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BIOMARKERS OF INFLAMMATION AND MULTISYSTEM TISSUE AND ORGAN DAMAGE IN PATIENTS WITH COVID-19

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BIOMARKERI INFLAMACIJE I MULTISISTEMSKOG OŠTEĆENJA TKIVA I ORGANA KOD BOLESNIKA SA KOVIDOM 19

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ABSTRACT

Objective. The importance of in vitro laboratory diagnostic tests for COVID-19 lies in assessing disease severity, monitoring patients, therapeutic monitoring, and predicting disease prognosis. The aim of our study was to evaluate inflammation biomarkers in COVID-19 patients and their association with biomarkers of cardiomyocyte, liver, and kidney damage, and their impact on disease progression.

Methods. The study included 50 patients, 38 (76%) male and 12 (24%) female, with an average age of 64.38 ± 10.95 years, treated for COVID-19 in 2021 at the Clinic for Infectious Diseases of the University Clinical Center Kragujevac. Biomarkers of inflammation, cardiomyocyte, liver, and kidney damage were analyzed at the beginning of hospitalization and on the tenth day using standard laboratory methods and autoanalyzer.

Results. Analysis showed a significant increase in inflammation parameters on the tenth day of hospitalization compared to the initial values: leukocytes (p=0.003), neutrophils (p=0.002), platelets (p<0.001), C-reactive protein (p<0.001), PCT (p=0.011), and IL-6 (p=0.004). Hepatocyte damage biomarkers (ALT (p=0.005), GGT

SAŽETAK

Cilj. Laboratorijska dijagnostika kod bolesnika sa kovidom 19 značajna je u proceni težine bolesti, terapijskom monitoringu, kao i predviđanju ishoda same bolesti. Cilj našeg istraživanja bio je da se procene biomarkeri inflamacije kod bolesnika sa kovidom 19, njihova povezanost s biomarkerima oštećenja kardiomiocita, jetre i bubrega, kao i njihov uticaj na progresiju bolesti.

Metode. Istraživanjem je obuhvaćeno ukupno 50 bolesnika, 38 (76%) muškog pola i 12 (24%) ženskog pola, prosečne starosti 64,38 ± 10,95 godina, lečenih od kovida 19 na Klinici za infektivne bolesti Univerzitetskog kliničkog centra Kragujevac tokom 2021. godine. Biomarkeri inflamacije, kao i biomarkeri oštećenja organa analizirani su na početku hospitalizacije i desetog dana hospitalizacije standardnim laboratorijskim metodama.

Rezultati. Rezultati istraživanja pokazali su značajno povećanje parametara inflamacije desetog dana hospitalizacije u odnosu na početne vrednosti: leukociti (p = 0,003), neutrofili (p = 0,002), trombociti (p < 0,001), C-reaktivni protein (p < 0,001), PCT (p = 0,011) i IL-6 (p=0.004). Biomarkeri oštećenja hepatocita (ALT (p = 0,005), GGT (p = 0,033), kao i biomarkeri funkcije bubrega (urea p <

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(p=0.033)), and kidney function biomarkers (urea (p<0.001) and creatinine (p=0.042)) also increased significantly. Positive correlations were found between inflammation biomarkers and cardiomyocyte and hepatocyte damage at admission. CRP and PCT concentrations were associated with increased risk of cardiomyocyte damage, while neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) predicted heart and kidney damage.

Conclusion. Systemic inflammation in COVID-19 patients leads to disruptions in body homeostasis, reflected in changes in inflammation biomarkers and multi-system tissue and organ damage. Monitoring these parameters can help predict disease progression and complications.

Key words: *COVID-19; biomarkers; inflammation; multiple organ failure.*

0,001) i kreatinin p = 0,042), takođe su pokazali značajan porast. Utvrđene su pozitivne korelacije između biomarkera inflamacije i biomarkera oštećenja kardiomiocita i hepatocita na prijemu. Koncentracije CRP-a i PCT-a bile su povezane s povećanim rizikom od oštećenja kardiomiocita, dok su odnos broja neutrofila i limfocita (NLR), kao i broja trombocita i limfocita (PLR) predviđali oštećenje srca i bubrega.

Zaključak. Sistemska inflamacija kod bolesnika sa kovidom 19 dovodi do poremećaja homeostaze, koja se ogleda u promenama biomarkera inflamacije, kao i multisistemskog oštećenja tkiva i organa. Praćenje ovih parametara značajno je za predviđanje progresije ove bolesti, kao i nastanak mogućih komplikacija.

Ključne reči: *kovid 19; biomarkeri; zapaljenje; multiorganska disfunkcija.*

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) is the cause of the 2019 Coronavirus Disease (COVID-19), which first appeared in Wuhan, China, in December 2019 and quickly spread worldwide. The World Health Organization (WHO) declared the COVID-19 pandemic, in March 2020, posing a significant challenge to the global health system, including clinicians and clinical biochemical laboratories (1). Since then, numerous research studies have been conducted to better understand the epidemiology, mechanisms, clinical evolution, and management of this disease (2). Research data showed that COVID-19 had significant medical, social, and economic consequences globally, as it affected a large number of individuals (3). While the majority of patients infected with the virus were asymptomatic or experienced mild respiratory symptoms, approximately 20% of patients required hospitalization due to severe pneumonia or other, systemic complications (1, 4, 5).

The key characteristics of the SARS-CoV-2 virus are presented with rapid transmissibility and high virulence capacity (6). The virus binds to the angiotensin-converting enzyme 2 (ACE2), which is present in various cells including respiratory epithelial cells, myocardial cells, neurons, vascular endothelial cells, and renal proximal tubule cells. This makes these cells susceptible to potential damage induced or caused by the virus (7, 8). Literature has shown that in severe cases of SARS-CoV-2 infection, a large number of immune cells (innate and adaptive) are being activated (9). These cells produce pro-inflammatory cytokines, leading to an increased inflammatory feedback loop. The cytokine storm in COVID-19 patients is caused by an uncontrolled inflammatory response and it causes severe forms of the disease, with the development of acute respiratory distress syndrome (ARDS), multiorgan dysfunction, and a fatal outcome (10, 11).

Laboratory diagnostics play a crucial role in the management of emerging infectious diseases (12). When it comes to COVID-19, the role of laboratory diagnostics goes beyond identifying the cause and tracking the spread of the disease. In vitro laboratory diagnostic tests are also used to assess disease severity, monitor patients, track the effectiveness of treatments, and predict the course of the disease (13). The results published so far have shown conflicting findings considering the levels of blood elements, the ratio of different types of white blood cells, markers of inflammation, and how these factors relate to the stage of the disease, the severity of symptoms, and the clinical characteristics of patients (14–16).

Many studies have highlighted the importance of deep analysis of various prognostic markers, but the results published so far have shown conflicting findings. A large number of authors have shown significantly increased concentrations of inflammation markers in patients with severe COVID-19, indicating an acute inflammatory reaction and the risk of cytokine storm (14–16). On the other hand, some studies showed normal concentrations of these markers, which may indicate individual variations in the immune response or the influence of other factors such as age, gender, and the presence of comorbidities (17). Also, in some cases, high concentrations of inflammatory markers may be associated with a good clinical outcome, while in other situations they have shown a correlation with a poor prognosis (18). The heterogeneity of results highlights the complexity of the pathophysiology of COVID-19 and the need for more detailed research to establish reliable prognostic indicators. In addition to inflammatory markers, heart, liver and kidney function markers also attract significant attention. Dysfunctions of these organs are among the fatal complications that contribute to mortality (19). The elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyltransferase (γ-GT), total bilirubin, and elevated levels of troponin, a marker of cardiac damage, are the most common laboratory disturbances in COVID-19 patients (20, 21). However, other studies do not report significant

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changes in these parameters, which may also depend on the severity of the clinical image (22).

The objective of this study was to evaluate the levels of inflammatory biomarkers in COVID-19 patients and investigate their associations with markers indicative of cardiac, hepatic, and renal injury. By analyzing these correlations, we aimed to elucidate the potential role of continuous laboratory monitoring in predicting disease progression.

PATIENTS AND METHODS

The research was designed as a retrospective observational study, conducted through the analysis of results from patients with COVID-19. The study included 50 patients: 38 (76%) male and 12 (24%) female, with an average age of 64.38 ± 10.95 years, who were treated at the Clinic for Infectious Diseases of the University Clinical Center Kragujevac in 2021. The study included only subjects who had not been vaccinated prior to infection with COVID-19. COVID-19 infection was confirmed using real-time polymerase chain reaction (RT-PCR), based on the WHO criteria (23). The study did not include patients under the age of 18, patients with a previous diagnosis of cardiovascular diseases, liver and kidney diseases, patients with malignant diseases (on chemotherapy), patients with chronic inflammatory diseases, patients suffering from autoimmune diseases, immunocompromised patients and pregnant women. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the University Clinical Center Kragujevac (01/20-407, dated April 3rd 2020).

Blood samples were collected from the patients on two occasions: at the beginning of hospitalization (admission) and on the tenth day of hospitalization. The study analyzed inflammation biomarkers including the total number of leukocytes, leukocyte subpopulations (neutrophil leukocytes and lymphocytes), the ratio of neutrophil leukocytes to lymphocytes (NLR), the ratio of platelets to lymphocytes (PLR), as well as concentrations of C-reactive protein (CRP), procalcitonin (PCT), and interleukin 6 (IL-6). Additionally, biomarkers to assess myocardial damage were determined, including the activity of creatine kinase (CK), its isoenzyme CK-MB, LDH, high-sensitivity troponin I (hsTNI I), and N-terminal pro-brain natriuretic peptide (NT-proBNP). Biomarkers used to assess liver damage were also determined, including AST, ALT, AST/ALT ratio (De Ritis), γ-GT, and total bilirubin concentration. Urea and creatinine concentrations were used to assess kidney damage. All measurements were conducted at the Laboratory Diagnostic Service of the University Clinical Center Kragujevac.

The DxH 800 Hematology Analyzer (Beckman Coulter Inc. Brea, USA) was used to analyze formed blood elements. The biochemical analyzer Oly AU 680 (Beckman Coulter Inc. Brea, USA) was used for determining biochemical parameters, except for PCT concentration which was measured using the immunochemical analyzer Cobas e 411 (Roche Diagnostics GmbH, Mannheim Germany). Regular internal and external quality controls were implemented in accordance with good laboratory practice recommendations. Reference ranges for the parameters were as follows: leukocytes (3.70-10.0 x 10^9/L), neutrophils (2.10-6.50 x 10^9/L), lymphocytes (1.20-3.40 x 10^9/L), platelets (135-450 x 10^9/L), CRP (<5.00 mg/L), PCT (<0.5 ng/mL), IL-6 (<7 pg/ml), CK (<171 U/L), LDH (220-450 U/L), hsTNI (<0.010 ng/mL), NT-proBNP (<125 pg/mL), AST (0-40 IU/L), ALT (0-40 IU/L), γ-GT (7-50 U/L), total bilirubin (5.0-21.0 μmol/L), urea (3.0-8.0 mmol/L), creatinine (49-106 μmol/L).

IBM SPSS (Statistical Package for Social Sciences, USA) version 22.0 for Windows was utilized for statistical analysis of the collected data. The normality of the distribution of data was assessed by the Kolmogorov-Smirnov test. Data was presented as mean ± standard deviation. The differences in the analyzed parameters at the reception and tenth day of testing were evaluated using either Paired samples T-test or the Wilcoxon test, depending on the distribution of the variables. The correlation between the variables under examination was assessed using the Bivariate correlation test, with the Pearson/Spearman coefficient being determined. Linear regression analysis was applied to identify predictors of organ damage. The threshold for statistical significance was set at $p<0.05$.

RESULTS

We studied the levels of inflammatory biomarkers and markers of heart, liver, and kidney damage in patients with COVID-19 and their potential association during the first and tenth days of hospitalization. The laboratory characteristics of the studied population are presented in Table 1.

Throughout the ten-day hospitalization period, there was a statistically significant increase in inflammatory parameters compared to the baseline values, including leukocyte count, neutrophils, CRP, PCT, and IL-6. Specifically, the leukocyte count increased from 7.62 to 10.97 × 10^9/L ($p=0.003$), while CRP and PCT levels showed significant increases ($p<0.001$ and $p=0.011$, respectively). This increase in inflammatory markers indicates an escalation of inflammation during hospitalization.

In contrast, the markers of cardiomyocyte damage, such as creatine kinase (CK) activity, showed a decrease

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Table 1. Laboratory characteristics of the study population on the first and tenth days of hospitalization.

Variable	Day[1]	Mean±SD	Significance*
Leukocyte ($\times 10^9$/L)	1	7.62 ± 3.752	p=0.003*
	10	10.97 ± 5.85	
Neutrophils ($\times 10^9$/L)	1	5.95 ± 3.463	p=0.002*
	10	8.89 ± 5.125	
NLR	1	0.85 ± 1.012	p=0.304
	10	1.48 ± 2.518	
PLR	1	24.17 ± 21.921	p=0.128
	10	33.42 ± 30.38	
CRP (mg/L)	1	43.48 ± 64.853	p<0.001*
	10	108.83 ± 100.095	
PCT (ng/mL)	1	0.176±0.253	p=0.011*
	10	1.774±7.536	
IL-6 ()	1	43.68±48.277	p=0.004*
	10	282.69±826.16	
CK (U/L)	1	291.26 ± 451.699	p<0.001*
	10	113.58 ± 196.683	
CK-MB (U/L)	1	17.46 ± 9.595	p=0.111
	10	15.47 ± 10.425	
LDH (U/L)	1	701.04 ± 383.373	p=0.115
	10	539,93 ± 290,653	
hsTNI (ng/mL)	1	0.5 ± 3.412	p=0.765
	10	0.08 ± 0.327	
NT-proBNP (pg/mL)	1	994.93 ± 2529.476	p=0.362
	10	952.5 ± 2059.634	
AST (IU/L)	1	38.19 ± 23.425	p=0.007*
	10	53.9 ± 34.039	
ALT (IU/L)	1	53.26 ± 42.13	p=0.005*
	10	81.58 ± 77.194	
γ-GT (U/L)	1	68.44±71.085	p=0.033*
	10	83.93±85.092	
Total bilirubin (μmol/L)	1	10.62 ± 7.07	p=0.124
	10	11.3 ± 7.373	
Urea (mmol/L)	1	6.71 ± 3.783	p<0.001*
	10	9.82 ± 6.183	
Creatinine (μmol/L)	1	97.86 ± 38.372	p=0.042*
	10	96.48 ± 57.148	
AST/ALT	1	0.68±0.529	p<0.001*
	10	1.41±1.491	

[1]-day of hospitalization; NLR, the ratio of neutrophil leukocytes to lymphocytes; PLR, the ratio of platelets to lymphocytes; CRP, C-reactive protein; PCT, Procalcitonin; IL-6, interleukin 6; CK, creatine kinase; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase; hsTNI, high-sensitivity troponin I; NT-proBNP, N-terminal pro-brain natriuretic peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, gamma-glutamyltransferase. *Statistically significant differences

during the study period, with statistical significance observed only for the change in CK levels (p<0.001).

Regarding liver damage, AST, ALT, and γ-GT activities significantly increased over the ten days of hospitalization, with the AST/ALT ratio (p<0.001) also indicating increased liver injury. Similarly, kidney function markers, such as urea and creatinine, showed a statistically significant rise during the hospitalization period (p<0.001 and p=0.042, respectively). In further research, statistically significant relationships were established between inflammation parameters and markers of organ damage at admission (Table 2) as well as on the tenth day of hospitalization (Table 3) in patients with COVID-19.

Bivariate correlation analysis confirmed the existence of a statistically significant positive relationship between individual inflammatory biomarkers and biomarkers of organ damage on the first and tenth days of hospitalization. On the first day of hospitalization, a statistically significant correlation was found between the

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Table 2. Correlation of the concentration of inflammation markers with markers of organ damage on the first day of hospitalization

Correlation	CK	CK-MB	LDH	hsTNI	NT-proBNP	AST	ALT	γ-GT	Total bilirubin	Urea	Creatinine	AST/ ALT
Leukocyte	-0.225/ 0.117	0.017/ 0.909	-0.064/ 0.677	-0.250/ 0.083	0.231/ 0.132	0.052/ 0.722	0.306/ 0.031	0.171/ 0.261	0.080/ 0.614	0.159/ 0.271	0.019/ 0.896	-0.250/ 0.083
Neutrophils	-0.149/ 0.302	-0.010/ 0.946	0.042/ 0.782	-0.088/ 0.546	0.377/ 0.012	0.196/ 0.177	0.372/ 0.008	0.199/ 0.191	0.198/ 0.209	0.161/ 0.263	0.022/ 0.879	-0.234/ 0.106
NLR	-0.092/ 0.527	-0.050/ 0.732	0.151/ 0.321	0.018/ 0.904	0.492/ 0.001	0.340/ 0.017	0.345/ 0.014	0.197/ 0.195	0.172/ 0.276	0.162/ 0.260	0.128/ 0.375	-0.118/ 0.418
PLR	-0.103/ 0.478	-0.040/ 0.786	0.179/ 0.238	0.000/ 0.998	0.556/ 0.000	0.365/ 0.006	0.396/ 0.004	0.301/ 0.045	0.196/ 0.212	0.223/ 0.119	0.155/ 0.282	-0.093/ 0.524
CRP	0.136/ 0.345	0.295/ 0.040	0.450/ 0.002	0.118/ 0.420	0.480/ 0.001	0.529/ 0.001	0.464/ 0.001	0.406/ 0.006	0.147/ 0.354	0.235/ 0.100	0.015/ 0.916	-0.126/ 0.387
Procalcitonin	0.259/ 0.069	0.318/ 0.026	0.276/ 0.067	0.232/ 0.109	0.254/ 0.097	0.430/ 0.002	0.285/ 0.045	0.290/ 0.053	0.065/ 0.685	0.320/ 0.024	0.291/ 0.040	0.013/ 0.931
IL-6	-0.078/ 0.610	0.155/ 0.308	0.115/ 0.467	0.071/ 0.645	0.095/ 0.567	0.095/ 0.535	0.045/ 0.771	0.004/ 0.978	-0.294/ 0.065	-0.040/ 0.794	-0.008/ 0.959	0.196/ 0.198

Table 3. Correlation of the concentration of inflammation markers with markers of organ damage on the tenth day of hospitalization.

Correlation*	CK	CK-MB	LDH	hsTNI	NT-proBNP	AST	ALT	γ-GT	Total bilirubin	Urea	Creatinine	AST/ ALT
Leukocyte	-0.192/ 0.191	0.054/ 0.737	0.305/ 0.047	0.215/ 0.166	-0.133/ 0.425	-0.163/ 0.295	0.243/ 0.096	0.302/ 0.044	0.378/ 0.016	0.431/ 0.002	0.296/ 0.037	-0.220/ 0.156
Neutrophils	-0.167/ 0.257	0.079/ 0.625	-0.266/ 0.085	0.279/ 0.070	0.066/ 0.695	-0.092/ 0.558	0.241/ 0.099	0.346/ 0.020	0.423/ 0.007	0.435/ 0.002	0.175/ 0.224	-0.216/ 0.163
NLR	0.014/ 0.926	0.127/ 0.428	-0.030/ 0.850	0.331/ 0.030	0.251/ 0.129	-0.011/ 0.943	0.139/ 0.345	0.216/ 0.154	0.557/ 0.0001	0.485/ 0.001	0.222/ 0.122	-0.112/ 0.476
PLR	0.021/ 0.886	0.246/ 0.122	0.075/ 0.632	0.332/ 0.030	0.229/ 0.167	0.114/ 0.465	0.164/ 0.266	0.261/ 0.084	0.518/ 0.001	0.366/ 0.010	0.207/ 0.149	-0.104 0.505
CRP	0.353/ 0.014	0.195/ 0.223	0.236/ 0.128	0.224/ 0.148	0.321/ 0.049	0.161/ 0.303	-0.227/ 0.120	-0.095/ 0.535	0.054/ 0.741	0.019/ 0.897	0.038/ 0.795	0.198/ 0.203
Procalcitonin	0.111/ 0.452	0.056/ 0.728	0.068/ 0.668	0.440/ 0.004	0.550/ 0.001	0.296/ 0.054	-0.019/ 0.899	0.170/ 0.265	-0.106/ 0.516	0.327/ 0.022	0.284/ 0.048	0.079/ 0.612
IL-6	-0.001/ 0.996	0.163/ 0.372	0.100 0.573	0.142/ 0.437	0.455/ 0.015	0.000/ 0.999	-0.309/ 0.059	0.062/ 0.722	0.099/ 0.583	0.153/ 0.358	-0.080/ 0.629	0.560/ 0.001

concentration of CRP and the activity of CK-MB (Spearman, r=0.295, p=0.040), LDH (Spearman, r=0.450, p=0.002), NT-proBNP (Spearman, r=0.480 , p<0.001), AST (Spearman, r=0.529, p <0.001), ALT (Spearman, r=0.464, p <0.001) and γ-GT (Spearman, r=0.406, p =0.006), while the concentration PCT statistically significantly correlated with CK-MB activity (Spearman, r=0.318, p=0.026), AST (Spearman, r=0.430, p=0.002), ALT (Spearman, r=0.285, p=0.045) and urea concentration (Spearman, r=320, p=0.024) and creatinine (Spearman, r=0.291, p=0.040). Markers of systemic inflammation, NLR and PLR, also showed a significant correlation with biomarkers of of cardiomyocyte damage (NT-pro BNP (Spearman, r=0.492, p<0.001 for NLR; Spearman, r=0.556, p<0.001 for PLR) and hepatocyte damage (AST (Spearman, r=0.340, p =0.017 for NLR: Spearman, r=0.365, p=0.006 for PLR), ALT (Spearman, r=0.345, p =0.014 for NLR; Spearman, r=0.369, p=0.004 for PLR) and γ-GT (Spearman, r=0.301, p =0.045 for PLR)). On the tenth day of hospitalization, a statistically significant correlation was found between NT-proBNP and the concentration of CRP (Spearman, r=0.321, p=0.049), PCT (Spearman, r=0.550, p <0.001), IL-6 (Spearman, r=0.560, p<0.001), while PCT correlated with hsTNI (Spearman, r=0.440, p=0.004) and kidney damage markers, urea (Spearman, r=0.327, p=0.022) and creatinine (Spearman, r=0.284, p =0.048). NLR and PLR showed a significant positive relationship with hsTNI (Spearman, r=0.327, p=0.022 for NLR; Spearman, r=0.332, p=0.030 for PLR), total bilirubin (Spearman, r=0.557, p<0.001 for NLR; Spearman, r=0.518, p<0.001 for PLR) and urea (Spearman, r=0.485, p<0.001 for NLR; Spearman, r=0.366, p=0.010 for PLR).

Finally, the influence of inflammation parameters on the degree of organ damage was confirmed using regression analysis. CRP and PCT concentrations were

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Table 4. Influence of inflammation parameters on heart damage in patients with COVID-19 infection.

Variable	B	β	95% CI	Significance*
CK				
Leukocyte	23.322	0.502	-20.739–67.382	0.287
Neutrophils	-47.124	-0.869	-107.243–12.994	0.119
NLR	68.434	0.550	-26.843–163.710	0.152
PLR	-1.168	-0.121	-6.084–3.748	0.629
CRP	0.922	0.322	-0.369–2.212	0.154
Procalcitonin	8.148	0.185	-9.217–25.513	0.344
IL-6	0.030	0.078	-0.153–0.212	0.740
CK-MB				
Leukocyte	0.415	0.193	-1.406–2.236	0.640
Neutrophils	-1.293	-0.515	-3.777–1.192	0.291
NLR	1.778	0.309	-2.159–5.715	0.358
PLR	0.105	0.235	-0.098–0.309	0.293
CRP	0.049	0.369	-0.004–0.102	0.070
Procalcitonin	0.743	0.365	0.025–1.460	0.043
IL-6	0.002	0.116	-0.005–0.010	0.578
LDH				
Leukocyte	12.334	0.174	-62.956–87.624	0.737
Neutrophils	-44.816	-0.540	-147.546–57.913	0.375
NLR	39.622	0.208	-123.185–202.430	0.619
PLR	-0.890	-0.060	-9.291–7.510	0.828
CRP	1.820	0.415	-0.385–4.024	0.101
Procalcitonin	13.903	0.207	-15.770–43.577	0.342
IL-6	-0.175	-0.299	-0.486–0.137	0.258
NT-proBNP				
Leukocyte	215.230	0.463	-122.297–552.758	0.194
Neutrophils	-168.492	-0.311	-629.031–292.047	0.448
NLR	220.946	0.178	-508.923–950.815	0.529
PLR	2.054	0.021	-35.606–39.713	0.909
CRP	17.290	0.604	7.406–27.174	0.002
Procalcitonin	163.676	0.373	30.650–296.701	0.019
IL-6	-0.001	0.000	-1.397–1.395	0.999

found to be associated with an increased risk of cardiomyocyte damage, and NLR and PLR were identified as predictors of heart and kidney damage. Data obtained by regression analysis are presented in detail in Tables 4, 5 and 6.

DISCUSSION

The aim of our study was to evaluate biomarkers of inflammation in patients with COVID-19 and their association with biomarkers of cardiomyocyte, liver, and kidney damage. The obtained results showed a significant increase in the concentration of analyzed biomarkers of inflammation (CRP, PCT, IL-6) during the ten-day evaluation period of hospitalized COVID-19 patients, and statistically significant association of these biomarkers with biomarkers of tissue damage.

It is known that the presence of the SARS-CoV-2 virus in the host's body triggers a battery of inflammatory reactions to fight the pathogen. The inflammatory response does not end only with the elimination of the virus but also implies tissue damage surrounding the area infected with the viral pathogen, as well as organs far from the site of infection. Consequently, there is a tendency to generalize the disease with damage to various organs such as the heart, liver, kidneys, central nervous system, blood vessels, and lungs, leading to the emergence of multiple organ dysfunction (24). Severe inflammatory response and the development of the so-called cytokine storm contribute to impaired adaptive immune status in patients with COVID-19 (25). For this reason, circulating biomarkers, which reflect the status of inflammation and immunity, are recognized as potential predictors in the prognosis of the outcome of COVID-19 and the potential induction of multisystem damage (26).

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Table 5. Influence of inflammatory parameters on liver damage in patients with COVID-19 infection.

Variable	B	β	95% CI	Significance*
AST				
Leukocyte	-0.498	-0.089	-5.266–4.269	0.831
Neutrophils	-0.352	-0.054	-6.858–6.153	0.912
NLR	-9.517	-0.633	-19.827–0.793	0.069
PLR	0.687	0.587	0.155–1.219	0.014
CRP	0.026	0.074	-0.114–0.165	0.709
Procalcitonin	-1.218	-0.229	-3.097–0.661	0.194
IL-6	-0.005	-0.099	-0.024–0.015	0.636
ALT				
Leukocyte	0.423	0.038	-8.596–9.442	0.924
Neutrophils	9.734	0.753	-2.572–22.039	0.116
NLR	-28.952	-0.977	-48.454–-9.450	0.005
PLR	0.531	0.230	-0.476–1.537	0.288
CRP	-0.093	-0.136	-0.357–0.171	0.477
Procalcitonin	-3.492	-0.334	-7.047–0.062	0.054
IL-6	-0.032	-0.352	-0.069–0.005	0.089
γ-GT				
Leukocyte	0.513	0.065	-7.973–8.999	0.902
Neutrophils	3.142	0.342	-8.437–14.722	0.581
NLR	-7.819	-0.371	-26.170–10.531	0.388
PLR	0.136	0.083	-0.811–1.083	0.769
CRP	-0.045	-0.094	-0.294–0.203	0.709
Procalcitonin	-1.408	-0.189	-4.753–1.936	0.393
IL-6	-0.009	-0.132	-0.044–0.027	0.619
Total bilirubin				
Leukocyte	0.365	0.565	-0.164–0.894	0.166
Neutrophils	-0.144	-0.190	-0.865–0.578	0.683
NLR	-0.956	-0.552	-2.100–0.188	0.097
PLR	0.088	0.656	0.029–0.147	0.005
CRP	0.004	0.089	-0.012–0.019	0.640
Procalcitonin	0.103	0.168	-0.106–0.311	0.317
IL-6	0.001	0.183	-0.001–0.003	0.365
AST/ALT				
Leukocyte	-0.043	-0.391	-0.120–0.035	0.266
Neutrophils	-0.089	-0.700	-0.195–0.016	0.094
NLR	0.219	0.748	0.052–0.386	0.012
PLR	0.006	0.285	-0.002–0.015	0.133
CRP	-0.001	-0.170	-0.003–0.001	0.308
Procalcitonin	0.008	0.073	-0.023–0.038	0.614
IL-6	0.001	0.788	0.000–0.001	0.000

Available literature data indicate an elevation of the number of white blood cells, a decrease in the number of lymphocytes, as well as an increase in biomarkers that indicate damage to liver and kidney function in severe COVID-19. Additionally, an increase in the concentration of CRP and IL-6was recorded in more severe forms of the disease compared to milder cases (4,27). The results of our research are in agreement with previously conducted studies that indicate the useful role of CRP, PCT, and IL-6 in predicting the severity of the clinical picture and eventual evolution towards a more severe form of the disease of COVID-19 (14,28). In this sense, the assumption is that CRP, as a non-specific positive reactant of the acute phase, whose synthesis is induced by the action of IL-6 in the liver, could be the most effective and sensitive biomarker whose levels positively correlate with the severity of the disease (29). *Lippi et al* showed that an increased concentration of PCT was also associated with a fivefold increase of the risk of developing severe SARS-CoV-2 infection (30). However, in uncomplicated

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Table 6. Influence of inflammation parameters on kidney damage in patients with COVID-19 infection.

Variable	B	β	95% CI	Significance*
Urea				
Leukocyte	-0.498	-0.089	-5.266–4.269	0.831
Neutrophils	-0.352	-0.054	-6.858–6.153	0.912
NLR	-9.517	-0.633	-19.827–0.793	0.069
PLR	0.687	0.587	0.155–1.219	0.014
CRP	0.026	0.074	-0.114–0.165	0.709
Procalcitonin	-1.218	-0.229	-3.097–0.661	0.194
IL-6	-0.005	-0.099	-0.024–0.015	0.636
Creatinine				
Leukocyte	0.423	0.038	-8.596–9.442	0.924
Neutrophils	9.734	0.753	-2.572–22.039	0.116
NLR	-28.952	-0.977	-48.454–-9.450	0.005
PLR	0.531	0.230	-0.476–1.537	0.288
CRP	-0.093	-0.136	-0.357–0.171	0.477
Procalcitonin	-3.492	-0.334	-7.047–0.062	0.054
IL-6	-0.032	-0.352	-0.069–0.005	0.089

infection with COVID-19, the serum concentration of PCT may remain in the normal physiological range, while a continuous increase of this biomarker may indicate bacterial co-infection and disease progression to more severe complications of COVID-19, such as the development of pneumonia and ARDS. It is believed that the increase in the synthesis of interferon-γ during viral infection, and the increased release of interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and IL-6 during bacterial superinfection suppress the synthesis and secretion of PCT (31). We have just discovered a significant increase in the concentration of inflammation markers (leukocytes, neutrophils, CRP, PCT, IL-6) in our patients during the ten-day follow-up period. The most significant change was seen in CRP levels, showing statistical significance. As expected, the ratios NLR and PLR were higher on the tenth day of hospitalization compared to initial values. Many authors have previously highlighted the importance of these ratios as indicators of systemic inflammatory response (32,33). *Liu et al* confirmed that a high platelet count, total leukocyte count, and high NLR predicted disease severity, while elevated NLR and PLR were independent biomarkers predicting disease severity in patients with COVID-19. When comparing NLR and PLR, it was found that NLR had a better diagnostic accuracy (34).

On the other hand, when it comes to biomarkers of liver damage, the available literature data indicates an increased activity of AST and ALT, or elevated AST/ALT ratio due to hepatocyte damage during COVID-19 infection. Some researchers have pointed to a transient increase in transaminase activity as a result of secondary damage to hepatocytes and not a direct effect of the virus on hepatocytes. Secondary hepatic injury in COVID-19 patients is attributed to multiple factors, with the inflammatory response being the most significant contributor. Additionally, the use of hepatotoxic drugs in COVID-19 treatment further exacerbates liver damage. In the study by Cai et al. of 417 patients with COVID-19, 76.3% had abnormal liver tests (35). Additionally, it has been shown that the hypoxia can cause hepatocellular necrosis by increase in reactive oxygen species, activation of redox-specific transcription factors and synthesis of hepatotoxic proinflammatory mediators (36, 37). In accordance with the aforementioned findings, a significant increase in ALT, AST, and γ-GT activity was observed. Elevated AST is less specific for liver damage compared to ALT, but may indicate multi-organ dysfunction(38). In addition, the De Ritis ratio has been shown to be an usueful, early indicator of liver damage (39). In our study, a significant increase in the De Ritis ratio was recorded on the tenth day of hospitalization, as well as its positive correlation with IL-6. An elevated AST/ALT ratio with high IL-6 levels may point to a dysregulation of the immune response and the onset of multi-organ failure, including hepatic injury. Thus, this parameter may indicate worsening of the COVID-19 infection (40). Regarding bilirubin levels, our findings align with those reported by Yusef et al. (41), demonstrating a slight increase in concentration among our patients. However, this increase was not statistically significant.

The link between COVID-19 infection and cardiovascular disease is well-documented (42–45). Studies have reported the association of SARS-CoV-2 infection with myocarditis, heart failure, arrhythmias and other cardiovascular diseases. During early phases of pandemic the heart failure was a commonly observed complication of COVID-19, with a reported incidence of 23-24% in all patients and 49-52% in fatal cases (16, 46). However, the exact mechanism linking myocardial

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damage to SARS-CoV-2 remains elusive. In some cases, cardiovascular complications can occur even in patients without hystory of previous cardiovascular illness (47). Patients with severe COVID-19 may have elevated concentrations of cardiac biomarkers, such as Nt-proBMP, CK-MB and troponin, which suggest serious and acute myocardial injury. These biomarkers are also associated with a higher mortality rate and should therefore be monitored throughout the care of patients with COVID-19 infection to identify high-risk patients in a timely manner (48). Systemic inflammation linked to COVID-19 may hasten the development of subclinical illness or trigger new cardiovascular damage (42,43). However, our research did not establish a direct link between inflammation and markers of cardiomyocyte damage. Additionally, a statistically significant progressive decrease in CK activity was noted during the ten-day study period. These results may require further evaluation due to the potential for cardiovascular complications later in the disease course, such as the post-COVID syndrome. In more severe cases of COVID-19, a gradual loss of functional muscle mass may occur, potentially accounting for the observed decrease in the concentrations of all analyzed biomarkers of myocyte damage in our study population. Age may also play a significant role in determining biomarker activity of myocyte damage, as older individuals tend to have a lower percentage of lean mass in their total body composition.

Based on literature data, kidney damage is a common in patient with COVID-19, particularly in severe clinical stages (49, 50). While the exact mechanism of kidney damage in COVID-19 patients is not fully understood, it is assumed that the SARS-CoV-2 virus can directly impact kidney cells (51, 52). Specifically, studies have shown that angiotensin-converting enzyme 2 (ACE 2) serves as a functional receptor involved in SARS-CoV-2 infection and cytokine storm (53, 54). Additionally, ACE 2 is prominently expressed in podocytes and proximal tubule cells (51). In addition to direct viral invasion, proposed mechanisms of renal damage in COVID-19 patients include acute tubular necrosis from sepsis and kidney hypoperfusion, cytokine storm, hypoxia of the renal medulla due to alveolar damage, and cardio-renal syndrome from viral myocarditis (55). Urea, the end product of protein metabolism, is eliminated from the body through the kidneys, with 40-50% of it being reabsorbed in the renal tubules, crucial for urine concentration. Elevated serum urea levels are important in assessing various diseases, including COVID-19. Consistent with previous studies suggesting the predictive value of urea in COVID-19 patients (56), our study found a statistically significant increase in urea concentration on the tenth day of hospitalization compared to admission, along with a positive correlation with all inflammatory parameters except CRP. Furthermore, our research confirmed a slight rise in creatinine levels, as well as a statistically significant positive correlation between creatinine concentration and PCT.

Finally, regression analysis confirmed the influence of analyzed inflammation parameters on liver, heart, and kidney damage in patients with COVID-19 infection. Elevated inflammatory markers can be predictive indicators of risk for liver, heart and kidney dysfunction, where higher values of these biomarkers can indicate more severe forms of the disease.

In conclusion, over a ten-day follow-up period in hospitalized COVID-19 patients, a significant increase in the concentrations of inflammatory biomarkers was observed. This increase positively correlated with changes in biomarkers indicative of liver, cardiac, and renal injury. These findings underscore the utility of laboratory monitoring of these parameters in predicting disease progression and potential complications.

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