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

Jingyuan Liu
Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China

Chunjing Du
Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China

Siyuan Yang
Laboratory of Infectious Diseases Center, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China

Lin Pu
Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China

Pan Xiang
Department of Critical Care Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, P. R. China

Ang Li (liang@ccmu.edu.cn)
Capital Medical University Affiliated Beijing Ditan Hospital https://orcid.org/0000-0002-1478-3072

Research

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Abstract

Background: 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 were collected 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).

Conclusions: Abnormal liver tests are commonly observed in severe and critical patients with COVID-19. The patients with severe illness should be closely observed to monitor liver function parameters, particularly when they present with independent risk factors of liver injury.

Background

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[1-3]. Patients with COVID-19 frequently present with pulmonary lesions, however, increasing data reveals that COVID-19 has systemic manifestations affecting multiorgan systems including liver injury, myocarditis, thrombosis, and coagulation[4-7]. While the impact of COVID-19 on the liver remains unclear, a considerable proportion of patients with elevated liver enzyme have been reported[7-12]. 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[6,13].

However, information regarding 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 of liver damage in these patients.

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. The diagnosis and severity assessment of COVID-19 were defined in accordance with the Chinese management guidelines for COVID-19 (version 7) released by the National Health Commission of China. Patients meeting any one of the following should be considered severe cases: oxygen saturation at rest ≤ 93% on room air; respiratory distress, or respiratory rate ≥ 30 breaths/min. Critical cases are any patients who have acute respiratory failure (PaO_2/FiO_2 < 300, 30 > breaths/min), 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[14]. Cases were excluded for patients who were younger than 18 years, 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[15]. 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 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 severe patients (p□0.05). In contrast, lymphocytes, percentage of monocytes, hemoglobin, and hematocrit were significantly lower in critical patients than 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, Fig. 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 (Fig. 1b-d). Compared with AST, the plasma TBIL 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, the time for these parameters to reach their extremes was also approximately 2-3 weeks (Fig. 1b-d, f). The liver injury group had similar characteristics (Supplemental Fig. 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 Fig. 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 Fig. 2b). The Ct values of PCR increased gradually during hospitalization and the time of virus clearance was approximately 2-3 weeks after admission (Fig. 2a-b).

Independent factors associated with severity of liver function

As shown in Fig. 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.

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 occurrence 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[16]. The increase was mainly manifested by elevated levels of ALT, AST, and TBIL accompanied by the slightly decreased albumin levels. Indeed, 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[17] 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[11,18,19]. The severity of damage to liver function was positively correlated with the percentage of neutrophils and CRP, and 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[20]. Notably, lymphopenia was commonly observed in COVID-19 studies and patients with lower counts of lymphocytes are more susceptible to fatal outcomes[21]. Second, whether SARS-CoV-2 can directly infect hepatocytes remain undetermined[19,22]. 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*. ACE2 is abundantly expressed in the hepatocytes, especially in biliary epithelial cells, and the liver may be a potential target for direct infection [17], but this has not yet been demonstrated. Third, hypoxia induced by COVID-19-related complications (i.e., ARDS and multiple organ failure) may also induce hepatic ischemia and hypoxia-reperfusion dysfunction[23,24]. 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[25,26]. 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 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 loads 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

Declarations

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Author's Contributions

Jingyuan Liu, Chunjing Du and Siyuan Yang collected the clinical data. Lin Pu, Pan Xiang and Ang Li interpreted the data. Chunjing Du and wrote the manuscript. Jingyuan Liu proofread the manuscript. Ang

Li calculated the statistics and proofread the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval and consent to participate

This study was approved by the Institutional Review Board of Capital Medical University affiliated Beijing Ditan Hospital. Informed consent was waived because of the retrospective nature of the study and the usage of anonymous clinical data.

Competing interests

Jingyuan Liu, Chunjing Du, Siyuan Yang, Lin Pu, Pan Xiang, and Ang Li declare that they have no conflict of interest.

Consent for publication

Not applicable.

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Tables

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 (×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 (×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 (×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 (×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
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

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/lL),median (IQR)	66.20 (57.90, 82.30)	70.80 (51.00, 88.10)	76.70 (62.30, 91.70)	0.350
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

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

Figures

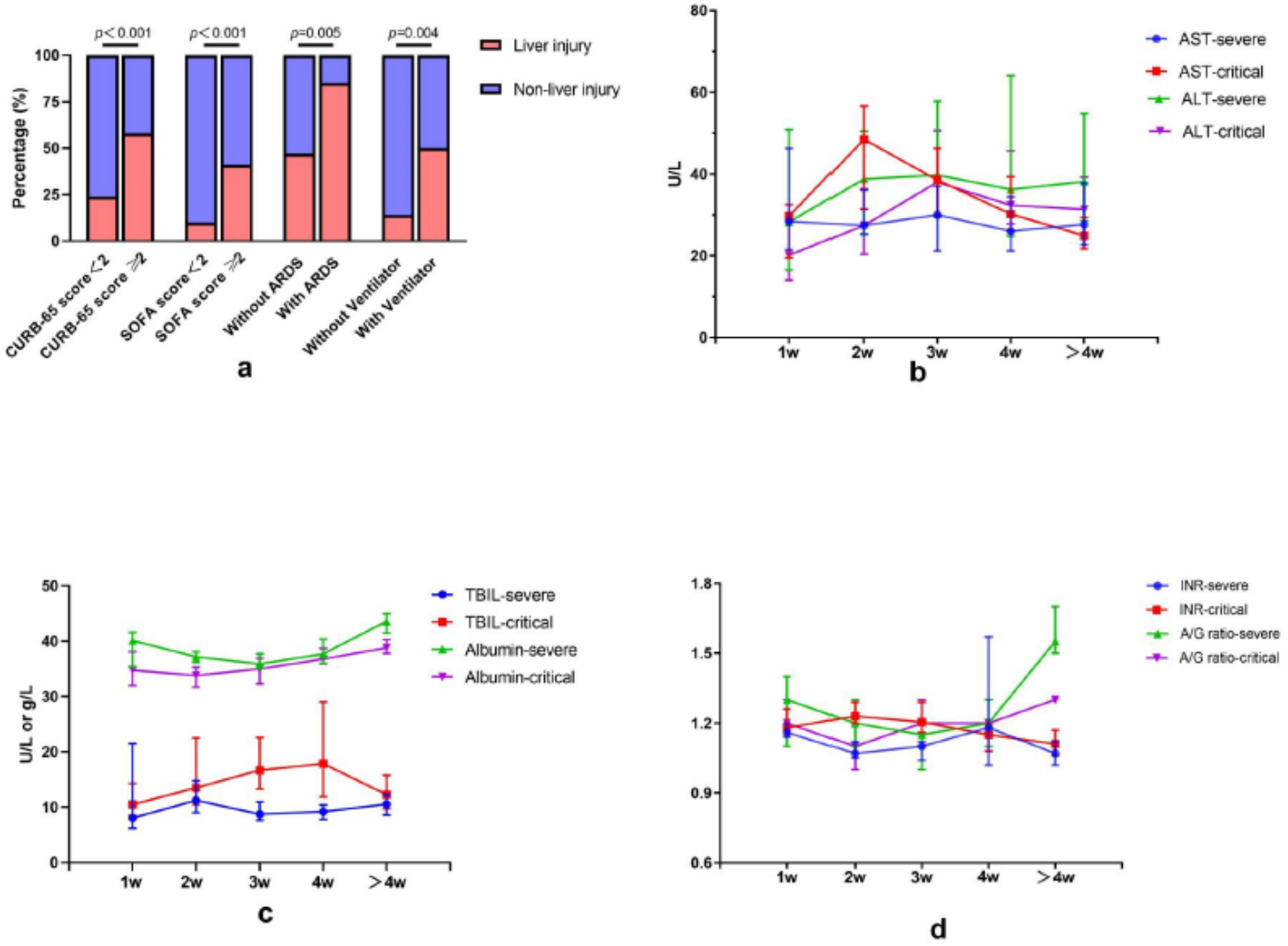

Figure 1

Caption: The l percentage of liver injury in different groups and dynamic profile of liver function indicators between the severe group and the critical group. a: Description text: The percentage of liver injury among CURB-65 score, sequential organ failure assessment (SOFA) score, acute respiratory distress syndrome (ARDS) and ventilator groups. b: Description text: Dynamic changes of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) between the severe group and the critical group. c: Description text: Dynamic changes of total bilirubin (TBIL) and albumin between the severe group and the critical group. d: Description text: Dynamic changes of INR and albumin/globulin (A/G) ratio between the severe group and the critical group.

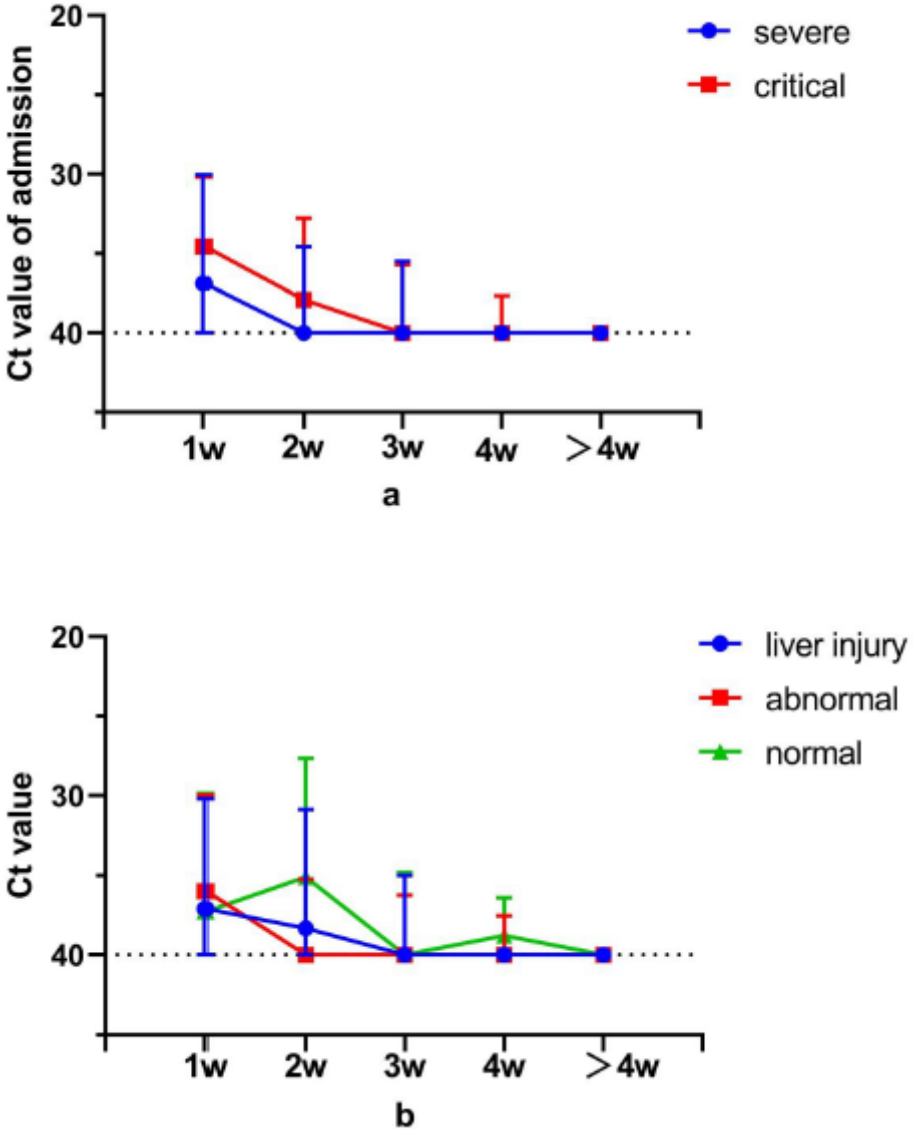

Figure 2

Caption: Dynamic changes o cycle threshold (Ct) values among different groups. a: Description text: Dynamic changes of Ct values between the severe group and the critical group. b: Description text: Dynamic changes of Ct values among the normal group, the abnormal group, and the liver injury group.

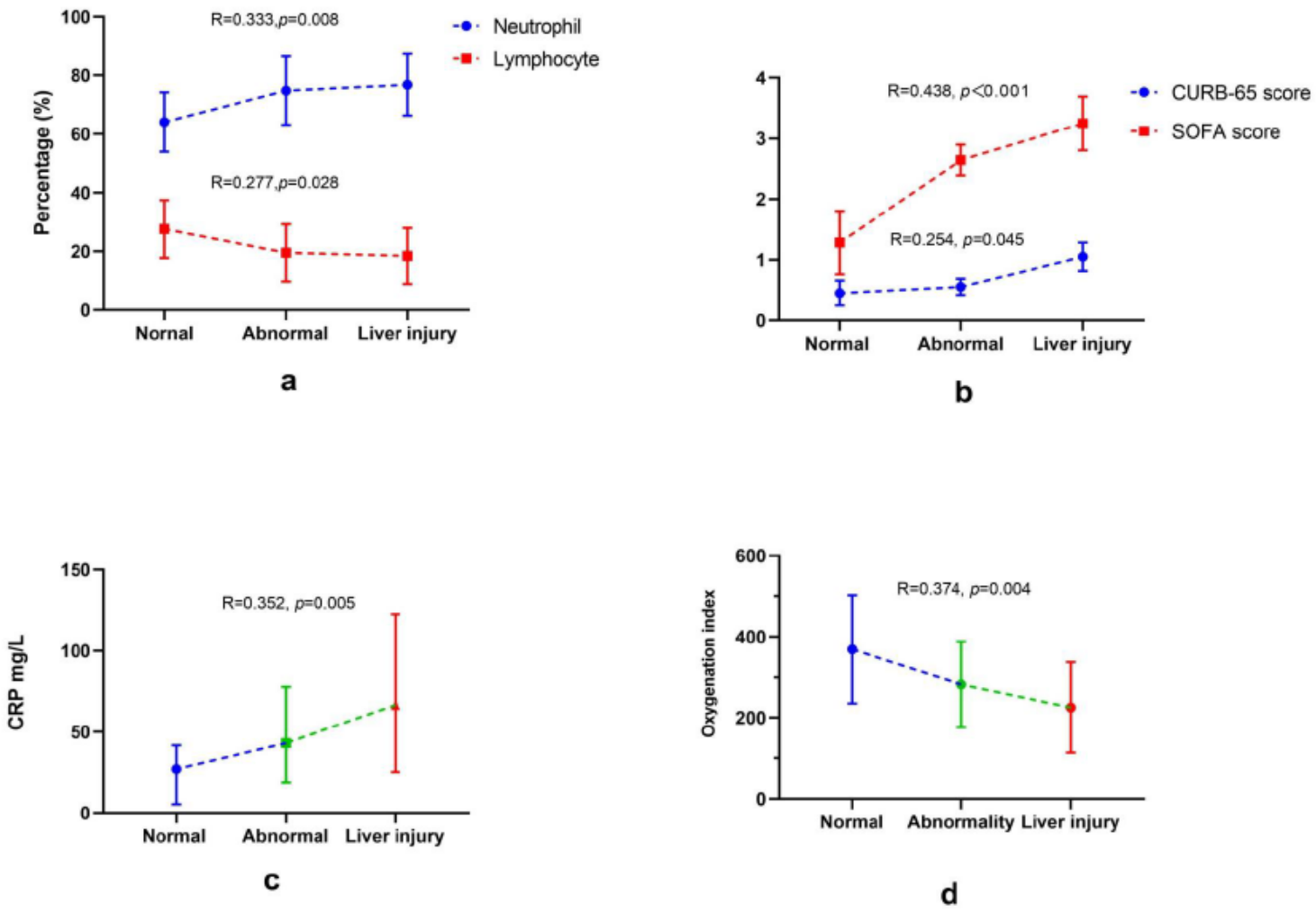

Figure 3

Caption: the correlation between the severity of liver injury and laboratory results. a: Description text: the correlation between the severity of liver injury and the percentage of neutrophils and lymphocytes. b: Description text: the correlation between the severity of liver injury and CURB-65 score and sequential organ failure assessment (SOFA) score. c: Description text: the correlation between the severity of liver injury and C-reactive protein (CRP). d: Description text: the correlation between the severity of liver injury and oxygenation index.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementalfigure1.pdf
- supplementalfigure2.pdf