
DM type 2, n (%)	100 (32.8)	25 (8.1)	χ^2 = 50.024 p < 0.001
HTA, n (%)	175 (57.0)	61 (27.6)	χ^2 = 81.042 p < 0.001
Asthma/COPD, n (%)	18 (5.9)	8 (2.6)	χ^2 = 4.155 p = 0.042
Body mass index (kg/m^2), mean ± SD	28.81 ± 4.33	24.84 ± 3.97	t = -11.957 p < 0.001
Leukocytes (x10^9/L), mean ± SD	7.40 ± 3.62	5.99 ± 2.80	t = 5.436 p < 0.001
Lymphocytes (x10^9/L), mean ± SD	0.93 ± 1.46	1.46 ± 1.06	t = -7.101 p < 0.001
Platelets (x10^9/L), mean ± SD	220.95 ± 104.07	223.20 ± 86.18	t = -0.293 p = 0.770
Glucose (mmol/L), mean ± SD	8.43±4.83	6.10 ± 2.30	t = 7.537 p < 0.001
Urea (mmol/L), mean ± SD	7.74 ± 4.81	5.19 ± 2.30	t = -8.391 p < 0.001
Creatinine (μmol/L), mean ± SD	106.16 ± 108.91	88.08 ± 56.72	t = -2.583 p = 0.010
Potassium (mmol/L), mean ± SD	3.99 ± 0.54	4.15 ± 0.42	t = -4.208 p < 0.001
Sodium (mmol/L), mean ± SD	137.79 ± 4.10	138.63 ± 2.85	t = -2.837 p = 0.005
Albumins (g/L), mean ± SD	34.79 ± 4.87	41.18 ± 4.28	t = -17.327 p < 0.001
CRP (mg/L), mean ± SD	114.67 ± 87.23	28.19 ± 49.35	t = -15.227 p < 0.001
PCT (ng/mL), mean ± SD	0.54 ± 2.68	0.08 ± 0.35	t = 3.041 p = 0.002
AST (IU/L), mean ± SD	59.72 ± 94.68	38.25 ± 49.94	t = 3.507 p < 0.001
ALT (IU/L), mean ± SD	56.73 ± 81.12	42.93 ± 63.38	t = -2.343 p = 0.019
Bilirubin total (μmol/L), mean ± SD	10.92 ± 4.75	10.02 ± 5.56	t = 2.130 p = 0.034
GGT (IU/L), mean ± SD	68.35 ± 89.51	43.89 ± 54.99	t = 4.222 p < 0.001
CK-MB (U/L), mean ± SD	15.52 ± 14.50	11.58 ± 4.93	t = -4.508 p < 0.001
CK (U/L), mean ± SD	227.81 ± 397.13	127.87 ± 163.92	t = -4.082 p < 0.001
LDH (U/L), mean ± SD	755.84 ± 439.27	433.27 ± 185.53	t = -11.770 p < 0.001
D-dimer (μg/mL FEU), mean ± SD	2.38 ± 7.99	0.85 ± 3.20	t = -3.096 p = 0.002
Fibrinogen (g/L), mean ± SD	6.03 ± 1.79	4.28 ± 1.86	t = 11.219 p < 0.001
PT (sec), mean ± SD	15.01 ± 6.01	12.15 ± 2.83	t = -7.051 p < 0.001
INR, mean ± SD	1.21 ± 0.48	1.07 ± 0.26	t = -4.027 p < 0.001
Troponin (ng/mL), mean ± SD	0.05 ± 0.30	0.01 ± 0.02	t = 2.382 p = 0.018
Ferritin (μg/L), mean ± SD	977.86 ± 901.19	353.22 ± 435.26	t = -10.757 p < 0.001
Fe (μmol/L), mean ± SD	5.25 ± 4.31	10.17 ± 11.54	t = -10.757 p < 0.001

DM – diabetes mellitus; HTA – hypertensio arterialis; COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; PCT – procalcitonin; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; CK – creatine kinase; CK-MB – creatine kinase-MB fraction; LDH – lactate dehydrogenase; FEU – fibrinogen equivalent units; PT – prothrombin time; INR – international normalized ratio; SD – standard deviation.

Statistical analysis

The data were described by descriptive statistics, using measures of central tendency (mean), variability (standard deviation from the mean), and relative numbers. After testing for normality of the data distribution with the Kolmogorov-Smirnov test, the significance of the difference in values of continuous variables between the study groups defined by categorical variables was tested by Student's *t*-test for independent samples. The significance of the difference in categorical variables between the study groups was tested by the Chi-squared test. The differences were considered significant if the probability of the null hypothesis was ≤ 0.05. Associations between putative risk factors and the study outcome were tested by the multivariate logistic regression model. All calculations were performed by the SPSS (Statistical Package for Social Science for Windows) software, version 18.

Results

A total of 632 patients, who were hospitalized for COVID-19, participated in the study. Among them, 312 (49.4%) were patients with severe clinical pictures, while 320 (50.6%) were patients with mild clinical pictures. Patients with severe clinical pictures required some types of O_2 therapy (O_2, HFNO, NIV, MV). Fatal outcomes were recorded in 57 (11.08%) patients. On O_2 were 177 (56.7%) patients with severe clinical pictures, while on HFNO were 80 (25.6%) patients. There were 55 (17.6%) patients on MV with the most severe clinical status, of which 4 (7.27%) had a favorable outcome. On hospital admission, the initial O_2 was 6 L/min, while the average number of days on O_2 therapy was 11 days. The average duration of HFNO in patients was 6 days, while the average duration of MV was 11 days.

The average age of patients with a severe clinical picture was 61.64 ± 13.08 years, while of patients with mild clinical pictures was 48.41 ± 15.18 years. There was a higher percentage of patients with comorbidities in the group of patients with severe clinical pictures compared to those with mild clinical pictures. Hypertension was recorded in 175 (57.0%) patients with severe clinical pictures, while diabetes mellitus was recorded in 100 (32.8%) patients with severe clinical pictures. The number of patients with asthma/chronic obstructive pulmonary disease (COPD) during the second and third waves of COVID-19, in the group of mild 8 (2.6%) and severe patients 18 (5.9%), was significantly lower than the number of patients with cardiovascular diseases and diabetes mellitus.

The results of the univariate analyses of the possible risk factors for the development of a severe clinical picture are shown in Table 1.

In the group of patients with severe clinical pictures, a significant number of patients with higher BMI values was observed, and their average score of X-ray findings of the lungs was higher than in the group of patients with mild clinical pictures.

The results of hematological and biochemical parameters are shown in Table 1.

According to the multivariate logistic regression, factors associated with the development of a severe clinical picture of COVID-19 were BMI, prothrombin time, and RDG score (chest X-ray scoring system [10]), while blood albumin level was a protective factor (Table 2).

In this study, we analyzed risk factors for death in a group of severe patients. Binary logistic regression showed that the decisive parameter associated with fatal outcomes was the use of the mechanical ventilation (OR = 8,259.43; 95% CI = 219.60−310,646.90; $p < 0.001$), while the number of leukocytes in the blood was singled out as a protective factor in a group of severe patients (OR = 0.763; 95% CI = 0.602−0.968, $p = 0.026$).

Group of patients with fatal outcomes

Fatal outcomes occurred in 57 patients out of a total of 632 patients who participated in the study. The average age in the group of patients with fatal outcomes was 68 years (67.61 ± 10.93), unlike patients who survived COVID-19, where the average age was 53 years (53.59 ± 15.51) (Table 3).

The laboratory data of patients with fatal outcomes vs. the ones who survived COVID-19 are shown in Table 3.

In the group of patients with fatal outcomes, there were higher values of BMI, and a higher number of such patients had comorbidities (hypertension and diabetes mellitus) compared to the group of patients who survived.

As expected, radiological findings in the lungs had a high score in the group of patients with fatal outcomes, 13.04 ± 4.13, while the score in the group of patients that survived was 5.76 ± 4.94.

Blood count analysis indicates that significantly higher leukocyte counts and significantly lower lymphocyte counts were observed in patients with fatal outcomes ($t = 4.414$, $p < 0.001$ and $t = -2.179$, $p = 0.030$, respectively), while platelet

Table 2

Multivariate analysis in COVID-19 patients with severe and mild clinical pictures

Variable	AOR	95% CI	*p*-value
BMI	1.263	1.117–1.427	< 0.001
Albumins	0.878	0.804–0.958	0.003
PLT	1.170	1.004–1.364	0.045
RDG score	1.435	1.272–1.619	< 0.001

AOR – adjusted odds ratio; CI – confidence interval; BMI – body mass index; PLT – platelets; RDG score – chest X-ray scoring system for hospitalized patients with COVID-19 pneumonia [10].

Table 3

Variables measured in the group of patients with fatal outcome and patients who survived COVID-19

Variable	Patients with fatal outcome (n = 57)	Patients who survived COVID-19 (n = 570)	Significance
Age (years), mean ± SD	67.61 ± 10.93	53.59 ± 15.51	$t = 6.662$ $p < 0.001$
Radiology, mean ± SD	13.04 ± 4.13	5.76 ± 4.94	$t = 10.753$ $p < 0.001$
DM type 2, n (%)	24 (45.3)	101 (18)	$\chi^2 = 22.309$ $p < 0.001$
HTA, n (%)	37 (68.5)	205 (36.4)	$\chi^2 = 21.307$ $p < 0.001$
Asthma/COPD, n (%)	1 (1.8)	25 (4.5)	$\chi^2 = 0.877$ $p = 0.349$
Body mass index (kg/m^2), mean ± SD	28.95 ± 4.56	26.58 ± 4.57	$t = 3.701$ $p < 0.001$
Leukocytes (x10^9/L), mean ± SD	8.53 ± 4.23	6.52 ± 3.16	$t = 4.414$ $p < 0.001$
Lymphocytes (x10^9/L), mean ± SD	0.92 ± 1.56	1.22 ± 0.89	$t = -2.179$ $p = 0.030$
Platelets (x10^9/L), mean ± SD	212.23 ± 92.66	223.32 ± 95.91	$t = -0.835$ $p = 0.404$
Glucose (mmol/L), mean ± SD	10.37 ± 6.95	6.95 ± 3.40	$t = 6.364$ $p < 0.001$
Urea (mmol/L), mean ± SD	10.36 ± 6.22	6.06 ± 3.44	$t = 8.185$ $p < 0.001$
Creatinine (μmol/L), mean ± SD	141.01 ± 196.30	92.61 ± 65.54	$t = 4.044$ $p < 0.001$
Potassium (mmol/L), mean ± SD	4.04 ± 0.60	4.07 ± 0.48	$t = -0.481$ $p = 0.630$
Sodium (mmol/L), mean ± SD	138.47 ± 4.97	138.19 ± 3.49	$t = 0.533$ $p = 0.594$
Albumins (g/L), mean ± SD	32.87 ± 4.71	38.53 ± 5.64	$t = -7.507$ $p < 0.001$
CRP (mg/L), mean ± SD	144.55 ± 103.61	64.08 ± 77.06	$t = 7.253$ $p < 0.001$
PCT (ng/mL), mean ± SD	0.60 ± 0.85	0.2807 ± 1.99	$t = 1.204$ $p = 0.229$
AST (IU/L), mean ± SD	93.00 ± 207.01	44.54 ± 43.51	$t = 4.637$ $p < 0.001$
ALT (IU/L), mean ± SD	72.93 ± 161.91	47.56 ± 56.38	$t = 2.508$ $p = 0.012$
Bilirubin total (μmol/L), mean ± SD	11.74 ± 6.15	10.34 ± 5.06	$t = 1.946$ $p = 0.052$
GGT (IU/L), mean ± SD	84.37 ± 134.06	53.79 ± 65.95	$t = 2.936$ $p = 0.003$
CK-MB (U/L), mean ± SD	19.89 ± 16.03	12.89 ±10.13	$t = 4.659$ $p < 0.001$
CK (U/L), mean ± SD	329.91 ± 613.48	162.19 ± 252.68	$t = 3971$ $p < 0.001$
LDH (U/L), mean ± SD	1063.01 ± 746.19	549.11 ± 272.55	$t = 10.721$ $p < 0.001$
D-dimer (μg/mL FEU), mean ± SD	2.35 ± 3.44	1.54 ± 6.33	$t = 0.939$ $p = 0.348$
Fibrinogen (g/L), mean ± SD	6.09 ± 1.93	5.05 ± 2.01	$t = 3.366$ $p = 0.001$
PT (sec), mean ± SD	15.39 ± 4.34	13.40 ± 4.93	$t = 2.788$ $p = 0.005$
INR (INR), mean ± SD	1.20 ± 0.37	1.13 ± 0.40	$t = 1.234$ $p = 0.218$
Troponin (ng/mL), mean ± SD	0.07 ± 0.18	0.03 ± 0.22	$t = 1.263$ $p = 0.207$
Ferritin (μg/L), mean ± SD	1163.95 ± 997.50	619.67 ± 731.84	$t = 5.064$ $p < 0.001$
Fe (μmol/L), mean ± SD	4.59 ± 3.41	7.88 ± 9.21	$t = -2.220$ $p = 0.027$

For abbreviations see under Table 1.

counts (t = -0.835, p = 0.404) showed no statistical significance.

Inflammatory parameters, such as CRP (t = 7.253, p < 0.001), showed statistical significance in the group of deceased patients compared to surviving patients, while values of PCT (t = 1.204, p = 0.229) did not show statistical significance between the two groups.

Ferritin and LDH values (t =10.721, p < 0.001) were higher in the deceased patients' group in relation to the group of surviving patients, while the values of D-dimers (t = 0.939, p = 0.348) did not show a statistically significant difference between the two groups. In addition, analysis of cardiac markers, such as troponin, did not show significance in fatal outcomes (t = 1.263, p = 0.207).

According to the multivariate logistic regression, factors associated with death outcome were CRP ($OR_{adjusted}$ = 1.010; 95% CI = 1.001 – 1.019; p = 0.031), LDH ($OR_{adjusted}$ = 1.004; 95% CI = 1.001 – 1.006; p = 0.002), and RDG score ($OR_{adjusted}$ = 1.394; 95% CI = 1.170 – 1.661; p < 0.001); K blood level was a protective factor ($OR_{adjusted}$ = 0.261; 95% CI =0 .073 – 0.930; p = 0.038) (Table 4).

Table 4

Multivariate analysis in the group of patients with fatal outcome and patients who survived COVID-19

Variable	AOR	95% CI	*p*
Potassium blood level	0.261	0.073–0.930	
CRP	1.010	1.001–1.019	0.031
LDH	1.004	1.001–1.006	0.002
RDG score	1.394	1.170–1.661	< 0.001

AOR – adjusted odds ratio; CI – confidence interval; CRP – C-reactive protein; LDH – lactate dehydrogenase; RDG score – chest X-ray scoring system for hospitalized patients with COVID-19 pneumonia [10].

Patients who switched from a group of patients with mild clinical pictures to a group of patients with severe clinical pictures during clinical follow-up

A total of 320 patients who belonged to the group of patients with light clinical pictures participated in the study; during the hospital treatment, the general condition worsened, which meant switching to the group of patients with heavy clinical pictures. Worsening of the general condition meant a drop in saturation below 93% and the urgent need for O_2 therapy. Among patients who experienced exacerbations, 7 (30%) patients had a BMI over 30, indicating obesity. Moreover, in 8 (43%) patients, cardiac diseases were registered, primarily hypertension.

When comparing different variables between the group of patients with mild symptoms (321) and those who switched to the group of patients in severe state (21) during clinical follow-up, the statistical significance between certain biochemical parameters and radiographic findings in the lungs was achieved. Decreased albumin (< 0.001), increased CRP (< 0.001), ferritin (< 0.001), and LDH (< 0.001) were reported in patients whose clinical picture worsened and progressed to the severe clinical picture group. Furthermore, patients whose condition worsened during follow-up initially had a worse radiographic score (< 0.001) compared to patients in the light patient group.

Discussion

Although COVID-19 has been present worldwide for more than a year, it remains largely unexplored in clinical work. The main aim of the study was to discover parameters that could help us in our daily work with COVID-19 patients and indicate the development of severe clinical manifestations. Most clinical laboratory parameters are routine analyses performed on all patients in the first 24 hrs of hospitalization, which significantly facilitated our research.

Obesity was singled out as a predictive factor for the occurrence of the severe clinical picture in our sample, which is certainly one of the important characteristics of patients with severe outcomes. Obtained results showed that BMI values in our sample were significantly higher than in the results of Chinese authors [11], while an extensive study conducted in the UK showed that BMI over 23 kg/m^2 posed a risk for severe COVID-19 [12]. Obesity adversely affects the prediction of COVID-19 because lung function is associated with decreased expiratory reserve volume, functional capacity, and respiratory compliance [13]. It is considered that chronic inflammation in obese patients adversely affects the course of the disease [14]. The progression of the severe clinical picture is also influenced by the fact that the receptor for the human ACE is, to a greater extent, expressed in adipose tissue than in the lungs [15]. For that reason, obese people express a large number of receptors for the SARS-CoV-2 virus, so they are more susceptible to infection. The number of registered patients with cardiovascular comorbidities and diabetes mellitus was much higher compared to the Barcelona cohort examined in 322 patients [16]. Although comorbidities, primarily hypertension, and diabetes mellitus, were more common in the group of patients with a severe clinical picture, they did not exhibit predictive significance in our study.

When we analyzed basic biochemical analyses that could affect the progression of the severe clinical pictures, reduced albumin values that could exhibit predictive significance were singled out. Hypoalbuminemia in COVID-19 is considered to occur not only due to hepatocellular damage but also as a result of systemic inflammation and increased capillary permeability, causing albumin to disappear into the interstitial

space [17]. In this way, hypoalbuminemia, as a consequence of acute phase protein synthesis, reflects the strength of the SIRS and, therefore, has predictive significance in COVID-19.

Liver damage is quite common in COVID-19. It is known that in addition to the lungs, other organ systems are affected as well. Therefore, elevated values of transaminases, which did not exhibit predictive significance for the progression of the severe clinical picture, were registered. Liver damage in COVID-19 occurs primarily due to the direct action of the virus since the ACE receptor is expressed throughout the liver and the biliary tract [18]. Liver damage is also affected by pre-existing conditions such as obesity, chronic liver infection, and cirrhosis of various etiologies. We should not forget the toxic effect of drugs, especially antiviral drugs and macrolides, which are most often administered in the treatment of COVID-19 patients [19].

The analysis of coagulation status singled out only the elevated value of PT as a significant predictive marker for the severe clinical picture, as demonstrated by the results of other authors [20, 21], although further research is more than necessary. It is known that PT is prolonged in the case of a decrease in coagulation factors, most often in liver damage, as well as in the use of various inhibitors [22]. On the other hand, coagulation parameters did not prove to exhibit predictive significance for fatal outcomes.

When analyzing biochemical parameters, our results showed that elevated CRP values, elevated LDH values, and hypokalemia exhibited predictive significance for fatal outcomes.

Other authors have already shown that elevated CRP values exhibit predictive significance for the fatal outcomes of COVID-19. CRP as a protein of the acute phase of protein is elevated in infection but also inflammation [23]. It is functionally linked to interleukin-6, which induces gene expression and CRP release from the liver [24].

LDH is an intracellular enzyme present in many cells, as well as in the lungs, which is why its release is expected in severe interstitial pneumonia, which can progress to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction [25].

Many authors have noticed the association of hypokalemia with severe outcomes in COVID-19, as shown by the results of our study. Hypokalemia is a common electrolyte disorder in this viral infection and most likely occurs as multifactorial. Respiratory alkalosis caused by hyperventilation, as well as the use of diuretics, gastrointestinal loss, etc., is stated as a possible cause [26]. Chinese authors also mentioned the use of corticosteroid therapy as a possible cause of hypokalemia while, in addition, Italian authors emphasized the loss of K through urine measured during 24 hrs [26, 27]. Further additional research will certainly contribute to clarifying the occurrence of this electrolyte disorder.

If we look at the variables that were isolated in patients who went from mild to severe clinical picture due to the deterioration of the general condition, we can see that the variables showing significance largely coincided with the variables that stood out as prognostic factors during the examination of the severe clinical picture and fatal outcomes.

Conclusion

Our research showed that some routine clinical laboratory parameters, such as BMI, PT, albumin levels, CRP, and LDH, may have an important role in the early detection of patients developing severe clinical pictures and fatal outcomes. Lung X-ray showed predictive significance in all clinical forms with more severe outcomes. Similarly, the same parameters besides ferritin may promptly indicate the progression of clinical symptoms and signs in patients with an initially mild clinical picture. That is why monitoring these parameters is essential for the timely clinical assessment of patients with COVID-19 and, thus, the timely application of adequate therapeutic protocols in the treatment of these patients.

Conflict of interest

No potential conflict of interest was reported by the authors.

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