Annals of Gastroenterology (2022) **35,** 1-7

Prevalence of abnormal liver biochemistry and its impact on COVID-19 patients' outcomes: a single-center Greek study

Evangelos Cholongitas[a], Triada Bali[a], Vasiliki E. Georgakopoulou[b,e], Alexios Giannakodimos[a], Argyrios Gyftopoulos[a], Vasiliki Georgilaki[a], Dimitrios Gerogiannis[a], Dimitrios Basoulis[a,e], Irene Eliadi[e], Georgios Karamanakos[e], Konstantinos Mimidis[c], Nikolaos V. Sipsas[d,e], Michael Samarkos[a,e]

Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; Democritus University of Thrace, Alexandroupolis, Greece

Abstract

Background Abnormalities in aminotransferases are frequently observed in hospitalized COVID-19 patients, but their clinical impact is poorly characterized.

Methods A total of 1046 patients hospitalized to the non-intensive care unit ward with documented COVID-19 were included retrospectively. Demographic, clinical and laboratory characteristics on admission and during hospital stay, including the presence of liver injury (LI), defined as aspartate aminotransferase (AST) >200 IU/L, were recorded.

Results On admission, 363 (34.7%) and 269 (25.7%) patients had abnormal AST and ALT values (i.e., >40 IU/L), respectively, while during hospitalization 53 (5%) patients fulfilled the criteria for LI. In multivariate logistic regression analysis, AST (odds ratio [OR] 1.023, 95% confidence interval [CI] 1.016-1.029; P<0.001), and ferritin (OR 1.01, 95%CI 1.001-1.02; P<0.001) were the baseline factors independently associated with the development of LI during hospital stay. One hundred twenty-three (11.7%) patients died during hospitalization. The independent variables associated with mortality were: age (hazard ratio [HR] 1.043, 95%CI 1.029-1.056; P<0.001), ferritin (HR 1.1, 95%CI 1.05-1.2; P<0.001), platelets (HR 0.996, 95%CI 0.994-0.999; P=0.003), and administration of remdesivir (HR 0.50, 95%CI 0.30-0.85; P=0.009). The patients with abnormal baseline AST (i.e., >40 IU/L), compared to those with normal AST values, had worse outcomes (log rank test: 8.8, P=0.003).

Conclusions Elevated aminotransferases are commonly seen in COVID-19 patients. They possibly reflect disease severity and may be associated with in-hospital mortality.

Keywords COVID-19, liver injury, liver function tests, disease severity, mortality

Ann Gastroenterol 2022; 35 (X): 1-7

Introduction

COVID-19 is caused by the novel strain of SARS-CoV-2 [1], and, although the latter mainly involves the respiratory system, several other organs might be affected including the gastrointestinal, cardiovascular, hemopoietic, and central nervous systems, contributing to greater morbidity and mortality [2]. These extrapulmonary manifestations are probably due to multiple organs expressing the main viral entry receptor, the angiotensin-converting enzyme (ACE) 2 receptor [3].

Regarding hepatic involvement, abnormalities in liver biochemical parameters can range from asymptomatic to severe liver injury, while very rare cases with liver failure have been observed [4]. It has been reported that over half of the patients hospitalized for COVID-19 have at least one abnormal liver enzyme on admission, while more than 75% will develop abnormal liver enzymes during their hospitalization [5]. Interestingly, although the ACE2 receptor is highly expressed in bile duct cells, hepatocellular damage with aminotransferase elevation is more frequent, while a lower prevalence of increased bilirubin and cholestatic enzymes is observed [6]. On the histological level, it has been shown that COVID-19 patients have mild portal and lobular inflammation and steatosis, as well as hepatocellular necrosis attributable mainly to drug-

Conflict of Interest: None

Correspondence to: Evangelos Cholongitas, MD, PhD, Associate Professor, First Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Agiou Thoma 17, Athens 11527, Greece, e-mail: cholongitas@yahoo.gr

Received 4 December 2021; accepted 14 February 2022; published online 25 March 2022

DOI: https://doi.org/10.20524/aog.2022.0709

induced liver injury or systemic inflammatory syndrome caused by the SARS-CoV-2 infection, since no viral inclusions were observed [7,8].

Nevertheless, data in the literature suggest that hepatic involvement with abnormal liver enzymes during COVID-19 is associated with more frequent development of complications and poor outcomes of COVID-19 [8]. In this study, we aimed to evaluate the prevalence and severity of liver enzyme abnormalities on admission and during the hospital stay, as well as their impact on the outcome, in Greek patients hospitalized with COVID-19.

Patients and methods

Patient population

Consecutive adult patients who had been admitted and hospitalized with documented COVID-19 to the non-intensive care unit COVID-19 ward at Laiko General Hospital, Athens, Greece, between March 2020 and October 2021, were included retrospectively in this single-center study. The patients were enrolled if they fulfilled the following criteria: (a) adults ≥18 years old at the time of hospitalization; (b) at least one positive real-time polymerase chain reaction test for SARS-CoV-2 performed on a nasopharyngeal swab specimen; and (c) hospitalized for more than 3 days. Pregnant women and patients without available medical records were excluded. All patients were followed until discharge or death. The study protocol was approved by the Data Protection Officer and Institutional Review Board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki (as revised in 2000). Because of the retrospective design of the study, a waiver for informed consent was granted by the Institutional Review Board.

Baseline evaluation

Demographic, clinical and laboratory characteristics on admission (i.e., at baseline) were recorded, including age, sex, body mass index (BMI), as well as past medical history, including antihypertensive and antidiabetic drugs. The diagnosis of arterial hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in the sitting position, while severe (or class II) obesity was defined as the presence of BMI>35 kg/m^2 [9]. Administration of medications for COVID-19, including remdesivir, dexamethasone and tocilizumab, was also recorded. At baseline, laboratory variables during the first 24 h of admission were obtained from the electronic medical record system, including white blood cell count, platelets (PLT), albumin, creatinine, total bilirubin, clotting profile (international normalized ratio [INR], fibrinogen and D-dimers), aspartate (AST) and alanine (ALT) aminotransferases, alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GT), lactate dehydrogenase (LDH), C-reactive protein (CRP) and ferritin. In addition, HBsAg/anti-HCV serological status was recorded whenever available. Elevated serum aminotransferases at baseline were defined as ALT >40 IU/L or AST >40 IU/L. As in a previous study [10], since AST abnormalities are the most frequent laboratory finding regarding liver biochemistry, the patients were then divided on admission into two groups, based on the presence of liver injury (LI) according to the baseline serum AST levels: a) no LI with AST ≤200 IU/L; and b) LI with AST >200 IU/L [11].

Follow up and changes in baseline parameters during hospitalization

During their hospitalization, all patients received supportive care with a prophylactic dose of low-molecular-weight heparin (or a therapeutic dose in cases of confirmed thromboembolic event), fluid and electrolyte replacement therapy, and oxygen supplementation (delivered by nasal catheters, masks or high-flow nasal cannula), as needed according to the institutional guidelines. The administration of all medications, including antibiotics, was at the discretion of the attending physician. In addition, laboratory abnormalities were recorded during the hospitalization in order to identify the peak values of ALT and AST. The development of LI (i.e., AST >200 IU/L) during hospital stay was also recorded. The primary outcome of the study was in-hospital mortality.

Statistical analysis

Continuous variables in our cohort are presented as mean ± standard deviation (normally distributed) or median with range (non-normally distributed), while categorical variables are expressed as frequencies or percentages. Comparisons of variables between patients were performed using Student's *t* or Mann-Whitney *U* tests for normally and non-normally distributed continuous variables, respectively, and the chi-square test for categorical variables. We used multivariate Cox regression analysis to identify baseline factors independently associated with the outcome. The discriminative ability of the independent variable was evaluated using the area under the

[a]First Department of Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece (Evangelos Cholongitas, Triada Bali, Alexios Giannakodimos, Argyrios Gyftopoulos, Vasiliki Georgilaki, Dimitrios Gerogiannis, Dimitrios Basoulis, Michael Samarkos); [b]Pulmonology Department, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece (Vasiliki E. Georgakopoulou); [c]First Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis, Greece (Konstantinos Mimidis); [d]Pathophysiology Department, Medical School, National and Kapodistrian University of Athens, and Laiko General Hospital of Athens, Athens, Greece (Nikolaos V. Sipsas); [e]Infectious Diseases and COVID-19 Unit, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece (Dimitrios Basoulis, Eirini Iliadi, Georgios Karamanakos, Nikolaos V. Sipsas, Michael Samarkos)

receiver operating characteristic curve (AUC) [12]. A P-value of <0.05 (2-tailed) was considered statistically significant. Statistical analysis was conducted using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc for Windows (MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

One thousand forty-six COVID-19 patients (613 male, age 63.5±17 years) were evaluated. All patients had clinical manifestations of COVID-19, including fever and respiratory symptoms, with or without the diagnosis of pneumonia based on radiological findings. The baseline clinical and laboratory characteristics are shown in Table 1. Thirty-one (2.9%) patients were HBsAg positive, while 7 (0.7%) were anti-HCV positive. On admission, 363 (34.7%) and 269 (25.7%) patients, respectively, had abnormal AST and ALT values (i.e., >40 IU/L), while 83 (8%) of the patients had AST>80 IU/L and only 12 (1.14%) patients fulfilled the criteria for LI (i.e., AST >200 IU/L). Only 2 patients had AST >400 IU/L. In addition, 51 (4.8%) and 169 (16.2%) of the patients had abnormal levels of total bilirubin (i.e., >1.2 mg/dL) and ALP (i.e., >104 IU/L), respectively. The correlation between AST and ALT on admission was excellent (Spearman r=0.87, P<0.001). The patients with baseline AST≤40 (n=683), compared to those with AST >40 (n=363), were less frequently male (56% vs. 65%, P=0.037) or severe obese (5.5% vs. 11%, P=0.003), and they had significantly lower levels of CRP (22±9 vs. 79±28mg/L, P<0.001), ferritin (392 [10-789] vs. 829 [43-2940] ng/mL, P<0.001), and fibrinogen (545±213 vs. 634±237 mg/dL, P<0.001). However, no difference was observed between the 2 groups regarding the other baseline variables, including age (63±17 vs. 63±17 years), albumin (4.3±0.45 vs. 4.1±0.55 g/dL), and PLT (213±95 vs. 212±87 $\times 10^9$/L) (P-values always >0.05).

At baseline, men compared to women had significantly higher AST (35 [4-957] vs. 31 [7-834] IU/L, P<0.001), ALT (27 [3-825] vs. 22 [3-993] IU/L, P<0.001), γ-GT (39 [5-818] vs. 29 [6-746] IU/L, P<0.001), total bilirubin (0.5 [0.12-58] vs. 0.4 [0.11-11.6] mg/dL, P<0.001), LDH (370±55 vs. 340±70 IU/L, P=0.03), fibrinogen (562±151 vs. 518±141 mg/dL, P<0.001), ferritin (651 [28-2940] vs. 337 [10-2790] ng/mL, P<0.001), and albumin (3.9±053 vs. 3.78±0.55 g/dL, P<0.001), as well as lower PLT (198±82 vs. 225±95 $\times 10^9$/L, P<0.001).

Baseline factors associated with LI development during hospitalization

During hospitalization, 53 (5%) patients fulfilled the criteria for LI (i.e., AST >200 IU/L), while 16 (1.5%) patients developed AST >400 IU/L. In univariate analysis, the patients who developed LI, compared to those without LI during hospitalization, had significantly higher baseline AST (61 [14-957] vs. 32 [4-305] IU/L, P<0.001), ALT (52 [8-993] vs. 24 [3-199] IU/L, P<0.001), γ-GT (65 [12-714] vs. 33 [5-818] IU/L, P<0.001), ALP (72 [29-386] vs. 65 [25-1074] IU/L, P=0.002), total bilirubin (0.65 [0.17-58] vs. 0.46 [0.11-11.6] mg/dL, P<0.001), CRP (88 [4.7-508] vs. 53 [0.7-147] mg/L, P=0.003), ferritin (766 [43-1520] vs. 518 [10-2940] ng/mL, P=0.005), fibrinogen (585 [338-902] vs. 534 [40-1074] mg/dL, P=0.037), and LDH (418 [201-1136] vs. 317 [9-3552] IU/L, P<0.001) (Table 2).

In multivariate logistic regression backward analysis, baseline AST (odds ratio [OR] 1.023, 95% confidence interval [CI] 1.016-1.029; P<0.001) and ferritin (OR 1.01, 95%CI 1.001-1.02; P<0.001) were the only baseline factors independently associated with the development of LI during hospital stay, while excluding baseline liver biochemistry tests (AST, ALT, ALP, γ-GT and bilirubin), ferritin (OR 1.02, 95%CI 1.001-1.03; P=0.001), and LDH (OR 1.003, 95%CI 1.001-1.004; P=0.002) were the only admission factors independently associated with the development of LI during hospitalization. In addition, baseline ferritin and LDH showed relatively good discriminative ability for the development of LI during hospitalization (AUC

Table 1 Baseline clinical and laboratory characteristics of 1046 COVID-19 patients

Variable	Patients, n=1046
Age (mean±SD, years)	63.5±17
Sex, male n, (%)	613 (58.6)
Comorbidities, n (%)	
Diabetes mellitus	186 (18)
Severe (class II) obesity (body mass index ≥ 35 kg/m^2)	65 (6.2)
Arterial hypertension	330 (31.5)
Regular use of alcohol	152 (14.5)
AST (median, range, IU/L)	33 (4-957)
ALT (median, range, IU/L)	25 (3-993)
ALP (median, range, IU/L)	66 (25-1074)
γ-GT (median, range, IU/L)	34 (5-818)
Total bilirubin (median, range, mg/dL)	0.47 (0.11-58)
LDH (median, range, IU/L)	320 (9-3552)
Albumin (median, range, g/dL)	3.9 (1.8-5.4)
CRP (median, range, mg/L)	55 (0.7-508)
INR (median, range)	1.0 (0.7-9.9)
D-dimers (median, range, mg/dL)	0.9 (0.09-52)
Fibrinogen (median, range, mg/dL)	536 (40-1074)
Ferritin (median, range, ng/mL)	533 (10-2940)
WBC (median, range, x10^9/L)	6.2 (1.2-95)
PLT (mean±SD, ×10^9/L)	210±93

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood count; PLT, platelet

Table 2 Clinical and baseline laboratory characteristics of 1046 patients based on the development of liver injury (LI) during hospitalization for COVID-19

Variable	Patients with LI, n=53	Patients without LI, n=993	P-value
Age (mean±SD, years)	65±16	62±17	0.14
Sex, male n, (%)	32 (60)	581 (58)	0.52
Comorbidities, n (%)			
Diabetes mellitus	9 (17)	177 (17)	0.53
Severe obesity (BMI≥35)	4 (7.5)	61 (6)	0.37
Arterial hypertension	13 (25)	317 (32)	0.23
Regular use of alcohol	8 (15.1)	144 (14.5)	0.92
AST (median, range, IU/L)	61 (14-957)	32 (4-305)	<0.001
ALT (median, range, IU/L)	52 (8-993)	24 (3-199)	<0.001
ALP (median, range, IU/L)	72 (29-386)	65 (25-1074)	0.002
γ-GT (median, range, IU/L)	65 (12-714)	33 (5-818)	<0.001
Total bilirubin (median, range, mg/dL)	0.65 (0.17-58)	0.46 (0.11-11.6)	<0.001
LDH (median, range, IU/L)	418 (201-1136)	317 (9-3552)	<0.001
Albumin (median, range, g/dL)	3.9 (1.8-4.7)	3.9 (2.2-5.4)	0.55
CRP (median, range, mg/L)	88 (4.7-508)	53 (0.7-147)	0.003
INR (median, range)	1.0 (0.8-1.3)	1.0 (0.7-9.9)	0.79
D-dimers (median, range, mg/dL)	1.1 (0.3-52)	0.9 (0.09-21)	0.87
Fibrinogen (median, range, mg/dL)	585 (338-902)	534 (40-1074)	0.037
Ferritin (median, range, ng/mL)	766 (43-1520)	518 (10-2940)	0.005
WBC (median, range, $x10^9$/L)	7.2 (1.8-25)	6.1 (1.2-95)	0.83
PLT (mean±SD, $x10^9$/L)	226±100	209± 93	0.31
HBsAg (+)/anti-HCV (+), n, %	0 (0)/0 (0)	31 (3)/7 (0.7)	0.23/0.54
COVID-19 medication, n, (%)			
Remdesivir	27 (51)	725 (73)	0.28
Dexamethasone	32 (61)	763 (76)	0.58
Tocilizumab	7 (13)	93 (9.4)	0.07
Need for intubation, n, (%)	5 (9)	70 (7)	0.36
Length of hospital stay, days, median (range)	8 (4-35)	8 (3-72)	0.76

Values are presented as n (%) using the chi-square test and mean±SD, or median (range) using Student's t or Mann-Whitney U tests, respectively

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood count; PLT, platelet

0.78, 95%CI 0.65-0.84 and 0.71, 95%CI 0.58-0.79, respectively). Interestingly, ferritin was an independent factor associated with LI development in specific subgroups of patients (men, OR 1.023, 95%CI 1.016-1.031; P<0.001; women, OR 1.018, 95%CI 1.009-1.028; P<0.001; patients ≤65 years old, OR 1.024, 95%CI 1.016-1.032; P<0.001; and patients >65 years old, OR 1.016, 95%CI 1.006-1.025; P<0.001).

Factors associated with mortality of COVID-19

One hundred twenty-three (11.7%) patients died in hospital after a median of 8 (4-72) days of hospitalization. In univariate analysis, mortality was associated with age (hazard ratio [HR] 1.04, 95%CI 1.031-1.054; P<0.001), diabetes mellitus (HR 1.54, 95%CI 1.018-2.32; P=0.004), and baseline AST (HR 1.002, 95%CI 1.0-1.005; P=0.03), LDH (HR 1.001, 95%CI 1.0-1.01; P=0.012), albumin (HR 0.93, 95%CI 0.91-0.96; P<0.001), ferritin (HR 1.01, 95%CI 1.001-1.3; P<0.001), INR (HR 1.2, 95%CI 1.02-1.39; P=0.02), PLT (HR 0.97, 95%CI 0.95-0.99; P=0.013), as well as administration of remdesivir (HR 0.56, 95%CI 0.35-0.91; P=0.017). The presence of AST at levels 2 or more times the upper limits of normal (i.e., >80 IU/L) was not associated with mortality (HR 1.74, 95%CI 1.013-3.003; P=0.07) (Table 3). In multivariate Cox regression analysis, the only factors independently associated with mortality were age (HR 1.043, 95%CI 1.029-1.056; P<0.001), ferritin (HR 1.1, 95%CI 1.05-1.2; P<0.001), PLT (HR 0.996, 95%CI 0.994-0.999; P=0.003), and administration of remdesivir (HR 0.50, 95%CI 0.30-0.85; P=0.009). However, all these independent variables had low discriminative ability for mortality (AUC always <0.70).

Table 3 Baseline risk factors associated with mortality in 1046 COVID-19 patients (univariate analysis)

Variables	Hazard Ratio	95% Confidence Interval	P-value
Age, years	1.04	1.031-1.054	<0.001
Sex, male	1.16	1.0-1.005	0.38
Comorbidities			
Diabetes mellitus	1.54	1.018-2.32	0.004
Severe (class II) obesity (body mass index ≥35 kg/m^2)	0.51	0.19-1.40	0.19
Arterial hypertension	1.035	0.69-1.54	0.86
Regular use of alcohol	1.022	0.51-2.11	0.77
AST (IU/L)	1.002	1.0-1.005	0.03
AST >80 IU/L	1.74	1.013-3.003	0.07
ALT (IU/L)	0.99	0.98-1.004	0.52
ALP (IU/L)	1.001	1.0-1.002	0.074
γ-GT (IU/L)	1.001	1.0-1.002	0.45
Total bilirubin (mg/dL)	0.97	0.88-1.054	0.45
LDH (IU/L)	1.001	1.0-1.01	0.012
Albumin (g/dL)	0.93	0.91-0.96	<0.001
CRP (mg/L)	1.001	0.99-1.002	0.78
INR	1.2	1.02-1.39	0.02
D-dimers (mg/dL)	1.001	1.0-1.002	0.15
Fibrinogen (mg/dL)	1.0	0.99-1.001	0.55
Ferritin (ng/mL)	1.01	1.001-1.3	<0.001
WBC (x10^9/L)	0.995	0.991-1.004	0.62
PLT (x10^9/L)	0.97	0.95-0.99	0.013
HBsAg (+) or anti-HCV (+)	1.42	0.63-3.2	0.39
COVID-19 medication			
Remdesivir	0.56	0.35-0.91	0.017
Dexamethasone	1.55	0.72-3.3	0.26
Tocilizumab	0.89	0.53-1.47	0.39

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transpeptidase; LDH, lactate dehydrogenase; CRP, C-reactive protein (CRP); WBC, white blood count; PLT, platelet

Interestingly, the patients with abnormal baseline AST (i.e., >40 IU/L) had worse outcomes compared to those with normal AST values (log rank test: chi square: 8.8, P=0.003) (Fig. 1).

Discussion

This is the first single-center study to evaluate the prevalence and the impact of liver enzyme abnormalities in a Greek cohort of COVID-19 patients. In addition, it is currently the largest study from Greece reflecting our experience regarding the baseline characteristics and the outcomes of the COVID-19 patients admitted and managed in our center. In agreement with data in the literature [13], we found that abnormal values in serum aminotransferases were

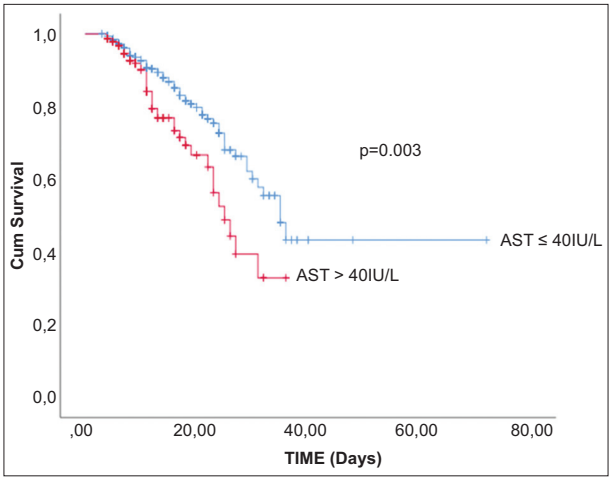

Figure 1 Kaplan-Meier curves showing difference of survival among COVID-19 patients based on the presence or not of abnormal values of aspartate aminotransferase (AST) on admission

frequently observed on admission (in our cohort 35% and 26%, respectively, of the patients had AST and ALT values >40 IU/L). However, at baseline, only 1% and 0.2% of the patients had LI (i.e., AST>200 IU/L) or AST >400 IU/L, respectively. Thus, in accordance with previous studies [10,14,15], we confirmed that liver biochemistry abnormalities in COVID-19 patients are usually mild and predominantly hepatocellular, while AST values are more frequently abnormal than ALT. Nevertheless, no indication for liver dysfunction was observed, since no severe abnormalities in INR were recorded (range 0.7-1.3 in patients not receiving anticoagulants). The exact pathogenetic mechanisms associated with COVID-19 liver enzyme abnormalities have not been elucidated, though direct SARS-CoV-2- or drug-induced liver injury, ischemic damage and a cytokine-driven effect have been proposed [8]. In our cohort, as in previous studies [10], we found that abnormal AST levels were associated with higher values of inflammatory markers reflecting the severity of COVID-19, such as CRP, ferritin and fibrinogen, indicating that aminotransferase abnormalities appear to be observed in the context of systemic hyperinflammatory syndrome and cytokine storm.

Although aminotransferase abnormalities were observed more frequently during hospitalization than at baseline, they remained mild in the majority of cases, since only 5% and 1.5% of the patients, respectively, developed LI (i.e., AST>200 IU/L) or AST>400 IU/L, and again without any evidence of liver failure. The use of several medications during hospital stay (antibiotics, drugs specific for COVID-19) could be an explanation for these findings. However, in multivariate analysis, and taking into account several baseline characteristics, underlying viral hepatitis status and COVID-related medications during hospitalization, it was found that baseline AST and ferritin were the only independent factors associated with LI development, suggesting that the same mechanisms (COVID-19-induced inflammatory storm) might be responsible for the aminotransferase abnormalities, both on admission and during hospital stay.

Regarding the variables associated with mortality, as might be expected, parameters such as age, ferritin and PLT were independently associated with the outcome. Thus, we were able to confirm previous studies, in which hyperferritinemia was an independent predictor of in-hospital mortality in COVID-19 patients [16]. In addition, low PLT were a risk factor for mortality (HR 0.996, 95%CI 0.994-0.999; P=0.003), possibly reflecting the severity of the systemic inflammatory response and the presence of multiple organ dysfunction in SARS-CoV-2 patients [17]. Interestingly, we found that diabetes mellitus was a risk factor for mortality (HR 1.54, 95%CI 1.018-2.32; P=0.004), but this finding was not confirmed in multivariate analysis. Nevertheless, literature data have revealed that diabetes mellitus may increase the replication of SARS-CoV-2 via immune system dysfunction and the release of proinflammatory cytokines, leading to a worse outcome [18]. Although there are conflicting literature data regarding the efficacy of remdesivir (a nucleotide prodrug that interferes with the viral RNA-dependent RNA polymerase activity of SARS-CoV-2) [19], in our study we found that its administration was a protective factor against mortality (HR 0.50, 95%CI 0.30-0.85; P=0.009).

In our cohort, low albumin on admission as a continuous variable was significantly associated with mortality (HR 0.93, 95%CI 0.91-0.96; P<0.001), while the patients with abnormal baseline albumin (i.e., <3.5 g/dL) had worse survival (log rank test: chi square 10.1, P=0.001) (data not shown). A previous study [20] has demonstrated that hypoalbuminemia at the time of admission to the hospital was associated with higher mortality, possibly reflecting poor nutritional status and severe underlying comorbidities. In the same study [20], it was shown that elevations of AST and ALT during hospitalization increased the risk for complications and a poor outcome. In our study we found that baseline AST was associated with poor survival, but this was not confirmed in multivariate analysis. In previous studies [7,14,21], abnormal liver biochemical tests have been related with severe course and poor outcome in patients admitted with SARS-CoV-2 infection, reflecting the prognostic impact of liver test abnormalities in this clinical setting. Nevertheless, in our cohort, the patients with abnormal baseline AST (i.e., >40 IU/L) had worse outcomes compared to those with normal AST values (log rank test: chi square: 8.8, P=0.003) (Fig. 1).

Our study has several limitations, including the fact that it was a single-center retrospective study without details regarding concomitant medication for previous comorbidities or development of extrapulmonary infections during hospital stay. However, all eligible patients were included, while their laboratory variables were recorded from the electronic medical record system of our hospital. In addition, it is the largest study from Greece and the first in which the prevalence and the clinical impact of aminotransferase abnormalities were evaluated in a COVID-19 Greek cohort of patients, showing that their baseline values can be used to predict LI development during hospital stay and might be related with the outcome of COVID-19.

Summary Box

What is already known:

- Although SARS-CoV-2 mainly involves the respiratory system, several other organs might be affected, including the liver
- Abnormalities in liver biochemical parameters are frequently observed
- These abnormalities have been associated with more frequent development of complications and poor outcomes of COVID-19

What the new findings are:

- This is the first and largest study from Greece to evaluate the prevalence and the clinical impact of aminotransferase abnormalities in a cohort of Greek COVID-19 patients
- It was confirmed that abnormal values in serum aminotransferases were frequently observed on admission and during hospital stay
- These liver biochemistry abnormalities were usually mild, and possibly in the context of systemic hyperinflammatory syndrome and cytokine storm
- The patients with abnormal baseline aspartate aminotransferase ([AST], i.e., >40 IU/L) had worse outcomes compared to those without normal AST values

Acknowledgments

The authors would like to thank the physicians of the Infectious Disease – COVID Unit of the Laiko General Hospital, Athens, Drs Sotiria Makrodimitri, Stamatina Samara, Maria Triantafylou, and Pantazis Voutsinas, for providing excellent care to COVID-19 patients and allowing access to their clinical data

References

1. Munster VJ, Koopmans M, van Doremalen N, van Riel D, de Wit E. A novel coronavirus emerging in China - key questions for impact assessment. *N Engl J Med* 2020;**382**:692-694.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;**395**:497-506.
3. Shirbhate E, Pandey J, Patel VK, et al. Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention. *Pharmacol Rep* 2021;**73**:1539-1550.
4. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int* 2020;**40**:998-1004.

5. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver functional abnormality. *Clin Gastroenterol Hepatol* 2020;**18**:1561-1566.
6. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. *J Hepatol* 2020;**73**:566-574.
7. McGrowder DA, Miller F, Anderson Cross M, Anderson-Jackson L, Bryan S, Dilworth L. Abnormal liver biochemistry tests and acute liver injury in COVID-19 patients: current evidence and potential pathogenesis. *Diseases* 2021;**9**:50.
8. Spearman CW, Aghemo A, Valenti L, Sonderup MW. COVID-19 and the liver: A 2021 update. *Liver Int* 2021;**41**:1988-1998.
9. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Consultation. WHO Technical Report Series Number 854. Geneva: World Health Organization, 1995.
10. Chew M, Tang Z, Radcliffe C, et al. Significant liver injury during hospitalization for COVID-19 is not associated with liver insufficiency or death. *Clin Gastroenterol Hepatol* 2021;**19**:2182-2191.
11. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol* 2017;**112**:18-35.
12. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;**148**:839-843.
13. Du M, Yang DS, Liu M, Liu J. COVID-19 and liver dysfunction: epidemiology, association and potential mechanisms. *Clin Res Hepatol Gastroenterol* 2022;**46**:101793.
14. Paštrovic F, Lucijanic M, Atic A, et al. Prevalence and prognostic impact of deranged liver blood tests in COVID-19: experience from the regional COVID-19 center over the cohort of 3812 hospitalized patients. *J Clin Med* 2021;**10**:4222.
15. Sobotka LA, Esteban J, Volk ML, Elmunzer BJ, Rockey DC; North American Alliance for the Study of Digestive Manifestation of COVID-19. Acute liver injury in patients hospitalized with COVID-19. *Dig Dis Sci* 2021 Sep 6 [Epub ahead of print]. doi: 10.1007/s10620-021-07230-9
16. Alroomi M, Rajan R, Omar AA, et al. Ferritin level: a predictor of severity and mortality in hospitalized COVID-19 patients. *Immun Inflamm Dis* 2021;**9**:1648-1655.
17. Ogura H, Gando S, Iba T, et al; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation Study Group. SIRS-associated coagulopathy and organ dysfunction in critically ill patients with thrombocytopenia. *Shock* 2007;**28**:411-417.
18. Ali Kazem T, Zeylabi F, Filayih Hassan A, Paridar P, Pezeshki SP, Pezeshki SMS. Diabetes mellitus and COVID-19: review of a lethal interaction from the cellular and molecular level to the bedside. *Expert Rev Endocrinol Metab* 2022;**17**:1-19.
19. Angamo MT, Mohammed MA, Peterson GM. Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis. *Infection* 2022;**50**:27-41.
20. Wagner J, Garcia-Rodriguez V, Yu A, et al. Elevated transaminases and hypoalbuminemia in Covid-19 are prognostic factors for disease severity. *Sci Rep* 2021;**11**:10308.
21. Medetalibeyoglu A, Catma Y, Senkal N, et al. The effect of liver test abnormalities on the prognosis of COVID-19. *Ann Hepatol* 2020;**19**:614-621.