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ORIGINAL RESEARCH

Clinical Course and Risk Factors for Liver Injury of Severe and Critical Patients with COVID-19

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Introduction: Information regarding the clinical course of COVID-19 patients with liver injury is very limited, especially in severe and critical patients. The objective of this study was to describe the characteristics and clinical course of liver function in patients admitted with severe and/or critical SARS-CoV-2 infection, as well as explore the risk factors that affect liver function in the enrolled COVID-19 patients.

Methods: Information on clinical characteristics of 63 severe and critical patients with confirmed COVID-19 was collected. Data on patients' demographics, laboratory characteristics, laboratory examination, SARS-CoV-2 RNA results and liver test parameters were acquired and analyzed.

Results: The incidence of abnormal aspartate aminotransferase, alanine aminotransferase, and total bilirubin in the critical group was significantly higher than in the severe group (respectively 81.48%, 81.49%, 62.67%, and 45.71%, 63.88%, 22.86%, $p < 0.05$). The time for liver function parameters to reach their extremes was approximately 2–3 weeks after admission. The independent factors associated with liver injury were patients with invasive ventilators, decreased percentages of neutrophils, lymphocytes and monocytes, and sequential organ failure assessment (SOFA) score ≥2 ($p < 0.05$).

Conclusion: Abnormal liver tests are commonly observed in severe and critical patients with COVID-19. Severe patients infected by SARS-CoV-2 should be closely observed and monitored the liver function parameters, particularly when they present with independent risk factors for liver injury.

Keywords: abnormal liver tests, coronavirus disease 2019, COVID-19, liver injury, pneumonia, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an unprecedented threat to public health.[1,2] Patients with COVID-19 frequently present with pulmonary lesions; however, increasing data reveal that COVID-19 has systemic manifestations affecting multiorgan systems including liver injury, myocarditis, thrombosis, and coagulation.[3–6] While the impact of COVID-19 on the liver remains unclear, a considerable proportion of patients with elevated liver enzyme have been reported.[6–8] Some studies found a mild [1–2 times the upper limit of normal (ULN)] increase in transaminases, while severe liver injury has also been reported.[3,9,10]

However, information related to the clinical course of COVID-19 patients with liver injury is very limited, especially in severe and critical patients. Knowledge of the clinical characteristics of liver injury in this disease is vital to answering questions about the therapy and management for patients infected with SARS-CoV-2. To this end, we present detailed characteristics and the clinical course of liver function in patients admitted with severe or critical COVID-19 illness. Additionally, we further explore the independent risk factors for liver damage in these patients.

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Methods

Study Design and Participants

This retrospective study included 63 severe and critical patients with confirmed COVID-19 hospitalized in Beijing Ditan Hospital from January 20, 2020 to April 06, 2020. SARS-CoV-2 infection was diagnosed by RT-PCR assays of respiratory tract samples from nasopharyngeal swabs performed by the local Center for Disease Control or by our institutional laboratory. The severity of COVID-19 was defined in accordance with the Chinese management guidelines for COVID-19 (Trial version 9.0) released by the National Health Commission of China. Patients meeting any one of the following should be considered severe cases: respiratory rate ≥30 breaths/min, oxygen saturation at rest ≤93% on room air, PaO_2/FiO_2 ≤300mmHg, or the clinical symptoms progressively aggravated, and the lung imaging lesions progressed more than 50% within 24 ~ 48 hours. Critical cases are any patients who have respiratory failure, shock, or any organ failure that requires mechanical ventilation or intensive care management. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.[11] Cases were excluded for patients who were younger than 18 years, accompanied by underlying liver disease, as well as mild and moderately ill patients. This study was approved by the Institutional Review Board of the Capital Medical University affiliated Beijing Ditan Hospital, and patient-level informed consent was waived owing to its retrospective nature.

Data Collection

The medical records of patients with COVID-19 were collected by the research team. Data on patients' demographics, comorbidities, vital signs, laboratory characteristics and treatment were acquired by the hospital information system.

Laboratory Examination and Liver Test Parameters

On admission, laboratory parameters including peripheral blood leukocyte count, neutrophils, lymphocytes, monocytes, platelets, hemoglobin, hematocrit, C-reactive protein (CRP), international normalized ratio (INR), D-dimer, creatine kinase, aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin (TBIL), serum albumin, and A/G (albumin/globulin) ratio were collected. Since COVID-19 is an emerging infectious disease, consensus or guidance on the classifications of liver injury are lacking, so we classified the pattern of liver tests into three groups: normal liver, abnormal liver, and liver injury. Abnormal liver test was defined as the elevation of serum liver enzymes exceeding the upper limit of normal (ULN), that is, AST > 40 U/L, ALT > 40 U/L, and TBIL >17.1 μmol/L. Liver injury was defined when ALT and/or AST were over 3 × ULN, and/or TBIL was over 3 × UL. Furthermore, the dynamic changes of liver enzymes, serum albumin, INR, and A/G ratio were recorded.

SARS-CoV-2 RNA Detection

COVID-19 was diagnosed according to the cycle threshold (Ct) values of open reading frame 1ab (ORF1ab) and nucleocapsid protein (N) gene by RT-PCR assay. The assay was performed by the National Center for Disease Control or the Clinical Laboratory of Beijing Ditan hospital using a commercial kit (Daan, Guangzhou, China). The SARS-CoV-2 viral loads were measured by the copy number of the N gene from sputum samples or throat swabs of the COVID-19 cases. Ct values were negatively correlated with viral RNA copy numbers.[12] According to the instructions of the RT-PCR kit, patients with Ct values less than 40 were considered positive.

Statistical Analysis

All statistical analyses were performed with SPSS 19.0 for Windows (IBM, USA). Continuous variables were described as mean and SD or median and IQR, and categorical variables as frequency and percentages. Normally distributed variables were analyzed using independent group *t*-test or one-way ANOVA, whereas the Mann–Whitney nonparametric test was used for non-normally distributed variables. Categorical variables were analyzed using the chi-square ($\chi 2$) or Fisher's exact tests. Pearson's correlation coefficient was used to assess the correlation between the severity of liver injury and laboratory results. Ordinal logistic regression analysis was conducted to evaluate the association of baseline characteristics with the severity of liver injury. Two-sided p-values of less than 0.05 were considered statistically significant.

Results

Baseline Characteristics of Enrolled Patients with COVID-19

The clinical characteristics of enrolled patients with COVID-19 are shown in Table 1. A total of 63 patients were enrolled in the study. The average age of the patients was 56.75 years and 41 patients (65.08%) were male. According to the

Table 1 Demographic, Clinical, and Laboratory Findings of Patients with COVID-19 on Admission

	Severe (n=36)	Critical (n=27)	Total (n=63)	*P*-value
Demographics and clinical characteristics				
Male, n (%)	26 (72.22)	15 (55.56)	41 (65.08)	0.134
Age (years), mean (SD)	48.39 (16.03)	67.89 (12.02)	56.75 (17.33)	<0.001
Comorbidities, n (%)				
Diabetes	4 (11.11)	5 (18.52)	9 (14.29)	0.317
Hypertension	6 (16.67)	13 (48.15)	19 (30.16)	0.008
Cardiovascular disease	2 (5.56)	2 (7.41)	4 (6.35)	0.577
Chronic pulmonary disease	1 (2.78)	4 (14.82)	5 (7.94)	0.101
Tumor	1 (2.78)	2 (7.41)	3 (4.76)	0.392
Hyperlipemia	2 (5.56)	1 (3.70)	3 (4.76)	0.608
Cerebrovascular disease	0	2 (7.41)	2 (3.17)	0.180
Fever (temperature ≥37.3°C), n (%)	34 (94.44)	24 (88.89)	58 (92.06)	0.364
Heart rate (rate/min), mean (SD)	92.69 (14.84)	94.89 (13.91)	93.63 (14.37)	0.553
Respiratory rate (rate/min), median (IQR)	20 (20, 21)	20 (20, 29)	20 (20, 22)	0.150
Mean blood pressure (mmHg), mean (SD)	94.71 (10.96)	95.10 (10.82)	94.88 (10.81)	0.890
Oxygen therapy, n (%)				
High flow oxygen/Non-invasive ventilator	4 (11.11)	6 (22.22)	10 (15.87)	0.198
Invasive ventilator	0	16 (59.26)	16 (25.40)	<0.001
ECMO	0	5 (18.52)	5 (7.94)	0.011
Drug use, n (%)				
Antibiotics	21 (58.33)	23 (85.19)	44 (69.84)	0.020
Hormone	3 (8.33)	8 (29.63)	11 (17.46)	0.031
Antiviral drug	35 (97.22)	12 (44.44)	47 (74.60)	<0.001
Vasoactive drugs	0	12 (44.44)	12 (19.05)	<0.001
Oxygenation index, mean (SD)	319.98 (107.84)	220.81 (107.87)		0.001
ARDS, n (%)	15 (41.67)	22 (81.48)	37 (58.73)	<0.01
CURB-65 score, median (IQR)	0 (0, 0)	1 (1, 2)	0 (0, 1)	<0.001
CURB-65 score, n (%)				<0.001
CURB-65<2	35 (97.22)	16 (59.26)	51 (80.95)	
CURB-65≥2	1 (2.78)	11 (40.74)	12 (19.05)	
SOFA score, median (IQR)	2 (0, 3)	3 (2, 4)	3 (1, 3)	<0.001
SOFA score, n (%)				0.004
SOFA<2	16 (44.44)	3 (11.11)	19 (30.16)	
SOFA≥2	20 (55.56)	24 (88.89)	44 (69.84)	
Laboratory findings				
White-cell count ($\times 10^9$/L), median (IQR)	4.67 (3.81, 6.25)	6.78 (4.23, 10.47)	5.01 (3.92, 7.50)	0.012
Neutrophil %, mean (SD)	69.02 (10.93)	79.63 (10.19)	73.57 (11.79)	<0.001
Neutrophil count ($\times 10^9$/L), median (IQR)	3.16 (2.34, 5.46)	5.30 (3.02, 9.43)	3.85 (2.65, 6.22)	0.011
Lymphocyte %, mean (SD)	24.17 (9.39)	15.84 (9.10)	20.60 (10.09)	0.001
Lymphocyte count ($\times 10^9$/L), median (IQR)	1.07 (0.91, 1.31)	0.90 (0.73, 1.16)	0.98 (0.81, 1.24)	0.042
NLR (%), median (IQR)	3.14 (2.03, 5.02)	5.51 (3.31, 12.02)	3.87 (2.35, 6.49)	0.002
Monocyte %, mean (SD)	6.54 (3.86)	4.01 (1.95)	5.45 (3.41)	0.003
Monocyte count ($\times 10^9$/L), mean (SD)	0.30 (0.14)	0.28 (0.18)	0.30 (0.16)	0.654
Haemoglobin (g/L), mean (SD)	139.50 (11.83)	131.04 (16.84)	135.87 (14.69)	0.022
Hematocrit (%), mean (SD)	41.43 (3.80)	38.39 (4.49)	40.12 (4.35)	0.005

(*Continued*)

Table 1 (Continued).

	Severe (n=36)	Critical (n=27)	Total (n=63)	*P*-value
Platelet count (×10^9/L), median (IQR)	153.50 (133.25, 228.50)	157.00 (113.00, 213.00)	154.00 (132.00, 218.00)	0.527
CRP (mg/L), median (IQR)	31.90 (12.30, 58.50)	71.75 (39.80, 110.58)	42.60 (17.70, 96.50)	0.002
D-dimer (mg/L), median (IQR)	0.60 (0.37, 0.88)	0.91 (0.31, 1.67)	0.68 (0.36, 1.31)	0.115
BUN (mmol/L), median (IQR)	3.80 (2.96, 4.28)	5.56 (4.72, 7.33)	4.27 (3.61, 5.39)	<0.001
Serum creatinine (μmol/L), median (IQR)	73.00 (58.90, 82.20)	70.60 (55.10, 95.30)	72.35 (55.75, 84.98)	0.739
INR (mmol/L), mean (SD)	1.15 (0.12)	1.16 (0.13)	1.15 (0.12)	0.749
LDH (U/L), median (IQR)	273.30 (213.25, 341.45)	387.50 (291.65, 524.85)	316.00 (235.53, 397.15)	0.004
Creatine kinase (U/L), median (IQR)	80.95 (45.25, 177.83)	100.40 (54.70, 144.75)	89.40 (48.40, 152.80)	0.713
Ct value on admission				
N-gene (cycle), median (IQR)	33.26 (27.67, 36.95)	33.37 (29.77, 36.36)	33.32 (28.40, 36.67)	0.908
ORF1ab-gene (cycle), median (IQR)	29.38 (26.57, 36.29)	33.36 (28.55, 35.64)	30.23 (26.77, 35.99)	0.414
Ct <40 on day 7, n (%)	29 (80.56)	20 (74.07)	49 (77.78)	0.377
Ct <40 on day 14, n (%)	19 (52.78)	13 (48.15)	32 (50.79)	0.457
Days from RNA positive to negative (days)	13.00 (8.25, 28.50)	19 (10.00, 27.00)	16.00 (9.00, 27.00)	0.527

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; A/G, albumin/globulin; BUN, blood urea nitrogen; CRP, C-reactive protein; Ct, cycle threshold; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SOFA, Sequential Organ Failure Assessment.

severity of the disease, subjects were classified into the severe group (36, 57.14%) or the critical group (27, 42.86%). There were significant differences between the two groups in drug use and oxygen therapy except for the requirement of high-flow oxygen or non-invasive ventilator use. In terms of laboratory results, blood indices including peripheral white blood cell count, neutrophil, C-reactive protein (CRP), blood urea nitrogen (BUN), and lactate dehydrogenase (LDH) were significantly higher in critical patients than in severe patients ($p < 0.05$). In contrast, lymphocytes, percentage of monocytes, hemoglobin, and hematocrit were significantly lower in critical patients than in severe patients ($p < 0.05$).

Clinical Features of Enrolled Patients with COVID-19 and Liver Function Tests During Hospitalization

The serum liver enzyme parameters of enrolled patients were further analyzed. Results showed that there were no differences between severe and critical group in AST, ALT, TBIL, INR, albumin, and A/G ratio on admission (Supplemental Table), whereas the extreme values of these parameters had significant differences, except for ALT (Table 2). The incidence of abnormal AST, ALT, and TBIL in the critical group was significantly higher than in the severe group (81.48%, 81.49%, 62.67%, and 45.71%, 63.88%, 22.86%, respectively, $p < 0.05$) during hospitalization. Based on the test of liver function, subjects were further classified as normal liver (11, 17.46%), abnormal liver (32, 50.79%), and liver injury group (20, 31.75%) (Table 3). Patients in the three groups were not significantly different in distributions of gender or age. The CRP, percentage of neutrophils, BUN, and LDH in the liver injury group were significantly higher than in the normal liver group, while the percentages of lymphocytes and monocytes were significantly lower ($p < 0.05$). Additionally, the oxygenation index of the liver injury group was significantly lower than that of the other groups ($p = 0.015$), while the CURB-65 score, sequential organ failure assessment (SOFA) scores, the incidence of ARDS, and the application of an invasive ventilator were significantly higher in the liver injury group than in the non-liver group ($p < 0.05$) (Table 3 and Figure 1A).

Dynamic Profile of Liver Function Indicators and Viral Clearance

To explore the correlation of dynamic changes in liver function parameters and virus clearance in enrolled patients, data of liver enzymes and Ct values were monitored during hospitalization. Results showed that the plasma levels of AST, TBIL, and INR were significantly higher in the critical group than in the severe group, and the time for these indicators to reach their peak was approximately 2–3 weeks after admission (Figure 1B–D). Compared with AST, the plasma TBIL

Table 2 Peak Values of Serum Liver Enzyme Parameters in Severe and Critical Patients with COVID-19

	Severe (n=36)	Critical (n=27)	*P*-value
AST (U/L)	37.80 (29.60, 56.50)	93.50 (46.30, 119.30)	<0.001
AST, n (%)			0.009
Normal	19 (54.29)	5 (18.52)	
1–3 ULN	14 (40.00)	16 (59.26)	
>3 ULN	2 (5.71)	6 (22.22)	
ALT (U/L)	63.25 (31.93, 107.03)	88.90 (51.30, 134.90)	0.187
ALT, n (%)			0.309
Normal	13 (36.11)	5 (18.52)	
1–3 ULN	16 (44.44)	15 (55.56)	
>3 ULN	7 (19.44)	7 (25.93)	
TBIL (umol/L)	13.50 (9.80, 18.40)	24.60 (15.90, 68.10)	<0.001
TBIL, n (%)			0.001
Normal	27 (77.14)	10 (37.04)	
1–3 ULN	8 (22.86)	10 (37.04)	
>3 ULN	0	7 (25.93)	
Albumin (g/L), mean (SD)	35.49 (3.68)	29.38 (3.85)	<0.001
A/G ratio, median (IQR)	1.10 (1.00, 1.30)	0.90 (0.80, 1.10)	<0.001
INR (mmol/L), median (IQR)	1.22 (1.14, 1.27)	1.39 (1.20, 1.61)	<0.001

Abbreviations: AST, aspartate aminotransferase; ALT, alanine transaminase; A/G, albumin/globulin; INR, international normalized ratio.

Table 3 Clinical Characteristics of COVID-19 Patients in Different Liver Test Groups at Admission

Characteristics	Normal Liver Test (n=11)	Abnormal Liver Test (n=32)	Liver Injury (n=20)	*P*-value
Male, n (%)	5 (45.45,)	21 (65.63)	15 (75.00)	0.255
Age (years), mean (SD)	53.73 (20.95)	56.41 (16.42)	58.95 (17.28)	0.722
Oxygen therapy, n (%)				
High flow oxygen/Non-invasive ventilator	1 (9.09)	5 (15.63)	4 (20.00)	0.728
Invasive ventilator	0	6 (18.75)	10 (50.00)	0.004
ECMO	0	0	5 (25.00)	0.003
Drug use, n (%)				
Antibiotics	5 (45.45)	22 (68.75)	17 (85.00)	0.070
Hormone	0	7 (21.88)	4 (20)	0.241
Antiviral drug	10 (90.91)	24 (75.00)	13 (65.00)	0.284
Vasoactive drug	0	4 (12.50)	8 (40.00)	0.010
White-cell count (×10^9/L), median (IQR)	4.34 (3.95, 4.84)	5.33 (3.61, 7.44)	6.09 (4.11, 7.99)	0.238
Neutrophil %, mean (SD)	64.09 (10.18)	74.82 (14.71)	76.77 (10.48)	0.009
Neutrophil count (×10^9/L), median (IQR)	2.75 (2.33, 3.29)	4.15 (2.66, 6.73)	4.73 (2.81, 6.45)	0.086
Lymphocyte %, mean (SD)	27.63 (9.85)	19.52 (9.74)	18.47 (9.54)	0.034
Lymphocyte count (×10^9/L), median (IQR)	1.29 (0.92, 1.71)	0.94 (0.73, 1.15)	1.04 (0.85, 1.17)	0.109
NLR (%), median (IQR)	2.24 (1.48, 3.62)	5.08 (2.41, 8.47)	4.37 (3.12, 6.40)	0.032
Monocyte %, mean (SD)	7.93 (4.77)	5.35 (3.25)	4.26 (1.92)	0.013
Monocyte count (×10^9/L), mean (SD)	0.36 (0.17)	0.27 (0.14)	0.30 (0.17)	0.283
Haemoglobin (g/L), mean (SD)	135.91 (16.20)	135.38 (14.53)	136.65 (14.86)	0.956
Hematocrit (%), mean (SD)	40.72 (5.07)	39.88 (4.37)	40.20 (4.08)	0.858
Platelet count (×10^9/L), median (IQR)	207.00 (153.00, 238.00)	149.50 (129.00, 181.75)	155.50 (113.00, 224.25)	0.177
CRP (mg/L), median (IQR)	27.10 (5.40, 41.70)	43.10 (18.80, 77.85)	66.65 (25.23, 122.70)	0.044
D-dimer (mg/L), median (IQR)	0.85 (0.67, 1.43)	0.59 (0.31, 1.08)	0.67 (0.32, 1.67)	0.356
BUN (mmol/L), median (IQR)	4.09 (2.40, 4.27)	4.35 (3.64, 5.22)	5.07 (3.85, 7.33)	0.044
Serum creatinine (μmol/IL), median (IQR)	66.20 (57.90, 82.30)	70.80 (51.00, 88.10)	76.70 (62.30, 91.70)	0.350

(*Continued*)

Table 3 (Continued).

Characteristics	Normal Liver Test (n=11)	Abnormal Liver Test (n=32)	Liver Injury (n=20)	*P*-value
Albumin (g/L), median (IQR)	35.90 (33.30, 39.60)	36.55 (32.78, 40.93)	35.75 (30.40, 38.70)	0.675
A/G ratio, mean (SD)	1.06 (0.40)	1.15 (0.36)	1.06 (0.33)	0.573
INR (mmol/L), mean (SD)	1.12 (0.08)	1.17 (0.13)	1.14 (0.13)	0.471
LDH (U/L), median (IQR)	236.30 (190.90, 315.80)	306.90 (234.35, 382.83)	387.50 (322.65, 595.90)	0.002
Creatine kinase (U/L), median (IQR)	53.80 (42.50, 142.80)	87.80 (44.95, 202.18)	117.30 (62.15, 154.05)	0.374
Ct value on admission				
N-gene (cycle), median (IQR)	35.71 (28.54, 37.19)	34.30 (28.14, 37.03)	31.23 (27.64, 34.76)	0.390
ORF1ab-gene (cycle), median (IQR)	28.92 (26.77, 32.63)	33.66 (26.88, 38.90)	29.62 (26.54, 34.69)	0.197
Ct <40 on day 7, n (%)	10 (90.91)	25 (78.13)	14 (70.00)	0.407
Ct <40 on day 14, n (%)	7 (63.64)	17 (53.13)	8 (40.00)	0.422
Virus duration (day), median (IQR)	16 (11, 30)	13.50 (10.25, 29.50)	16 (4.75, 25.25)	0.711
CURB-65 score, median (IQR)	0 (0, 1)	0 (0, 1)	1 (0, 2)	0.146
CURB-65 score, n (%)				0.086
CURB-65<2, n (%)	10 (90.91)	28 (87.50)	13 (65.00)	
CURB-65≥2, n (%)	1 (9.09)	4 (12.50)	7 (35.00)	
Oxygenation index	368.59 (133.43)	282.39 (105.70)	225.47 (111.67)	0.015
ARDS, n (%)	3 (27.27)	17 (53.13)	17 (85.00)	0.005
SOFA score, median (IQR)	0 (0, 1.00)	3.00 (1.25, 3.00)	3 (2, 4)	0.001
SOFA score, n (%)				<0.001
SOFA<2	9 (81.82)	8 (25.00)	2 (10.00)	
SOFA≥2	2 (18.18)	24 (75.00)	18 (90.00)	

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; A/G, albumin/globulin; BUN, blood urea nitrogen; CRP, C-reactive protein; Ct, cycle threshold; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SOFA, Sequential Organ Failure Assessment.

level more slowly reached its peak at about 4 weeks, then gradually decreased. Conversely, the levels of ALT, albumin and A/G ratio were significantly lower in the critical group than in the severe group, and the time for these parameters to reach their extremes was also approximately 2–3 weeks (Figure 1B–D and F). The liver injury group had similar characteristics (Supplemental Figure 1A–C). The level of Ct values in the critical group was higher than in the severe group, but there was no significant difference either on admission or at the peak level (Table 1, Supplemental Figure 2A). In addition, there was no significant difference in the level of Ct values among liver injury group, abnormal group and normal group (Table 3, Supplemental Figure 2B). The negative rates at 1 week after admission in the critical group (74.1%) were lower than in the severe group (80.6%) if binarized the tested patients into positive (Ct < 40) and negative (Ct = 40) in spite of no significant difference. The Ct values of PCR increased gradually during hospitalization and the time of virus clearance was approximately 2–3 weeks after admission (Figure 2A–B).

Independent Factors Associated with Severity of Liver Function

As shown in Figure 3A–D, the severity of damage to liver function was positively correlated with the percentage of neutrophils, CRP, CURB-65 score and SOFA score and negatively correlated with percentage of lymphocytes and oxygenation index. To further analyze the correlation between the severity of liver injury and clinical or laboratory index and identify independent factors associated with severity of damage to liver function, we conducted ordinal logistic regression analysis. The variables included in the ordinal logistic regression and statistical univariate analysis results are shown in Table 3. Variables with p-values of <0.05 in univariate analyses were included in the ordinal logistic analysis to identify the significant indicators affecting liver function in enrolled COVID-19 patients (Table 4). Results revealed that SOFA score ≥2 [OR = 165.41, 95% confidence interval (CI) = (1.57, 8.64); p = 0.005] was positively associated with abnormality or injury as indicated by liver tests. After adjustment for age, sex, and comorbidities, patients with invasive ventilators, decreased percentages of neutrophils, lymphocytes and monocytes, and SOFA score ≥2 were the independent factors associated with abnormal liver tests or liver tests showing injury.

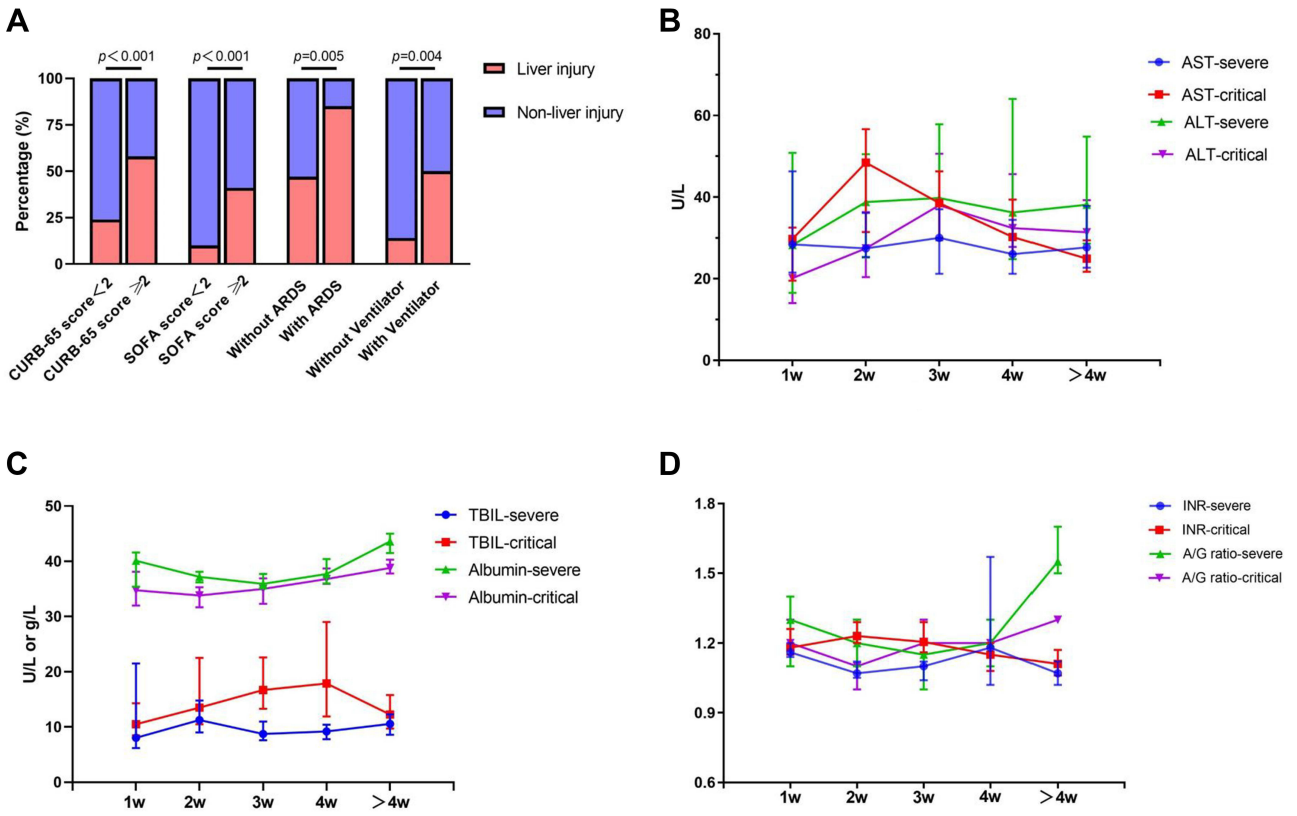

Figure 1 The percentage of liver injury in different groups and dynamic changes of liver function indicators between the severe group and the critical group. (**A**) The percentage of liver injury in CURB-65 score, sequential organ failure assessment (SOFA) score, acute respiratory distress syndrome (ARDS) and ventilator groups. (**B**) Dynamic changes of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) between the severe group and the critical group. (**C**) Dynamic changes of total bilirubin (TBIL) and albumin between the severe group and the critical group. (**D**) Dynamic changes of INR and albumin/globulin (A/G) ratio between the severe group and the critical group.

Discussion

In this cohort of 63 cases, we demonstrate that abnormal liver tests are common in patients with severe and critical COVID-19. Patients with critical COVID-19 should be aware of the occurrence of liver injury at 2–3 weeks after admission. Particular attention should be paid to patients with decreased ratios of neutrophils, lymphocytes and monocytes, the requirement of an invasive ventilator, and SOFA score ≥2 during hospitalization, as these are independent risk factors for the occurrence of liver injury.

The incidence of liver enzyme elevation observed here ranged from 22.86% to 81.49% in severe and critical patients during hospitalization, higher than in a previous study, which showed a range from 14% to 53% in patients including those with mild and moderate COVID-19.[13] The increase was mainly manifested by elevated levels of ALT, AST, and TBIL accompanied by the slightly decreased albumin levels. The increased liver enzymes were observed more commonly in the critical group than in the severe group. Interestingly, we observed that the levels of AST and TBIL were higher in the critical group than in the severe group, while no differences in ALT were observed between groups. Elevated AST could be from muscle damage rather than directly reflecting liver injury, and the levels of INR in this study were primarily within the range of 1.5. Thus, the discovery that SARS-CoV-2 virus binds to angiotensin-converting enzyme 2 (ACE2) on hepatocytes, especially on biliary epithelial cells, and then causes liver injury[14] may partially explain the results in our patients. In other words, COVID-19 patients with liver injury were more likely to be a cholestatic type than a hepatocellular type.

Currently, the underlying mechanisms of COVID-19 related liver injury remain unclear. In fact, liver injury may be multifactorial and individualized. First, a hyper-inflammatory response to COVID-19 may contribute to liver injury.[15,16] The severity of damage to liver function was positively correlated with the percentage of neutrophils and CRP and

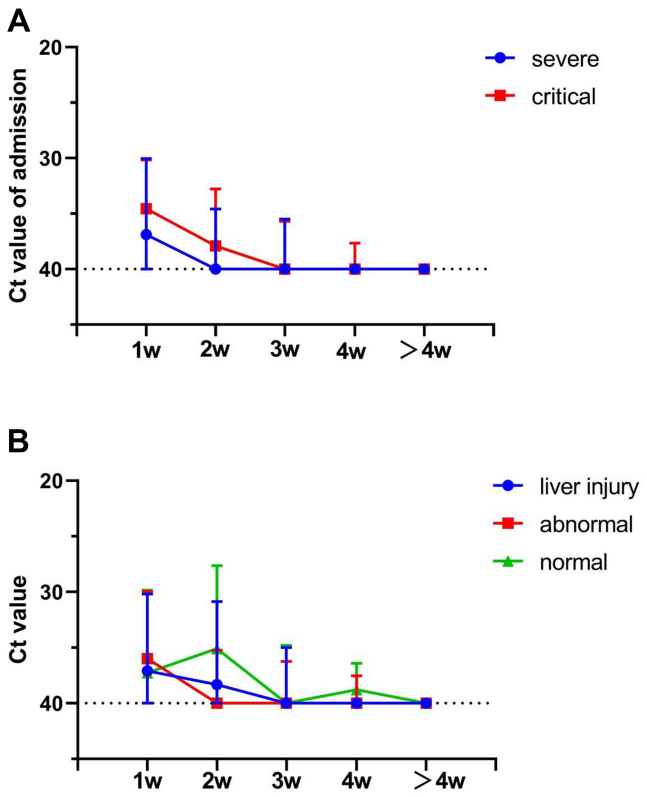

Figure 2 Dynamic changes of cycle threshold (Ct) values among different groups. (**A**) Dynamic changes of Ct values between the severe group and the critical group. (**B**) Dynamic changes of Ct values in the normal, abnormal, and liver injury group.

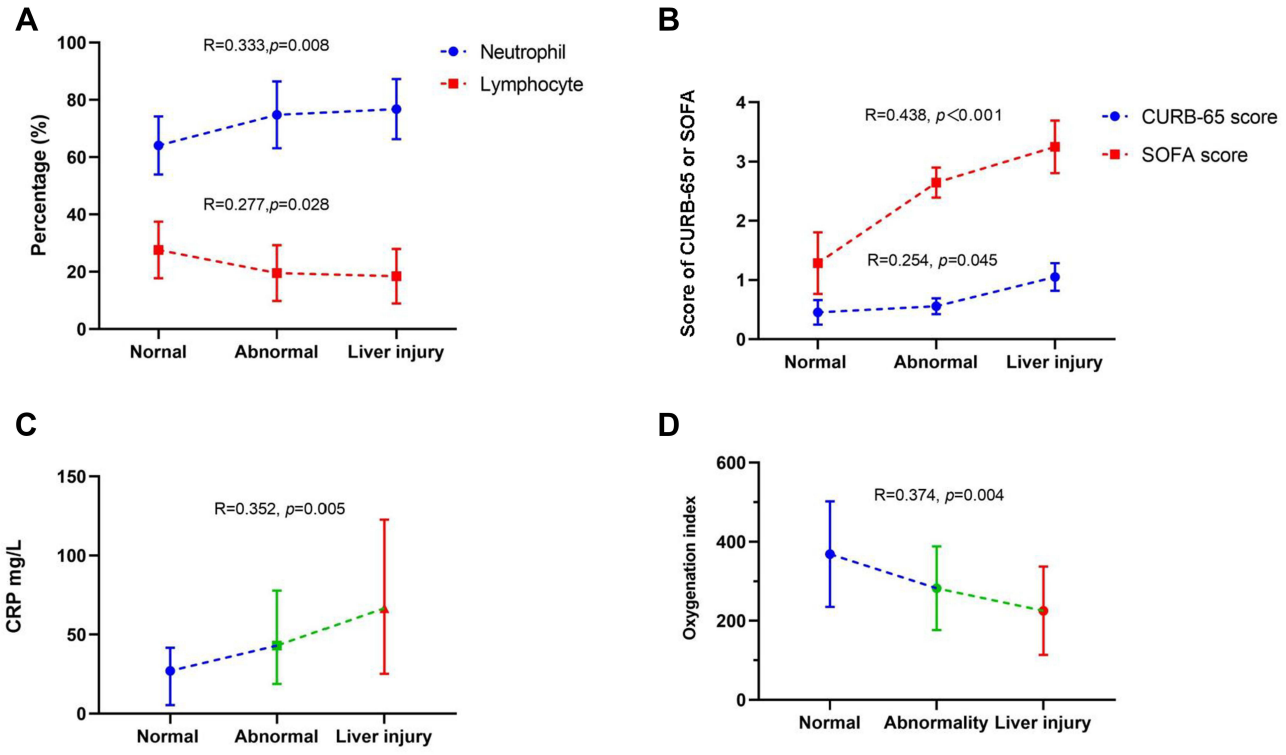

Figure 3 The correlation between the severity of liver injury and laboratory results. (**A**) the correlation between the severity of liver injury and the percentage of neutrophils and lymphocytes. (**B**) the correlation between the severity of liver injury and CURB-65 and sequential organ failure assessment (SOFA) score. (**C**) the correlation between the severity of liver injury and C-reactive protein (CRP). (**D**) the correlation between the severity of liver injury and oxygenation index.

Table 4 Independent Factors Associated with Severity of Liver Injury

	Crude OR (95% CIs)	*P*-value	Adjusted OR (95% CIs)	*P*-value
Invasive ventilator	7.79 (−1.07, 5.18)	0.198	60.99 (0.23, 8.00)	0.038
ECMO		NS		NS
Vasoactive drugs	0.68 (−0.90, 0.12)	0.134	0.59 (−1.24, 0.18)	0.143
Neutrophil %	0.28 (−3.70, 1.16)	0.306	0.03 (−7.03, −0.14)	0.042
Lymphocyte %	0.27 (−3.74, 1.11)	0.289	0.03 (−7.14, −0.18)	0.039
NLR	0.89 (−0.34, 0.11)	0.321	0.83 (−0.47, 0.11)	0.224
Monocyte %	0.25 (−3.95, 1.14)	0.280	0.03 (−7.14,-0.08)	0.045
CRP	1.00 (−0.01, 0.02)	0.448	1.01 (−0.01, 0.04)	0.247
BUN	1.06 (−0.13, 0.26)	0.528	1.15 (−0.11, 0.39)	0.265
LDH	1 (−0.01, 0.01)	0.580	1.00 (−0.01, 0.01)	0.485
Oxygenation index	0.99 (−0.03, 0)	0.149	0.99 (−0.03, 0.01)	0.198
ARDS	0.20 (−4.38, 1.19)	0.263	0.09 (−5.67, 0.93)	0.159
SOFA score	0.31 (−2.49, 0.14)	0.081	0.51 (−2.10, 0.77)	0.365
SOFA score ≥2	165.41 (1.57, 8.64)	0.005	1630.70 (2.52, 12.27)	0.003

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BUN, blood urea nitrogen; CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; SOFA, Sequential Organ Failure Assessment.

negatively correlated with percentages of lymphocytes and monocytes; decreased ratios of neutrophils, lymphocytes and monocytes are independent risk factors for the occurrence of liver injury. Hepatic inflammation involving activation of the innate immune system accompanied by a cytokine storm is a well-established driver of liver injury.[17] Notably, lymphopenia was commonly observed in COVID-19 studies and patients with lower counts of lymphocytes are more susceptible to fatal outcomes.[18] Second, the increased ACE2 expressed on hepatocytes that infected by SARS-CoV-2 virus might provide a mechanistic link between disease severity and liver injury.[19,20] In the present study, no significant difference was observed in Ct values on admission or at the peak among the liver injury group, abnormal group and normal group. However, it is impossible to demonstrate whether the virus has an impact on liver cytopathy owing to the lack of liver biopsy and Ct values of the liver in situ. Preclinical studies demonstrated that at least in vitro hepatocytes can be directly infected, albeit at considerably lower levels than airway or endothelial cells.[20–22] Third, hypoxia induced by COVID-19-related complications (ie, ARDS and multiple organ failure) may also induce hepatic ischemia and hypoxia-reperfusion dysfunction.[23] The severity of damage to liver function was positively correlated with CURB-65 score and SOFA score and negatively correlated with oxygenation index. Moreover, the requirement of an invasive ventilator and SOFA score ≥2 are independent risk factors for the occurrence of liver injury. Lastly, drug-elicited liver injury may also account for laboratory test abnormalities.[3,24] However, there was no significant difference in drug use among the liver injury group, abnormal group and normal group in this study, except for a vasoactive drug. However, the vasoactive drug was not an independent risk factor for the occurrence of liver injury in the logistic analysis. Thus, the enrolled drugs in this study may not directly induce liver injury.

Our results showed that the time for liver parameters to reach their extremes was approximately 2–3 weeks after admission, which is critical for clinical implications in managing patients infected with SARS-CoV-2. Thus, regular monitoring of liver function tests should be performed, particularly in patients with severe and critical COVID-19.

This study has some limitations. First, not all laboratory tests were collected in enrolled patients, including alkaline phosphatase and gamma-glutamyl transferase owing to the retrospective design. Additionally, it is impossible to demonstrate whether the virus has an impact on liver cytopathy owing to the lack of liver biopsy and viral load results of the liver in situ. Further studies should corroborate the pathogenic mechanism. The relatively small sample size is also a limitation of this study. Future studies needed to enroll larger sample sizes to strengthen the accuracy of the results.

Conclusions

In summary, abnormal liver tests are commonly observed in severe and critical patients with COVID-19. In particular, patients with critical COVID-19 should be closely monitored at 2–3 weeks after admission in case of the occurrence of liver injury. Independent risk factors for the occurrence of liver damage are decreased ratios of neutrophils, lymphocytes and monocytes, the requirement of an invasive ventilator, and SOFA score ≥2; patients with these abnormal parameters should be of particular concern during hospitalization.

Abbreviations

ARDS, acute respiratory distress syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; A/G, albumin/globulin; BUN, blood urea nitrogen; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Ct, cycle threshold; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, Sequential Organ Failure Assessment; TBIL, total bilirubin.

Data Sharing Statement

Data of this study can be available upon request from the author.

Ethics Approval and Consent to Participate

This clinical study was conducted in compliance with the ethical principles of the Declaration of Helsinki and its later amendments. The Ethics Committee of Beijing Ditan Hospital approved our study protocol [approval No. NA2018(005)-01]. As a de-identified retrospective study, the ethics committee did not require us to obtain written or verbal informed consent from participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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