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Association between COVID-19 severity with liver abnormalities: A retrospective study in a referral hospital in Indonesia

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Abstract

Coronavirus disease 2019 (COVID-19) is characterized by an acute respiratory infection with multisystem involvement and the association of its severity to liver function abnormalities is not well characterized. The aim of this study was to assess the association between the severity of COVID-19 patients and liver function abnormalities. This retrospective study included adult patients with confirmed COVID-19, which were classified as non-severe or severe according to World Health Organization guidelines. Liver function test results were compared between the severity groups. A total of 339 patients were included of which 150 (44.25%) were severe cases. The male-to-female ratio was 0.9:1 and 3:2 in the non-severe and severe groups, respectively (*p*=0.031). Aspartate aminotransferase (AST), alanine transaminase (ALT), and total bilirubin levels and acute liver injury (ALI) incidence were significantly higher in the severe group compared to non-severe group (*p*<0.001, *p*<0.001, *p*=0.025, *p*=0.014, respectively). In contrast, albumin levels were significantly lower (*p*=0.001). Multivariate analysis showed that ALI was significantly associated with human immunodeficiency virus (HIV) infection (odds ratio (OR): 5.275; 95% confidence interval (CI): 1.165–23.890, *p*=0.031), hemoglobin level (OR: 1.214; 95%CI: 1.083–1.361, *p*=0.001), and hypoalbuminemia (OR: 2.627; 95%CI: 1.283–5.379, *p*=0.008). Pre-existing liver diseases were present in 6.5% of patients. No significant differences were observed between the groups based on COVID-19 severity and ALI presence. Liver function test abnormalities, including ALI, are more prevalent in patients with severe COVID-19 infection. HIV infection, high hemoglobin levels, and hypoalbuminemia may be potential risk factors for ALI.

Keywords: Acute liver injury, COVID-19, disease severity, liver function abnormality, risk factors

Introduction

*I*n December 2019, the first coronavirus disease 2019 (COVID-19) case, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was documented in Wuhan province, China and soon became a pandemic by March 2020 [1]. COVID-19 has a wide clinical spectrum of disease presentations, ranging from mild to critical. The most common clinical feature is

impaired respiratory system, characterized by cough and shortness of breath, with radiographic results consistent with pneumonia [2]. However, extrapulmonary manifestations, including cerebrovascular stroke, liver damage, acute kidney injury, and gastroenteritis, have also been reported [2]. These findings may result from either extrapulmonary dissemination and replication of SARS-CoV-2 or extensive immunopathological sequelae of the disease. Liver function abnormalities in adult patients with COVID-19 have been reported; however, their relationship with the severity of COVID-19 remains unclear.

Previous studies have reported that 37.2–76.3% of patients with COVID-19 had elevated liver biochemical parameters [3,4]. Pathological examination of liver tissues from deceased patients with COVID-19 has confirmed that liver involvement is characterized by microvesicular steatosis, focal necrosis with lymphocyte infiltration, and microthrombosis in the portal area [5]. The presence of SARS-CoV-2 RNA in various other organs outside the respiratory tract, including the liver, has been demonstrated using quantitative reverse transcription–polymerase chain reaction (qRT-PCR) [6]. These findings suggest that SARS-CoV-2 may cause liver damage.

During COVID-19 progression, patients with liver dysfunction may experience acute liver failure and even death [7]. Therefore, liver damage must be investigated in patients with COVID-19. Previous studies have reported associations between liver function and the duration of hospital stay [5,7], risk of progression to severe COVID-19 [5,7], and mortality [8]. The aim of this study was to determine the effect of COVID-19 severity on liver biochemical parameter abnormalities and determine the factors associated with the incidence of acute liver injury (ALI).

Methods

Study design
This retrospective study was conducted at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from May to September 2020. All confirmed COVID-19 patients treated in the isolation room of the internal medicine ward of the hospital were considered eligible. The hospital is the primary referral hospital in Eastern Indonesia.

Study variables
This study evaluated the severity of COVID-19 as the independent variable. The dependent variables of the study were the liver abnormalities indicators (level of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, and albumin). In addition, the incidence of ALI was also assessed and treated as a dependent variable. ALI was defined as the presence of one of the following: (1) jaundice with total bilirubin level ≥3 mg/dL; (2) acute increase in ASL, ALT, or gamma-glutamyl transferase (GGT) levels ≥2 times the upper normal limit (UNL); and (3) prothrombin time-international normalized ratio ≥1.5, with previously normal liver parameters [9]. We also evaluated potential risk factors for ALI, including gender, diabetes, chronic kidney disease (CKD), human immunodeficiency virus (HIV), COVID-19 severity, hemoglobin, platelet, neutrophil, lymphocyte, neutrophil-to-lymphocyte ratio (NLR), hypoalbuminemia, creatinine, and C-reactive protein (CRP).

Patient selection and data collection
All RT-PCR confirmed COVID-19 patients aged ≥18 years were eligible as sample of the study. The patients were classified into non-severe (mild and moderate) and severe (severe and critically ill) based on World Health Organization (WHO) criteria [10]. Demographics and clinical data of all patients were collected, including sex, age, clinical presentations, comorbidities, and outcomes. The laboratory parameters (ALT, AST, total bilirubin, direct bilirubin, and albumin) were assessed on the day of admission.

Statistical analyses
Categorical variables were presented as percentages and continuous variables as mean and standard deviation (SD). Associations between COVID-19 severity and liver function abnormality were assessed using Chi-squared test, Fisher's exact, Student t-test or Mann–Whitney U test as appropriate. Logistic regression analysis was conducted to evaluate the risk factors for ALI

incidence. A *p*<0.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Comparison of demographic, clinical, and laboratory characteristics between non-severe and severe COVID-19

A total of 339 COVID-19 patients (189 non-severe and 150 severe cases) were included in this study and the clinical characteristics of the patients at admission are presented in **Table 1**. The mean ages of all patients were 51.22±13.04 years. The male-to-female ratio was 0.9:1 for non-severe cases and 3:2 for severe cases (*p*=0.031). The initial symptoms, including dyspnea, cough, and fever, were all significantly more pronounced in the severe group as compared to those in the non-severe group (78.7% vs 29.6%, *p*<0.001; 54.75% vs 39.2%, *p*=0.006; 38.7% vs 26.5%, *p*=0.023, respectively) (**Table 1**).

Pre-existing liver diseases were present in 6.5% of the patients; these included hepatitis B (2.9%), hepatitis C (0.9%), hepatic cirrhosis (2.4%), and hepatocellular carcinoma (0.3%) (**Table 1**). There were no significant differences between the two groups concerning the presence of preexisting liver disease. Among all comorbidities, a significant difference between the two groups was only found for chronic kidney disease (CKD) (*p*=0.049) (**Table 1**).

The results of the liver function tests at admission are presented in **Table 1**. The mean AST level was lower in non-severe cases than in severe cases (70.84±71.98 U/L vs 100.71±143.55 U/L, *p*<0.001). The mean ALT level was also lower in the non-severe group compared to the severe COVID-19 group (*p*<0.001). In addition, albumin levels were significantly higher in the non-severe group than those in the severe group (3.22±0.42 g/dL vs 3.15±0.32 g/dL, *p*=0.001). The bilirubin tests at admission were available for 195 patients only and the total bilirubin was significantly lower in the non-severe group than in the severe group (1.01±2.95 mg/dL vs 1.26±2.22 mg/dL, respectively; *p*=0.026). There were no significant differences in direct bilirubin levels between the two groups (**Table 1**).

Table 1. Comparison of demographic, clinical, and laboratory characteristics between non-severe and severe coronavirus disease 2019 (COVID-19) at hospital admission

Parameters	n	Overall	Group		*p*-value
			Non-severe	Severe	
Sex, male n (%)	339	180 (53.1)	90 (47.6)	90 (47.6)	0.031
Age (years)	339	51.22±13.04	49.15±13.00	53.84±12.66	0.001
Symptoms, n (%)					
Dyspnea	339	174 (51.3)	56 (29.6)	118 (78.7)	<0.001
Cough	339	156 (46)	74 (39.2)	82 (54.7)	0.006
Anosmia	339	4 (1.2)	2 (1.1)	2 (1.3)	0.597
Fever	339	108 (31.9)	50 (26.5)	58 (38.7)	0.023
Odynophagia	339	14 (4.1)	6 (3.2)	8 (5.3)	0.473
Diarrhea	339	35 (10.3)	24 (12.7)	11 (7.3)	0.152
Nausea	339	56 (16.5)	30 (15.9)	26 (17.3)	0.832
Vomiting	339	29 (8.6)	15 (7.9)	14 (9.3)	0.649
Decreased appetite	339	35 (10.3)	14 (7.4)	21 (14.0)	0.072
Fatigue	339	54 (15.9)	30 (15.9)	24 (16.0)	1.000
Cephalgia	339	12 (3.5)	10 (5.3)	2 (1.3)	0.096
Myalgia	339	2 (0.6)	1 (0.5)	1 (0.7)	0.690
Comorbidities, n (%)					
Pre-existing liver disease	339	22 (6.5)	14 (63.6)	8 (36.4)	0.584
Hepatitis B	339	10 (2.9)	6 (3.2)	4 (2.7)	0.524
Hepatitis C	339	3 (0.9)	1 (0.5)	2 (1.3)	0.414
Hepatic cirrhosis	339	8 (2.4)	7 (3.7)	1 (0.7)	0.066
Hepatocellular carcinoma	339	1 (0.3)	0 (0.0)	1 (0.7)	0.442
Diabetes	339	102 (30.1)	51 (27.0)	51 (34.0)	0.201
Thyroid disease	339	6 (1.8)	4 (2.1)	2 (1.3)	0.456
Obesity	339	6 (1.8)	2 (1.1)	4 (2.7)	0.241
Chronic kidney disease	339	52 (15.3)	22 (11.6)	30 (20.0)	0.049
Hypertension	339	95 (28.0)	47 (24.9)	48 (32)	0.183
Coronary arterial disease	339	9 (2.7)	5 (2.6)	4 (2.7)	0.623

Parameters	n	Overall	Group		p-value
			Non-severe	Severe	
HIV	339	9 (2.7)	6 (3.2)	3 (2.0)	0.377
Malignancy*	339	20 (5.9)	14 (7.4)	6 (4.0)	0.276
Laboratory parameters mean±SD					
Hemoglobin (g/dL)	339	12.01±2.72	12.21±2.74	12.27±2.81	0.224
White blood cell (10^3/μL)	339	10.37±8.08	8.90±4.98	11.33±7.32	0.001
Platelet (10^3/μL)	339	286.14±161.63	276.92±143.80	286.58±158.54	0.420
Neutrophils (%)	339	78.43±13.35	73.19±10.69	78.30±13.16	<0.001
Lymphocytes (%)	339	15.52±9.01	17.35±8.44	12.12±6.86	<0.001
NLR	339	8.79±16.82	6.11±5.35	10.04±7.89	<0.001
AST (U/L)	339	73.91±88.67	70.84±71.98	100.71±143.55	<0.001
ALT (U/L)	339	60.99±78.04	52.67±35.72	88.36±143.13	<0.001
Total bilirubin (mg/dL)	195	1.11±2.46	1.01±2.95	1.26±2.22	0.026
Direct bilirubin (mg/dL)	195	0.57±1.59	0.51±1.64	0.72±1.78	0.079
Albumin (g/dL)	339	3.19±0.38	3.22±0.42	3.15±0.32	0.001
Blood glucose (mg/dL)	324	159.18±85.43	157.95±91.47	170.47±92.61	0.096
Blood urea (mg/dL)	335	27.90±33.14	25.84±30.82	28.29±34.81	0.011
Creatinine (mg/dL)	335	2.52±4.47	1.99±3.31	2.37±5.17	0.169
CRP (mg/dL)	303	15.45±62.96	15.27±52	15.66±55.85	<0.001
D-dimer (ng/mL)	294	4273.0±6542.4	4612.0±7261.6	4333.2±6016.4	0.009
Prothrombin time (s)	314	16.94±21.19	19.32±25.73	14.12±13.63	0.711
aPTT (s)	314	28.72±6.98	28.88±5.63	28.54±8.32	0.026
Course/outcome					
Acute liver injury	339	98 (28.9)	44 (23.3)	54 (36.0)	0.014
Death	339	81 (23.9)	19 (10.1)	62 (41.3)	<0.001

ALT: alanine aminotransferase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; COVID-19: coronavirus 2019; CRP: C-reactive protein; HIV: human immunodeficiency virus; NLR: neutrophil-lymphocyte ratio; PT: prothrombin time
*Malignancies other than hepatocellular carcinoma

Association between COVID-19 severity and liver function abnormality

The distribution of liver function test results of the two groups are presented in **Table 2**. There were significant differences in the distributions of AST (p=0.004), ALT (p=0.001), total bilirubin (p=0.016), and albumin (p<0.001), but not in that of direct bilirubin (p=0.448) between non-sever and severe COVIOD-19 (**Table 2**).

Table 2. Incidence of abnormalities in liver function test results according to severity of coronavirus disease 2019 (COVID-19)

Liver test and categories		COVID-19 severity		Total	p-value
		Non-severe	Severe		
Aspartate aminotransferase, n (%)	Normal	79 (41.8)	43 (28.7)	122 (36.0)	0.004**
	>1–<2 ×UNL	76 (40.2)	66 (44.0)	142 (41.9)	
	≥2–3 ×UNL	20 (10.6)	18 (12)	38 (11.2)	
	>3 ×UNL	14 (7.4)	23 (15.3)	37 (10.9)	
Alanine aminotransferase, n (%)	Normal	107 (56.6)	61 (40.7)	168 (49.6)	0.001**
	>1–<2 ×UNL	57 (30.2)	52 (34.7)	109 (32.2)	
	≥2–3 ×UNL	20 (10.6)	17 (11.3)	37 (10.9)	
	>3 ×UNL	5 (2.6)	20 (13.3)	25 (7.4)	
Total bilirubin, n (%)	Normal	81 (79.4)	60 (64.5)	141 (72.3)	0.016*
	>1–<2 ×UNL	17 (16.7)	23 (24.7)	40 (2.5)	
	≥2–3 ×UNL	1 (1.0)	5 (5.4)	6 (3.1)	
	>3 ×UNL	3 (2.9)	5 (5.4)	8 (4.1)	
Direct bilirubin, n (%)	Normal	95 (93.1)	84 (90.3)	179 (91.9)	0.448
	>1–<2 ×UNL	4 (3.9)	2 (2.2)	6 (3.1)	
	≥2–3 ×UNL	1 (1.0)	4 (4.3)	5 (2.6)	
	>3 ×UNL	2 (2.0)	3 (3.2)	5 (2.6)	
Albumin, n (%)	>3.5	69 (36.5)	18 (12.0)	87 (25.7)	<0.001**
	3.0–3.49	75 (39.7)	89 (59.3)	164 (48.4)	
	2.50–2.99	39 (20.6)	35 (24.7)	76 (922.4)	
	<2.5	6 (3.2)	6 (4.0)	12 (93.5)	

UNL: upper normal limit
* Statistically significant at p=0.05
** Statistically significant at p=0.01

Factors associated with acute liver injury in COVID-19 patient

Of the 339 patients, 28.9% had an ALI at admission, and the incidence was significantly higher in the severe group than in the non-severe group (36.0% vs 23.3%, p=0.014) (**Table 1**). Now, we assess factors associated with the incidence of ALI among both groups of COVID-19 patients. Our data indicated that pre-existing liver disease was not associated with ALI (p=0.298) (**Table 3**). Diabetes was the only comorbidity that was significantly associated with ALI (p=0.009). ALT, AST, total bilirubin, direct bilirubin, hypoalbuminemia, hemoglobin, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels were significantly higher in patients with COVID-19 with ALI than in those without ALI. Additionally, the lymphocyte count was significantly lower in patients with COVID-19 with ALI than in those without ALI. In the present study, no association between ALI and mortality was observed (**Table 3**).

Table 3. Factors associated with acute liver injury presence among patients with coronavirus disease 2019 (COVID-19)

Parameters	n	Acute liver injury at admission (n=98)	No acute liver injury at admission (n=241)	p-value
Age (years)	339	52.18±11.73	50.83±13.54	0.374
Sex, male n (%)	339	59 (60.2)	121 (50.2)	0.121
Comorbidities, n (%)				
Pre-existing liver disease	339	9 (9.2)	13 (5.4)	0.298
Hepatitis B	339	3 (3.1)	7 (2.9)	0.590
Hepatitis C	339	1 (1.0)	2 (0.8)	0.642
Hepatic cirrhosis	339	4 (4.1)	4 (1.7)	0.172
Hepatocellular carcinoma	339	1 (1.0)	0 (0.0)	0.289
Diabetes	339	19 (19.4)	83 (34.4)	0.009[*]
Thyroid disease	339	1 (1.0)	5 (2.1)	0.443
Obesity	339	2 (2.0)	4 (1.7)	0.557
Chronic kidney disease	339	9 (9.2)	43 (17.8)	0.066
Hypertension	339	26 (26.5)	69 (28.6)	0.797
Coronary arterial disease	339	2 (2.0)	7 (2.9)	0.491
HIV	339	5 (5.1)	4 (1.7)	0.083
Malignancy [a]	339	8 (8.2)	12 (5.0)	0.382
COVID-19 disease severity				
Severe, n (%)	339	54 (55.1)	96 (39.8)	0.014[*]
Laboratory parameters				
Hemoglobin (g/dL)	339	12.86±2.73	11.83±2.80	0.005[*]
White blood cell (10^3/μL)	339	9.99±6.17	10.33±6.58	0.850
Platelet (10^3/μL)	339	285.57±154.09	289.66±149.91	0.190
Neutrophils (%)	339	76.53±10.19	75.28±13.31	0.055
Lymphocytes (%)	339	14.24±8.69	14.90±7.93	0.026[*]
Neutrophil-lymphocyte ratio	339	8.37±7.19	8.15±7.21	0.017[*]
Aspartate aminotransferase (U/L)	339	157.59±170.11	51.67±47.08	<0.001[**]
Alanine aminotransferase (U/L)	339	127.76±167.32	41.18±23.11	<0.001[**]
Total bilirubin (mg/dL)	195	2.28±4.57	0.67±0.47	<0.001[**]
Direct bilirubin (mg/dL)	195	1.33±2.94	0.29±0.36	0.014[*]
Albumin (g/dL)	339	3.14±0.36	3.19±0.38	0.102
Hypoalbuminemia, n (%)	339	81 (82.7%)	171 (71.0)	0.036[*]
Blood glucose (mg/dL)	324	143.74±56.77	173.92±107.69	0.972
Blood urea (mg/dL)	335	21.18±17.47	31.93±39.97	0.495
Creatinine (mg/dL)	335	1.18±1.19	2.91±5.39	0.052[*]
C-reactive protein (mg/dL)	303	16.64±39.21	11.72±21.38	<0.001[**]
D-dimer (ng/mL)	294	3,827.64±4,644.57	4,778.38±7,715.95	0.401
Prothrombin time (s)	314	20.72±29.50	20.72±22.88	0.132
aPTT (s)	314	27.48±6.31	29.15±6.31	0.090

aPTT: activated partial thromboplastin time; COVID-19: coronavirus disease 2019; HIV: human immunodeficiency virus
[a] Malignancies other than hepatocellular carcinoma
[*] Statistically significant at p=0.05
[**] Statistically significant at p=0.001

We then conducted a multivariate logistic regression analysis to evaluate potential risk factors for ALI incidence. The variables included sex, diabetes, CKD, HIV infection, COVID-19 severity, hemoglobin, platelet count, neutrophil count, lymphocyte count, NLR, hypoalbuminemia, creatinine, and CRP. We found that HIV infection, increased hemoglobin

levels, and hypoalbuminemia may be potential risk factors for ALI. Surprisingly, pre-existing diabetes was identified as a protective factor against the development of ALI (**Table 4**).

Table 4. Multivariate analysis of risk factors associated with acute liver injury incidence in coronavirus disease 2019 (COVID-19)

Variable	Adjusted odds ratio	95% confidence interval	p-value
Diabetes	0.27	0.14−0.54	<0.001
Human immunodeficiency virus	5.27	1.16−23.89	0.031
Hemoglobin	1.21	1.08−1.36	0.001
Neutrophil count	1.02	0.99−1.04	0.114
C-reactive protein	1.01	0.99−1.02	0.153
Hypoalbuminemia	2.62	1.28−5.37	0.008

Discussion

This study sought to examine the effect of COVID-19 severity on liver biochemical parameter abnormalities, as well as to determine the factors associated with the incidence of ALI. Our data indicated that compared to patients with non-severe COVID-19, those with severe disease had a significantly higher risk of liver test abnormalities, including the presence of ALI, at admission. Significant differences were noted in almost all liver assay parameters except for direct bilirubin levels. A retrospective study from the Shanghai Public Health Center found that COVID-19 severity was associated with abnormalities in liver function tests, including AST, ALT, total bilirubin, and albumin [11]. Moreover, a meta-analysis involving 128 studies showed that the relative risks of liver test abnormalities ((hypoalbuminemia: 2.65 (1.38–5.07); GGT: 2.31 (1.6–3.33); ALT: 1.76 (1.44–2.15); AST: 2.30 (1.82–2.90); bilirubin: 1.82 (1.22–2.73)) and acute hepatic injury (2.18 (1.49–3.18)) were higher in patients with severe COVID-19 than those in patients with non-severe COVID-19 [12].

Multiple theories have been proposed to explain the mechanism of liver injury in patients with COVID-19. SARS-CoV-2 uses angiotensin-2 converting enzyme (ACE2) as a means for cell entry. ACE2 receptors are commonly found on the epithelial surfaces of the respiratory tract (in type II alveolar-specific lung cells), upper esophageal epithelial cells, pancreatic vascular endothelium, ileal and colonic enterocytes, heart, smooth muscle cells, testes, brain, and kidneys. RNA sequencing studies focusing on the liver of COVID-19 patients revealed significantly higher receptor expression in cholangiocytes (59.7%) than in hepatocytes (2.6%) [13]. The SARS-CoV-2 spike (S) protein facilitates its entry into target cells by binding to cellular receptors; this facilitates the attachment of the virus to the target cell surface. The S protein must be cleaved at the S1/S2 and S2' sites to allow fusion of the virus and cellular membranes [14]. This knowledge establishes the premise that SARS-CoV-2 infection impairs liver function through cytopathic effects brought about by the binding of its spike protein to ACE receptors on cholangiocytes and hepatocytes, resulting in decreased function and hepatobiliary damage [15].

Additionally, immune-mediated inflammation, such as a cytokine storm, may be a critical factor associated with disease severity and mortality. Liver derangement can be caused by immune dysfunction, which occurs during disease progression. The immune system identifies the antigenic epitope of the SARS-CoV-2 through antigen-presenting cells such as dendritic cells and macrophages. Antigen-presenting cells process viral antigens and activate other immune cells, including cytotoxic T cells and B cells. Viral antigen presentation using major histocompatibility complexes ensures the activation of both innate and acquired immunity, and the production of proinflammatory cytokines, chemokines, and coagulation enzymes [16].

The early phase of COVID-19 involves endothelial damage and an extreme immune response to SARS-CoV-2, particularly in cases of moderate and severe disease. In this phase, proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and IL-8 are produced via activation of caspase-1 by inflammasomes [17]. These trigger the expression of other genes involved in the immune process via intracellular signaling, with IL-6 playing a major role in this process. This pathway increases the production of other proinflammatory cytokine biomarkers such as IL-2, IL-8, IL-17, IL-10, tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and granulocyte colony-stimulating factor monocyte chemoattractant protein (GCSF) [18]. Furthermore, IL-6 production in hyperactive and dysregulated immune systems activates many

downstream pathways, enhancing the synthesis of acute-phase proteins, including CRP, serum amyloid A, fibrinogen, haptoglobin, and α1-antitrypsin. In contrast, IL-6 diminishes the production of fibronectin, albumin, and transferrin [19]. IL-6 is also known to suppress T cell activation, which may explain the decrease in the lymphocyte count in patients with COVID-19 [20]. This study showed a significant reduction in lymphocytes and increased CRP levels in patients with ALI. A retrospective cohort study of 109 hospitalized COVID-19 patients with severe and critical illness found that those with ALI had significantly elevated inflammatory markers such as CRP, lactate dehydrogenase, ferritin, and IL-6 [21].

Liver injury or even liver failure is a common result of hypoxia and hypotension caused by pneumonia in critically ill COVID-19 patients. Hypoxic liver injury, also known as hypoxic hepatitis, is characterized by increased serum transaminase levels caused by an imbalance in the supply and demand of oxygen, and is diagnosed after other causes are ruled out. It is caused by insufficient oxygen uptake by centrilobular hepatocytes, resulting in a condition known as centrilobular necrosis [22]. SARS-CoV-2 infection often results in hypoxia and even respiratory failure. Hypoxic conditions can increase the expression of ACE2 receptors in the liver [23], leading to more virus invasion. Moreover, the release of proinflammatory factors results in hyper-viscosity of the blood, ultimately causing microvascular lesions in the liver [24].

Liver dysfunction can be affected by pre-existing chronic liver disease. The prevalence rates of liver disease in patients with COVID-19 reported in large observational studies range from 3–11% [25,26]. The APCOLIS study investigated the liver injury patterns of 228 patients with COVID-19, including 185 with chronic liver disease without cirrhosis and 43 with cirrhosis [9]. Forty-three percent of patients with chronic liver disease without cirrhosis presented with ALI, and 20% of patients with cirrhosis presented with either acute-on-chronic liver failure (n=5, 11.6%) or acute decompensation (n=4, 9%). This study also found that increased bilirubin levels and AST/ALT ratio predicted mortality among cirrhosis patients [9]. Pre-existing liver disease among the patients in this study was rare and was not found to be associated with ALI.

Our analysis revealed that potential risk factors for ALI in our patients include HIV infection, high hemoglobin levels, and hypoalbuminemia, whereas pre-existing diabetes may be a protective factor. Multiple mechanisms are responsible for promoting liver inflammation and fibrosis in HIV infection. In addition to the direct hepatotoxic effects of HIV, several ART treatment modalities have hepatotoxic effects [27]. The exact mechanisms of HIV-triggered chronic hepatitis progression have not yet been elucidated. In severe cases of COVID-19, the high levels of proinflammatory cytokines IL-2, IL-6, IL-10, and IFN-γ can promote a hypercoagulable state and increase prothrombotic activity [28,29]. Some studies have reported that impaired liver perfusion is secondary to microvascular thrombosis, mitochondrial dysfunction, and hepatic steatosis induced by SARS-CoV-2, which targets the liver [30,31]. HIV infection is a recognized prothrombotic condition [32]. Therefore, co-infection of COVID-19 and HIV may increase the risk of thrombosis, leading to liver injury.

Increased hemoglobin levels could potentially lead to LFT abnormalities [33]. A multicenter study from Italy and Spain reported that patients with blood hemoglobin levels above the median had a mortality risk that was greater than that for those with hemoglobin levels below the median [34]. In addition, hypoalbuminemia is an indicator of physiological stress caused by disease or trauma-related inflammation. Proinflammatory mediators such as IL-6 and TNF-α could reduce albumin mRNA transcription [35]. Although albumin synthesis may increase, its oxidation and scavenging can be upregulated in inflammatory states. Furthermore, albumin is used as an intracellular amino acid donor for cell proliferation, which increases in inflammatory states. Consequently, the breakdown of albumin is elevated in inflammatory states, leading to a decreased albumin mass regardless of increased synthesis [36]. As already mentioned, SARS-CoV-2 can invade liver cells and interfere with liver function, including albumin synthesis. In COVID-19, lower serum albumin at admission predicts a higher risk of severe respiratory failure, longer hospitalization and death [37].

Currently, studies on the prevalence of ALI in patients with diabetes are limited. However, a retrospective cohort study in the UK reported that the adjusted relative risk of ALI in diabetes compared with the general population was 1.0 (95%CI, 0.2–3.7). Compared with those not taking diabetic drugs, diabetic patients who were taking diabetic drugs had a relative risk of 2.8 (95%CI,

0.6–12.5). It is concluded that diabetes is not a significant risk factor for ALI, but a small increase in risk could be linked to the use of antidiabetic drugs [38]. The promotion of inflammation and fibrosis due to mitochondrial oxidative stress mediated by adipokines may contribute to liver damage in diabetes. Insulin resistance, which is aggravated by oxidative stress and aberrant inflammatory signals, has become one of the primary factors contributing to liver damage [39,40].

Up to 73.3% of COVID-19 patients with DM have abnormal liver function tests. This indicates that diabetes might be a risk factor for liver injury in COVID-19 [41]. Interestingly, another study involving 2,237 cases of COVID-19 in the US showed that DM incidence was inversely associated with ALT level elevation. Moreover, univariate analysis showed that patients with DM were less susceptible to severe liver injury (ALT >5 × the UNL) (OR: 0.87; 95%CI: 0.58–1.30, p=0.5) [42], which is in accordance with our findings. Immune system dysfunction and imbalances in CD4+ T and CD8+ T lymphocytes, natural killer cells, and B cells are present in diabetic mellitus patients [43,44]. These factors may further affect the inflammatory response. In this study, patients with diabetes were not categorized according to disease duration, glucose control status, or therapy administered; therefore, further studies are needed to determine the effects of diabetes on ALI incidence.

There were certain limitations in this study. First, this was a retrospective analysis of data collected from a single center. Second, we did not evaluate ALP and GGT levels. Third, since the patients' medication histories were unknown, there is a possibility that medications may have been responsible for inducing liver injury. Lastly, the data on pre-existing chronic liver disease were only obtained from anamnesis and laboratory examination due to pandemic restrictions, and we were unable to perform further examinations, such as ultrasonography or FibroScan.

Conclusion

Our data suggested that the severity of COVID-19 is correlated with liver function abnormalities and the incidence of ALI. Patients with ALI had significantly higher hemoglobin and CRP levels, NLR, and incidence of hypoalbuminemia but lower lymphocyte counts. HIV infection, high hemoglobin levels, and hypoalbuminemia might be potential risk factors for ALI. The development of liver damage in COVID-19 patients is caused by multiple factors, including hepatotoxicity from SARS-CoV-2, cytokine storm syndrome due to inflammation, and hepatic ischemia from hypoxia. Therefore, patients with COVID-19 should be closely monitored via liver biochemistry tests.

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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