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ALTERATIONS IN LIVER FUNCTION BIOMARKERS AMONG MODERATELY SEVERE COVID-19 PATIENTS IN SOUTHEASTERN SERBIA: A RETROSPECTIVE SINGLE-CENTER STUDY

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Liver biochemical abnormalities have been reported in nearly half of patients with SARS-CoV-2 infection. The study aimed to determine the prevalence of altered liver biomarkers (alanine transaminase—ALT, aspartate aminotransferase—AST, lactate dehydrogenase—LDH, gamma-glutamyl transferase—GGT, and albumin) in COVID-19 patients with a moderately severe clinical picture on hospital admission, and to assess the presence of altered liver-related biomarkers in the absence of a severe clinical presentation. Research material consisted of medical histories of patients with a moderately severe clinical picture of COVID-19 who were hospitalized at the Clinic for Infectious Diseases of the University Clinical Centre Niš. The study included 655 patients (425 male and 230 female) who were divided into three groups: patients without comorbidities (NC), patients with arterial hypertension (HTA), and patients previously diagnosed with diabetes mellitus (DM). Additionally, within each research group, patients were divided into three age subgroups: patients aged 20-40 years, 40-60 years, and over 60 years. AST, ALT, and LDH showed statistically significant differences across the defined groups, while GGT did not. Logistic regression confirmed increased odds for elevated AST and LDH values in all older and comorbid groups, with the most pronounced effects for LDH. For ALT, significantly increased odds were observed among patients with HTA (40–60 years) and DM (40–60 years). The most pronounced changes were observed in elderly patients and those with hypertension and diabetes, with LDH emerging as the most sensitive, although non-specific biomarker, likely reflecting systemic inflammation and disease severity in addition to possible hepatic involvement.

Keywords: COVID-19, aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), gamma-glutamyltransferase (GGT), lactate dehydrogenase (LDH), albumins

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INTRODUCTION

COVID-19 is a multisystem disease caused by SARS-CoV-2 that affects the respiratory, cardiovascular, central nervous system, liver, and kidneys (1). The virus enters the body by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which it uses to enter cells. ACE2 receptors are found in type 2 alveolar cells in the epithelium of the nose, mouth, lungs, in glandular cells of the stomach, in epithelial cells of enterocytes, in the ileum and colon, in most cholangiocytes, and in less than 3.0% of hepatocytes (2,3).

The reports indicate that almost half of patients with SARS-CoV-2 had liver biochemical abnormalities, including elevated aminotransferase levels (AST, ALT), gamma-glutamyltransferase (GGT), bilirubin, and alkaline phosphatase (3-5). Possible causes of liver function disorders during COVID-19 include direct damage by the virus itself, a severe inflammatory response in the sense of the appearance of a cytokine storm, damage due to hypoxia, the occurrence of microthrombosis of the sinusoid of the liver resulting from hypercoagulability of the blood, the toxic effect of drugs administered during treatment or a combination of several associated factors (6,7). Coagulation disorders and microthrombosis, that are commonly seen in COVID-19, may compromise liver perfusion, leading to hepatocyte damage and increased AST levels (8,9). Cholangiocyte damage index alkaline phosphatase is less susceptible to major changes in COVID-19, whereas aminotransferases and gamma-glutamyltransferase, as indicators of hepatocyte damage, were more commonly elevated and almost always changed in severe patients (10,11).

In pathohistological liver samples, the most common findings were preserved biliary and vascular elements without significant damage, along with pronounced Kupffer cell activation and marked regenerative changes in hepatocytes. No obvious viral inclusions were identified in liver tissue (12-14).

Several risk factors are associated with a more severe clinical course of COVID-19, the most prominent being male gender, older age, and the presence of previous comorbidities. Epidemiological data indicate that approximately 75% of hospitalized patients have at least one chronic disease, among which the most common are hypertension, diabetes, malignancies, neurodegenerative and cardiovascular diseases, obesity and kidney diseases (15). The frequency of individual comorbidities is further supported by findings indicating that arterial hypertension (15.8%), cardiovascular and cerebrovascular diseases (11.7%), and diabetes (9.4%) are the most frequently diagnosed comorbidities (16,17). However, little is known about the prevalence and pattern of liver laboratory abnormalities in moderately severe, non-ICU patients at the time of admission.

The study aimed to determine the prevalence of altered liver biomarkers (ALT, AST, LDH, GGT, and albumin) in COVID-19 patients with a moderately severe clinical picture on admission for hospital treatment, and to assess the presence of biochemical abnormalities potentially associated with hepatic involvement in the absence of a severe clinical presentation.

METHODS

The study included medical histories of patients with COVID-19 who were hospitalized at the Clinic for Infectious Diseases of the University Clinical Centre Niš from March to November 2020. A total of 655 patients' medical histories were analyzed, of whom 425 were male, and 230 were female. All patients presented with a moderately severe clinical picture.

For the study, laboratory findings of liver parameters of non-ICU patients with a moderately severe clinical picture of COVID-19 were collected. According to the national guide for the treatment of COVID-19 of the Republic of Serbia, a moderately severe clinical picture of COVID-19 in patients without comorbidities is defined by the development of hypoxia (saturation <90% on room air), rapid breathing with more than 30 breaths per minute, persistent fever and radiographic changes in the lungs that involve more than 50% of the parenchyma (or corresponding findings on CT). In patients with comorbidities, a moderately severe form of the disease was defined by the following parameters: signs of lower respiratory tract disease and oxygen saturation between 90% and 94%. In all patients, the nasopharyngeal swab for SARS-CoV-2 (PCR or antigen test) was positive.

The most common comorbidities associated with COVID-19, according to the literature, were arterial hypertension (HTA) and diabetes mellitus (DM). HTA and DM were therefore selected because they were the most prevalent comorbidities in our study population and had sufficient sample sizes to allow statistical comparisons, while other chronic conditions were either infrequent or heterogeneous and were therefore excluded from the study.

All patients were classified into three groups: patients without comorbidities (NC), patients with arterial hypertension (HTA), and patients with previously diagnosed diabetes mellitus (DM). Additionally, within each research group, patients were further stratified into three age categories: 20 to 40 years, 40

Table 1. *Classification of patients by research group, age and sex*

	NC			HTA		DM	
Age (in years)	20-40	40-60	60+	40-60	60+	40-60	60+
Male	43	114	84	38	77	18	51
Female	28	37	55	22	53	3	32
Total	71	151	139	60	130	21	83

NC – no comorbidities, HTA – arterial hypertension, DM – diabetes mellitus.

to 60 years, and over 60 years. Patients aged 20–40 years with comorbidities were not included due to their small number. The distribution of patients by age, sex, and comorbidity group is presented in Table 1.

Exclusion criteria for the study were: intensive care unit patients, previously diagnosed liver conditions, vascular and autoimmune disorders, previous hepatobiliary surgeries, and chronic conditions other than arterial hypertension and diabetes mellitus.

Data selection and statistical analysis

In this study, we analyzed the levels of the following liver function biomarkers in patients with COVID-19: ALT (alanine aminotransferase), AST (aspartate aminotransferase), LDH (lactate dehydrogenase), GGT (gamma-glutamyl transferase), and albumin. Biomarker values obtained upon patient admission to the Clinic for Infectious Diseases at the University Clinical Centre Niš were used to determine the percentage of patients in different age and comorbidity groups who had already developed COVID-19-related biochemical abnormalities potentially associated with hepatic involvement. All blood analyses of the patients included in the study were performed in the Central Laboratory of the University Clinical Centre Niš. For the examined biomarkers, the reference ranges were: ALT - 10-35 U/L, AST - 10-31 U/L, LDH - 220-450 U/L, GGT - 0-38 U/L, albumin - 62-81 g/L.

Descriptive and χ^2 analyses

Gender structure analyses were performed using a Pearson's Chi-square (χ^2) test. Initially, we compared the gender distribution of men versus women in the clinical groups (NC, HTA, and DM), and then we performed separate χ^2 tests in each group to evaluate the changes in the gender distribution by age group (20–40, 40–60, and >60 years).

The χ^2 test was also applied to evaluate differences in the prevalence of elevated liver enzyme levels (AST, ALT, LDH, GGT) between groups defined by age and comorbidity status, and to assess their association with arterial hypertension and diabetes mellitus across age categories.

Logistic regression

A binary variable (normal vs. elevated) was created for each enzyme based on standard clinical reference values. Binary logistic regression was conducted to assess the association of defined groups with elevated values of individual enzymes. A separate model was built for each enzyme, with the group included as an independent variable with seven levels. The NC 20–40 group was chosen as the reference category because it represents the least metabolically affected population and enables consistent comparison with older and comorbid groups. Results are presented as odds ratios (OR) with 95% confidence intervals (CI), both in tabular form and as a forest plot using a logarithmic scale.

All statistical tests were performed using R software (R Core Team, 2026) within RStudio (RStudio Team, 2026). Statistical significance was defined as $p < 0.05$.

This study was approved by the Ethical Board of the University Clinical Centre Niš, Republic of Serbia, number: 34794/3.

RESULTS

This study comprised the analysis of liver biomarkers in 655 patients upon admission to the Clinic for Infectious Diseases of the University Clinical Centre Niš.

Our results show that, in the total sample, men were overrepresented compared with women ($p < 0.0001$). Moreover, the gender distribution was statistically similar

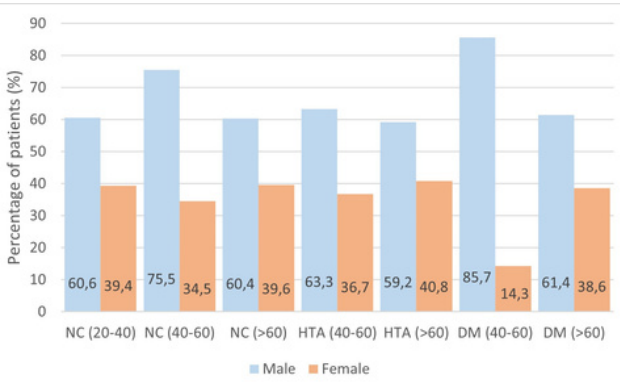

Figure 1. *Distribution of male and female patients per percentage across clinical groups and age categories. Bar chart showing the number of male (blue) and female (orange) patients within each age category (20–40, 40–60, >60 years) across the NC, HTA and DM groups.*

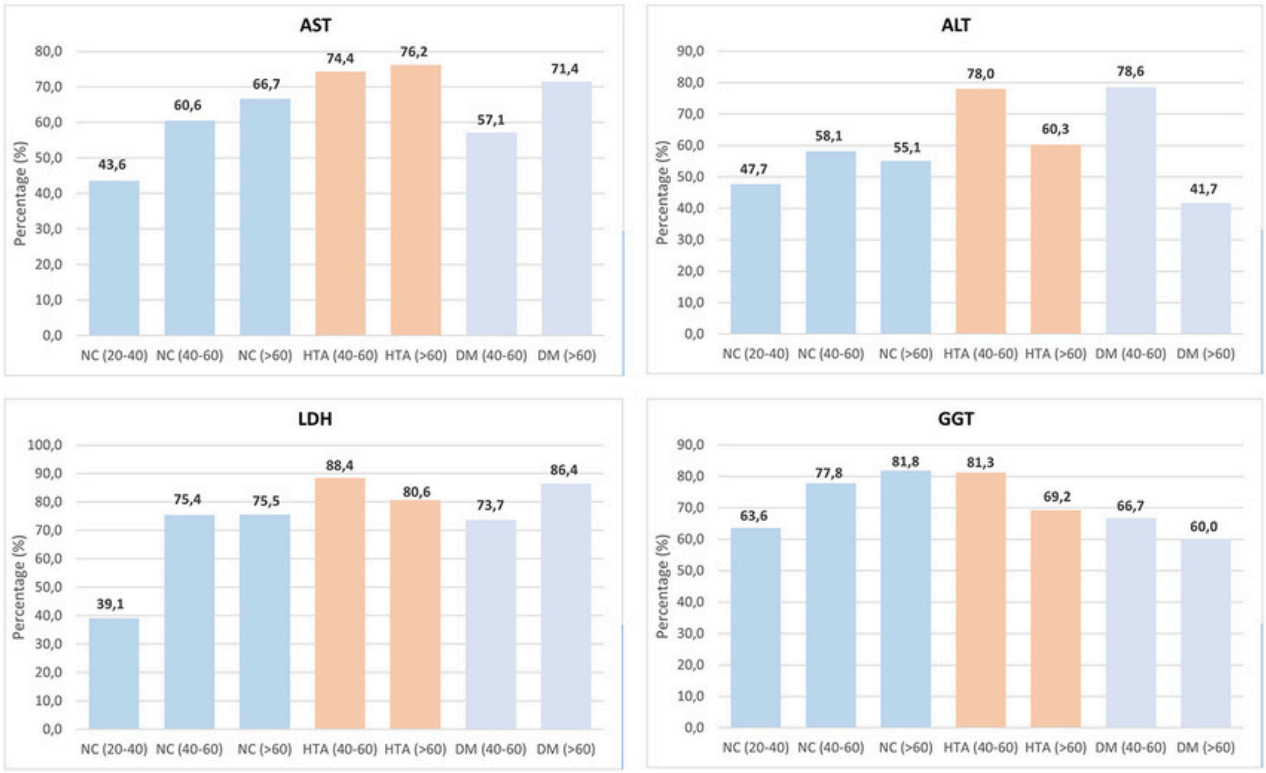

Figure 2. *Percentage of patients with elevated biomarker values in clinical (NC, HTA, DM) and age subgroups. The bar graph shows the percentage of patients with values above the reference range for each subgroup.*

across the clinical groups (χ^2 = 2.24, df = 2, p = 0.33), with a predominance of male patients in the NC, HTA, and DM groups. In the analysis by age categories, however, in the NC (χ^2 = 8.93, df = 2, p = 0.012) and DM (χ^2 = 6.94, df = 1, p = 0.008) groups, a statistically significant difference can be observed in the gender distribution between the age categories, but this is not observed in the HTA group (χ^2 = 0.004, df = 1 p = 0.95) (Figure 1).

The percentage of patients with elevated values of each examined biomarker per group is presented in Figure 2.

In the observed cohort, differences in the prevalence of elevated AST, ALT, and LDH values were observed between the defined groups, whereas no such differences were observed for GGT. The global χ^2 test showed statistically significant differences for AST (χ^2 = 22.9, p = 0.0008), ALT (χ^2 = 14.7, p = 0.022) and LDH (χ^2 = 34.6, p < 0.00001), while no significant difference was observed between groups for GGT (χ^2 = 4.9, p = 0.55).

For each enzyme, a binary logistic regression was performed using seven age-comorbidity categories, with the NC 20–40 group as the reference. Results are presented as odds ratios (ORs) with 95% confidence intervals (Figure 3, Tables 2 and 3).

Table 2. *Odds ratios (OR) with 95% CI for elevated AST and ALT across age- and comorbidity-defined groups, using NC 20–40 as the reference category*

Group	AST OR (95% CI)	p	ALT OR (95% CI)	p
NC 40–60	1.99 (0.95–4.24)	0.067	1.52 (0.75–3.10)	0.245
NC >60	2.59 (1.20–5.69)	0.015	1.34 (0.65–2.78)	0.42
HTA 40–60	3.75 (1.47–10.11)	0.006	3.89 (1.55–10.44)	0.004
HTA >60	4.14 (1.87–9.45)	<0.001	1.24 (0.59–2.58)	0.56
DM 40–60	1.73 (0.51–6.16)	0.38	4.02 (1.08–19.59)	0.047
DM >60	3.24 (1.39–7.78)	0.007	0.78 (0.36–1.71)	0.54

Table 3. *Odds ratios (OR) with 95% CI for elevated LDH and GGT across age- and comorbidity-defined groups, using NC 20–40 as the reference category*

Group	LDH OR (95% CI)	p	GGT OR (95% CI)	p
NC 40–60	4.77 (2.34–10.02)	<0.001	2.00 (0.45–8.13)	0.36
NC >60	4.79 (2.30–10.26)	<0.001	3.43 (0.61–21.54)	0.16
HTA 40–60	11.82 (4.20–39.52)	<0.001	2.48 (0.43–15.86)	0.31
HTA >60	6.47 (3.02–14.34)	<0.001	1.29 (0.27–5.63)	0.76
DM 40–60	4.36 (1.41–15.44)	0.013	1.14 (0.20–6.62)	0.88
DM >60	9.92 (3.98–27.13)	<0.001	0.86 (0.16–4.27)	0.85

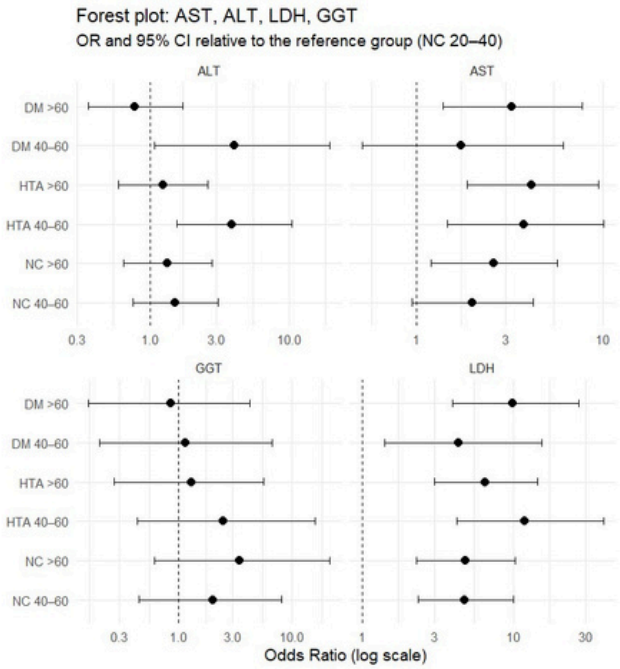

Figure 3. *Forest plot of odds ratios for elevated liver biomarkers (ALT, AST, LDH, GGT) across age- and comorbidity-defined groups. Forest plot showing odds ratios (OR) with 95% confidence intervals for elevated ALT, AST, LDH, and GGT levels in patients with arterial hypertension (HTA) and diabetes mellitus (DM) across two age categories (40–60 and >60 years), as well as in older NC groups (40–60 and >60 years), compared with the reference group (NC 20–40). OR values are displayed on a logarithmic scale.*

In AST, older NC categories, as well as all HTA and DM groups, had higher odds of elevated values than the reference group. The most pronounced risk was observed in the groups HTA 40–60 (OR 3.75, 95% CI 1.47–10.11) and HTA >60 (OR 4.14, 95% CI 1.87–9.45), while the group DM >60 also had significantly increased odds (OR 3.24, 95% CI 1.39–7.78).

For ALT, the groups HTA 40–60 (OR 3.89, 95% CI 1.55–10.44) and DM 40–60 (OR 4.02, 95% CI 1.08–19.59) had statistically significantly increased prospects, while the other categories did not show significant differences compared to NC 20–40.

LDH showed the greatest differences among the groups. All groups older than the reference (NC 20–40), including those with arterial hypertension and diabetes mellitus, had significantly increased odds of elevated LDH values. The highest risk was observed in the HTA 40–60 group (OR 11.82, 95% CI 4.20–39.52), while the DM >60 group also had significantly elevated odds (OR 9.92, 95% CI 3.98–27.13). Older NC categories showed a moderate but statistically significant increase in risk (OR 4.77–4.79). These findings indicate that LDH is the most sensitive marker among the analyzed enzymes.

For GGT, no statistically significant difference was found between age-comorbidity categories and elevated enzyme values. All OR estimates had wide confidence intervals that included 1, indicating no clear effect.

DISCUSSION

The results of our research show that hepatic biochemical markers—primarily AST, ALT, LDH, and GGT—are elevated in a significant number of patients with COVID-19 upon admission to the hospital, even in the absence of a severe clinical picture and without the need for intensive care. This finding is consistent with previous studies indicating that liver biochemical abnormalities occur in approximately 15-53% of hospitalized patients (5). The exact pathophysiological mechanisms of abnormal liver biochemistry in COVID-19 are still not completely elucidated, however, it is considered that the contributing factors might be the direct cytopathic effect of the virus, hypoxia, immunologically mediated damage, iatrogenic causes such as drugs and ventilation, as well as the exacerbation of underlying liver disease (6,18,19).

The AST and ALT levels were most frequently elevated in older patients and in those with hypertension or diabetes. These findings are consistent with reports that metabolic comorbidities, especially diabetes and hypertension, are associated with an increased risk of altered liver-related biomarkers during COVID-19 (20-23). Younger patients without comorbidities had the lowest prevalence of elevated transaminase values, suggesting that age-related metabolic and inflammatory changes play an important role in early liver involvement. Our findings indicate that a significant number of non-ICU patients with moderately severe COVID-19 have increased levels of aminotransferases upon admission to the hospital. Previous studies report a wide range of aminotransferase abnormalities (3.8–80%) (21,24–29), and that the degree of biochemical abnormalities potentially associated with hepatic involvement correlates with the severity of the clinical picture (30–32).

It is important to note that none of the patients in our study had decreased albumin levels, which is expected, given that all were non-ICU patients evaluated upon admission. Hypoalbuminemia is strongly associated with severe and fatal outcomes in the literature, but usually occurs later during hospitalization, which might explain the absence of this finding in our population (33-36).

LDH emerged as the most sensitive biomarker in this study, with prevalence ranging from 39.1% to as high as 88.4% across subgroups. This finding is consistent with meta-analyses that identify LDH as one of the most reliable predictors of disease severity and mortality (32,37). Its elevated values across nearly all older groups and among those with comorbidities are consistent with studies identifying LDH as an indicator of hepatocellular damage, systemic inflammation, hypoxia, and damage to other tissues, which are characteristic of COVID-19 (38,39). Multiple studies have found LDH to be a predictor of worse outcomes in hospitalized patients (40,41). It is particularly significant that the highest LDH values were observed in groups with comorbidities (HTA and DM), which is consistent with findings that patients with metabolic diseases exhibit a more pronounced inflammatory response and a more severe course of COVID-19 infection (38).

In our study, GGT was elevated in most patients (60–81,8%), but there was no clear association with age or comorbidities. This finding is consistent with the literature indicating that GGT may be elevated in patients with COVID-19, but its interpretation is complex, as it may also reflect drug-induced hepatotoxicity, inflammation, or cholangiocellular stress (21,29). Increased GGT levels were found in up to 72% of patients with a severe clinical picture (42,43). Given that our patients were evaluated on admission, before the administration of therapy, it is more likely that elevated GGT levels reflect direct or indirect effects of SARS-CoV-2 on the liver. ACE2 receptors are highly expressed in cholangiocytes, which may explain the relatively high prevalence of elevated GGT (29,44).

Logistic regression additionally confirmed that older age and the presence of hypertension or diabetes increase the likelihood of elevated AST and LDH values. The greatest effects were recorded in the HTA 40-60 and DM >60 groups. ALT showed a more selective pattern, with a significant increase only in the HTA 40-60 and DM 40-60 groups. In contrast to these markers, GGT did not show an independent association with age or comorbidities, indicating that its increase probably depends on other factors.

Although our results show that LDH was the most sensitive and consistent indicator in our study, it is important to emphasize that, unlike aminotransferases, LDH is not liver-specific and is released from a wide range of tissues. Therefore, the marked elevation of LDH observed in our cohort, particularly among older and comorbid patients, should not be interpreted as direct evidence of hepatocellular damage, but rather as a reflection of the overall systemic inflammatory state, tissue hypoxia, and disease severity characteristic of COVID-19 (37-39). Consequently, while LDH proved to be the most sensitive biomarker in our analysis, its elevation likely reflects a composite of pulmonary, cardiac, and systemic inflammatory injury in addition to any hepatic component and should be interpreted with this limitation in mind.

Different studies indicate that the most common comorbidities associated with hospitalized COVID-19 patients were arterial hypertension and diabetes mellitus (45). Our results clearly show that elderly patients and patients with comorbidities had a higher percentage of elevated liver biomarkers. This is in line with a large number of studies that indicate that hypertension and diabetes might significantly increase the risk of a more severe form of COVID-19 and of altered liver-related biomarkers (45-49). It is particularly interesting that patients without comorbidities in the 20-40-year age group had the lowest prevalence of elevated biomarkers, except for GGT, which confirms that the younger population without chronic diseases is less likely to present with biochemical signs of hepatic involvement on admission. Although elevated liver biomarkers are usually associated with a severe clinical picture and worse disease progression, some reports indicate that liver enzyme levels do not differ significantly between the mild/moderately severe and severe clinical pictures of COVID-19 (50).

Several biological mechanisms could contribute to the more pronounced hepatic biomarker alterations observed in older and comorbid patients (18,19). Aging has been associated with reduced hepatic blood flow, decreased hepatocyte regenerative capacity, and a degree of chronic low-grade inflammation, which could lower the threshold for liver involvement during an acute infection with COVID-19, which is in line with the generally more severe clinical course reported in elderly patients (46,50). In patients with arterial hypertension, pre-existing endothelial dysfunction and altered microvascular regulation may increase the susceptibility of the liver sinusoids to hypoperfusion or microthrombosis during the hypercoagulable state associated with COVID-19 (9,45). Similarly, in patients with diabetes mellitus, underlying insulin resistance and a heightened baseline inflammatory state may act together with the COVID-19-related immune response to increase hepatocellular vulnerability (23,47). These age- and comorbidity-related factors might act together with the direct and indirect hepatic effects of SARS-CoV-2 to produce the more pronounced biomarker elevations observed in these subgroups.

Overall, our results show that altered liver-related biomarkersare present even in COVID-19 patients with a moderately severe form of disease at the time of admission. This suggests that hepatic involvement may occur early and should not be interpreted exclusively as a marker of advanced disease. Routine assessment of liver biomarkers, particularly LDH and AST, may help identify patients at increased risk of clinical deterioration.

The key strength of our study is that all biomarker measurements were obtained at the time of hospital admission, before the initiation of any COVID-19-specific hospital therapy, allowing the observed alterations in AST, ALT, LDH, and GGT to be attributed more confidently to the disease process itself rather than to therapeutic interventions. However, this cross-sectional design at a single time point also represents a limitation, since we did not assess the potential influence of subsequently administered therapy on liver biomarkers, nor did we follow the evolution of these biomarkers or of the clinical picture throughout hospitalization. In addition, our findings are limited to non-ICU patients with a moderately severe clinical presentation and therefore cannot be directly extrapolated to patients with severe or critical disease.

Our results confirm that biochemical abnormalities of the liver are common in patients with moderately severe COVID-19 already on admission. The most pronounced changes were observed in elderly patients and those with hypertension and diabetes, which is in accordance with the existing literature. Our results indicate that AST and ALT are primarily associated with comorbidities, LDH predominantly with age, while GGT shows a specific pattern that requires additional research. These findings emphasize the importance of early liver function screening even in patients who do not yet present with a severe clinical picture. Routine monitoring of these biomarkers could provide insight into the underlying inflammatory state and guide more personalized therapeutic approaches.

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Author Contributions

Conceptualization: A.R. and V.P.; Methodology: A.R., B.K.; Formal analysis: A.R., V.P., B.K.; Data curation: M.C., M.Ć.P., L.P.D., J.S., N.M; Writing—original draft preparation: A.R., V.P.; Writing—review and editing: G.R., L.P.D. All authors have read and agreed to the published version of the manuscript.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Board of the University Clinical Centre Niš, Republic of Serbia, number: 34794/3 from 1.10.2019. Since only anonymized biochemical markers were used, without any personal or identifiable information, informed consent was not required.

Statement of Competing Interest

The authors declare no relevant conflicts of interest.

Statement of Data Availability

The data presented in this study are available on request from the corresponding author.

Statement of Generative AI Use

No generative AI was used.

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