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Original Article

Liver dysfunction on admission worsens clinical manifestations and outcomes of coronavirus disease 2019

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ABSTRACT

Background: Liver dysfunction was common in coronavirus disease 2019 (COVID-19), but its association with clinical features and poor prognosis has not been fully delineated. Our study aimed to determine the role of liver dysfunction in COVID-19 and understand the predictors for worse outcomes in patients with liver injury.
Methods: We conducted this multicenter, retrospective study in five designated hospitals for COVID-19 management. Laboratory-confirmed COVID-19 patients were enrolled and classified into the normal live function group and liver dysfunction group according to liver enzymes, bilirubin, and albumin on admission, respectively. Data of baseline, clinical manifestations, and outcomes were collected and compared in the paired groups.
Results: Of the 649 included COVID-19 patients, 200 (30.8%), 69 (10.6%), and 267 (41.1%) patients had elevated liver enzymes, increased bilirubin, and low-level albumin, respectively. Fever, cough, and dyspnea were the most common symptoms and showed an increased proportion in the liver dysfunction group. Compared with patients in the normal liver function group, patients with liver dysfunction manifested decreased lymphocytes, higher level of leukocytes, neutrophils, inflammatory indicators, and cytokines, as well as more severe impairment in kidney function and myocardium. They were more likely to show bilateral involvement and more pulmonary lobes involved according to chest images. With increased proportion of patients who developed severe/critical conditions and needed mechanical ventilation and systemic glucocorticoid therapy, patients with liver dysfunction on admission showed significantly higher in-hospital mortality. Moreover, cardiac troponin I ≥1.5 ng/mL was identified as an independent mortality predictor in the elevated liver enzymes group.
Conclusion: Patients with liver dysfunction on admission had worse clinical manifestation, and resulted in higher rate of severe/critical type, receiving mechanical ventilation and in-hospital mortality.

Introduction

Coronavirus disease 2019 (COVID-19), which arises from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a highly pathogenic and extremely contagious disease.[1] Since declared as a public health emergency of international concern by the World Health Organization (WHO), COVID-19 has attracted global attention and this ongoing pandemic has contributed to an enormous challenge to public health.[2] Hitherto, with more than 200 countries and districts affected, over 769 million cases were confirmed COVID-19 and more than 6.9 million individuals died of this disease around the world as of August 17, 2023.[3]

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Previous studies have reported that different degrees of liver dysfunction occurred in 20–40% of COVID-19 patients, especially for severe patients.[4–6] Pathological findings also identified degeneration, necrosis, and inflammatory infiltration in hepatocytes, as well as microthrombosis in hepatic sinusoids.[7] However, there was limited research focused on the relationship between abnormal liver function and COVID-19, as well as the significance of liver dysfunction in poor clinical outcomes and prognosis.[8,9]

Herein, we conducted a comprehensive evaluation of indicators associated with liver function in COVID-patients, including liver enzymes, bilirubin, and albumin. At the same time, we compared the clinical manifestations and outcomes between patients with and without abnormal liver function parameters. Although hypoalbuminemia is often regarded as malnutrition, its indeed relation to hepatic impairment makes patients more vulnerable to oxidative stress and exogenous injury.[10] Therefore, albumin was also included for analysis in this study. We aimed to determine the role of liver dysfunction in the COVID-19 and understand the predictors for poor prognosis in patients with liver injury.

Methods

Study design and participants

We conducted a multicenter retrospective study in Shanghai Public Health Clinical Center, Wuhan Jinyintan Hospital, Anhui Tongling People's Hospital, Wuhan Tongji Hospital, and Wuhan Fangcang Shelter Hospitals from December 29, 2019, to April 3, 2020. These hospitals were designated hospitals to specialize in the administration of COVID-19 patients. All subjects enrolled in the study were diagnosed with COVID-19 following the guideline of WHO, whose nasal and pharyngeal swab specimens were confirmed positive by real-time reverse transcription-polymerase chain reaction (RT-PCR) or next-generation sequencing assays.[6] Oral consent was obtained from patients and/or their immediate relatives given the context of emerging infectious diseases. And this study was approved by the institutional ethics board of Shanghai Ruijin Hospital (Approval Number: 2018-197).

According to the normal reference value of biochemical index, COVID-19 patients were classified into different groups by liver function indicators of admission in three aspects. Subjects with either alanine transaminase (ALT) >50 U/L or aspartate aminotransferase (AST) >40 U/L on admission were divided into the elevated liver enzymes group, and all the others were in the normal liver enzymes group. Patients who had total bilirubin >20.50 μmol/L or direct bilirubin >8.6 μmol/L belonged to the group of elevated bilirubin, while others belonged to normal bilirubin group. Similarly, with the cutoff value of albumin defined as 35 g/L, the observed patients were also assigned to the low-level albumin group (<35 g/L) and normal-level albumin group (≥35 g/L). Subjects were excluded if they met the following criteria: (1) with hepatitis or other underlying liver diseases; (2) without liver function parameters on admission; (3) admission was evaluated as critical type by clinicians; (4) clinical information data missed more than ≥20%.

Data collection and outcomes

Demographic and epidemiological baseline, clinical, laboratory, and radiological characteristics on admission, as well as treatment and outcome information were extracted from electronic medical records by a standardized format of data collection. All the records were reviewed by two experienced physicians (JH and DXY) and the data were checked by two researchers (RC and FYL). According to guideline for the diagnosis and treatment of COVID-19 infections (version 7), patients were divided into mild, common, severe, and critical types in terms of disease severity. The final time of data collection was April 3, 2020. Deceased was regarded as the primary endpoint. The secondary endpoint included the development into severe/critical type and the requirement of mechanical ventilation.

Statistical analysis

Continuous and categorical variables were presented as medians with interquartile range (Q_1, Q_3) (non-normally distributed) and counts with percentages (%), respectively. For the comparison between the two groups, we executed *t*-test, Mann–Whitney *U*-test, χ^2 test, or Fisher's exact test as appropriate. Excessive risks for worse outcomes of abnormal liver function indicators were analyzed by multivariable logistic regression model. For mortality predictors, variables related to prognosis in COVID-19 or viral pneumonia were included in univariable regression analysis, and those with $P < 0.05$ were further included in the multivariable regression model. All the results of logistic regression analysis were listed as odds ratios (ORs) and 95% confidence interval (95% CI). The Kaplan–Meier plot was applied to compare survival probability for those with or without liver impairment by the log-rank test. All statistical analyses were performed with SPSS 26.0 (IBM SPSS Inc., Chicago, IL, USA) and a two-tailed *P*-value less than 0.05 was considered statistically significant.

Results

Clinical manifestation in COVID-19 patients with elevated or normal liver enzymes

Of the 649 COVID-19 patients, 200 (30.8%) patients showed elevated liver enzymes and 449 (69.2%) subjects had normal ALT and AST on admission. Compared with the normal liver enzymes group, more male patients showed elevated liver enzymes (153/200 [76.5%] *vs.* 224/449 [49.9%]; $P < 0.001$; Table 1), with no significant difference in age and comorbidities. Fever (174/196; 88.8%), cough (142/196; 72.4%), and dyspnea (81/196; 41.3%) were the most common symptoms in patients with elevated liver enzymes, which also present larger proportion compared with normal liver enzymes group (all $P < 0.05$). Meanwhile, patients with elevated liver enzymes were more likely to have muscle pain (40/196 [20.4%] *vs.* 59/443 [13.3%]; $P = 0.022$).

Laboratory and radiological findings on admission were summarized in Table 1. Corresponding to liver impairment, patients with elevated liver enzymes also showed less albumin (33.3 [29.4–37.1] g/L *vs.* 37.9 [33.3–41.9] g/L; $P < 0.001$), more total bilirubin (12.0 [9.0–16.2] μmol/L *vs.* 9.0 [IQR, 6.9–12.9] μmol/L; $P < 0.001$), and increased direct bilirubin (4.8 [3.7–6.7] μmol/L *vs.* 3.8 [2.9–4.9] μmol/L; $P < 0.001$). Accompanied with increased leukocytes (6.2 [4.5–8.8] $\times 10^9$/L *vs.* 5.2 [4.2–6.7] $\times 10^9$/L; $P < 0.001$) and neutrophils (4.7 [2.9–7.6] $\times 10^9$/L *vs.* 3.4 [2.6–4.7] $\times 10^9$/L; $P < 0.001$), patients in the elevated liver enzymes group were of higher level of C-reactive protein (CRP), procalcitonin (PCT), and a series of cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-2r, and IL-10. Lymphocytes presented fewer counts (0.9 [0.6–1.2] $\times 10^9$/L *vs.* 1.1 [0.8–1.5] $\times 10^9$/L; $P < 0.001$) in elevated liver enzymes group, accompanied with significant lower counts of $CD3^+$ cells, $CD3^+CD4^+$ cells, and $CD3^+CD8^+$ cells. Moreover, compared with normal liver enzymes group, patients with elevated AST or ALT were also more likely to have kidney and myocardial dysfunction, represented as higher levels of urea nitrogen, creatinine, lactate dehydrogenase (LDH), creatine kinase (CK), CK-MB, myohemoglobin, and cardiac troponin I (cTnI). Difference in coagulation function also appeared between the two groups, manifested as increased level of fibrinogen and D-dimer in the elevated liver enzymes group. According to the chest image, there were no significant differences in patterns of lesions, while patients with elevated liver enzymes showed higher proportion of bilateral involvement (118/126 [93.7%] *vs.* 277/341 [81.2%]; $P = 0.001$) and more pulmonary lobes involved (5.0 [4.0–5.0] *vs.* 4.0 [2.0–5.0]; $P < 0.001$).

Table 1
Demographic and clinical characteristics of COVID-19 patients with elevated liver enzymes/normal liver enzymes.

Items	All ($n=649$)	Elevated liver enzymes group ($n=200$)	Normal liver enzymes group ($n=449$)	Statistics	*P* values
Age (years)	57.0 (43.0–66.0)	58.0 (45.0–66.0)	56.0 (41.0–67.0)	-1.250*	0.211
Male	377/649 (58.1)	153/200 (76.5)	224/449 (49.9)	40.248†	<0.001
Patients with comorbidities	345/649 (53.2)	115/200 (57.5)	230/449 (51.2)	2.188†	0.139
Symptoms					
Fever	527/639 (82.5)	174/196 (88.8)	353/443 (79.7)	7.770†	0.005
Chills	54/639 (8.5)	18/196 (9.2)	36/443 (8.1)	0.196†	0.658
Cough	416/639 (65.1)	142/196 (72.4)	274/443 (61.9)	6.717†	0.010
Sputum production	211/639 (33.0)	69/196 (35.2)	142/443 (32.1)	0.610†	0.435
Pharyngodynia	45/639 (7.0)	9/196 (4.6)	36/443 (8.1)	2.593†	0.107
Chest pain	35/639 (5.5)	14/196 (7.1)	21/443 (4.7)	1.515†	0.218
Dyspnea	193/639 (30.2)	81/196 (41.3)	112/443 (25.3)	16.593†	<0.001
Muscle pain	99/639 (15.5)	40/196 (20.4)	59/443 (13.3)	5.217†	0.022
Digestive symptoms	92/639 (14.4)	27/196 (13.8)	65/443 (14.7)	0.089†	0.766
Neurological symptoms	71/639 (11.1)	21/196 (10.7)	50/443 (11.3)	0.045†	0.832
Laboratory findings on admission					
CRP (mg/L)	18.9 (5.1–65.2)	56.0 (17.1–97.3)	12.6 (4.0–42.3)	-7.160*	<0.001
WBC ($\times 10^9$/L)	5.4 (4.3–7.3)	6.2 (4.5–8.8)	5.2 (4.2–6.7)	-4.156*	<0.001
Neutrophil count ($\times 10^9$/L)	3.6 (2.7–5.6)	4.7 (2.9–7.6)	3.4 (2.6–4.7)	-5.217*	<0.001
Lymphocyte count ($\times 10^9$/L)	1.0 (0.7–1.5)	0.9 (0.6–1.2)	1.1 (0.8–1.5)	-4.972*	<0.001
Hemoglobin (g/L)	131.0 (119.0–143.0)	135.5 (120.3–143.0)	130.0 (118.8–142.0)	-1.972*	0.049
Platelets ($\times 10^9$/L)	190.0 (146.0–255.0)	184.0 (141.0–243.0)	191.0 (149.0–256.8)	-1.466*	0.143
ALT (U/L)	26.0 (17.0–42.0)	56.0 (37.0–75.0)	20.0 (14.0–29.0)	-17.286*	<0.001
AST (U/L)	28.0 (21.0–40.0)	50.5 (42.0–63.8)	23.0 (19.0–30.0)	-18.507*	<0.001
Total bilirubin (μmol/L)	9.7 (7.4–13.7)	12.0 (9.0–16.2)	9.0 (6.9–12.9)	-6.355*	<0.001
Direct bilirubin (μmol/L)	4.0 (3.1–5.5)	4.8 (3.7–6.7)	3.8 (2.9–4.9)	-5.434*	<0.001
Albumin (g/L)	36.4 (31.9–41.0)	33.3 (29.4–37.1)	37.9 (33.3–41.9)	-8.101*	<0.001
Urea nitrogen (mmol/L)	4.8 (3.7–5.9)	5.1 (3.9–6.4)	4.7 (3.6–5.5)	-2.836*	0.005
Lactic acid (mmol/L)	2.7 (2.2–3.2)	2.7 (2.1–3.4)	2.6 (2.2–3.2)	-0.462*	0.644
Creatinine (μmol/L)	68.0 (55.0–81.6)	73.1 (60.2–87.7)	65.6 (53.2–78.7)	-4.282*	<0.001
LDH (U/L)	263.5 (207.0–355.8)	356.5 (275.8–489.8)	232.5 (193.0–295.0)	-11.289*	<0.001
CK (U/L)	80.0 (53.0–146.3)	100.0 (58.0–245.0)	76.0 (51.0–121.0)	-4.313*	<0.001
CK-MB (U/L)	12.3 (9.0–16.3)	13.6 (9.5–19.4)	12.0 (9.0–15.3)	-2.385*	0.017
Myohemoglobin (ng/mL)	27.6 (7.6–59.6)	49.7 (22.5–114.4)	20.5 (4.8–44.5)	-8.164*	<0.001
cTnI (ng/mL)	0.10 (0.02–4.80)	2.40 (0.03–8.70)	0.06 (0.01–3.60)	-4.294*	<0.001
Fibrinogen (g/L)	4.5 (3.7–5.6)	5.2 (4.1–6.0)	4.3 (3.6–5.4)	-4.325*	<0.001
D-dimer (μg/mL)	0.6 (0.4–1.3)	0.9 (0.5–2.1)	0.5 (0.3–1.0)	-6.451*	<0.001
PCT (μg/L)	0.05 (0.02–0.13)	0.10 (0.05–0.26)	0.05 (0.02–0.08)	-7.141*	<0.001
ESR (mm/h)	48.0 (28.6–78.0)	50.0 (36.0–74.0)	46.2 (26.2–81.0)	-0.459*	0.646
BNP (pg/mL)	49.9 (25.1–145.9)	53.5 (28.7–158.3)	48.1 (23.5–128.5)	-1.138*	0.255
IL-1b (pg/mL)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	5.0 (5.0–5.0)	-0.366*	0.715
IL-2r (pg/mL)	567.0 (372.8–923.0)	797.0 (452.5–1131.0)	518.0 (286.5–778.5)	-2.594*	0.010
IL-6 (pg/mL)	7.6 (5.2–12.5)	8.1 (6.3–14.7)	7.3 (4.1–11.0)	-2.962*	0.003
IL-8 (pg/mL)	11.7 (6.8–21.4)	15.9 (7.3–25.5)	10.8 (6.2–18.0)	-1.339*	0.181
IL-10 (pg/mL)	5.0 (5.0–5.1)	5.0 (5.0–5.7)	5.0 (5.0–5.0)	-2.073*	0.038
TNF-α (pg/mL)	7.9 (5.2–10.5)	9.6 (6.9–11.4)	7.3 (4.0–10.2)	-2.341*	0.019
$CD3^+$ cell counts (cell/μL)	718.5 (492.3–1075.0)	577.0 (354.0–994.0)	785.0 (536.5–1083.5)	-2.945*	0.003
$CD4^+$ cell counts (cell/μL)	423.0 (286.0–660.0)	371.0 (185.0–591.0)	447.0 (313.5–670.5)	-2.608*	0.009
$CD8^+$ cell counts (cell/μL)	254.0 (159.8–413.3)	208.0 (121.0–334.0)	258.0 (171.0–422.0)	-2.633*	0.008
$CD3^+$ cell percentage (%)	68.1 (61.0–75.5)	68.0 (52.0–74.4)	69.0 (63.0–76.0)	-1.910*	0.056
$CD4^+$ cell percentage (%)	40.7 (33.0–46.8)	39.4 (30.0–45.0)	41.0 (33.7–47.0)	-1.555*	0.120
$CD8^+$ cell percentage (%)	25.0 (18.9–30.0)	22.9 (15.0–28.1)	25.0 (19.0–30.0)	-1.825*	0.068
Chest CT findings on admission					
Bilateral involvement	395/467 (84.6)	118/126 (93.7)	277/341 (81.2)	10.882†	0.001
Pulmonary lobes involved	5.0 (3.0–5.0)	5.0 (4.0–5.0)	4.0 (2.0–5.0)	-4.645*	<0.001
Consolidation	106/467 (22.7)	28/126 (22.2)	78/341 (22.9)	0.022†	0.881
Ground-glass opacity	436/467 (93.4)	119/126 (94.4)	317/341 (93.0)	0.326†	0.568
Linear opacity	116/467 (24.8)	37/126 (29.4)	79/341 (23.2)	1.893†	0.169
Pleural effusion	25/467 (5.4)	9/126 (7.1)	16/341 (4.7)	1.091†	0.296
Pleural thickening	209/467 (44.8)	62/126 (49.2)	147/341 (43.1)	1.384†	0.239

Data are presented as median (Q_1, Q_3) or No./total No. (%). *Z values. †χ^2 values. ALT: Alanine transaminase; AST: Aspartate aminotransferase; BNP: Brain natriuretic peptide; CD: Cluster of differentiation; CK: Creatine kinase; CK-MB: Creatine kinase isoenzyme-MB; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; CT: Computed tomography; cTnI: Cardiac troponin I; ESR: Erthrocyte sedimentation rate; IL: Interleukin; LDH: Lactate dehydrogenase; PCT: Procalcitonin; TNF-α: Tumor necrosis factor-α; WBC: White blood cell count.

Clinical manifestation in COVID-19 patients with abnormal level of bilirubin or albumin

Either total bilirubin or direct bilirubin, which served as other indicators that reflected liver function, was found elevated in 10.6% (69) of the COVID-19 patients. And patients with elevated bilirubin were more likely to suffer dyspnea, which was the only different manifestation compared with normal bilirubin group [Supplementary Table 1]. When we evaluated liver function according to albumin, 267 (41.1%) individuals were in the group with decreased level of albumin and they were older, of more male and with more comorbidities. Moreover, patients with low-level albumin were also more prone to manifest cough, dyspnea, chills, and muscle pain [Supplementary Table 2].

For laboratory test findings [Supplementary Tables 1 and 2], both elevated bilirubin group and low-level albumin group showed higher levels of leukocytes, neutrophils, and inflammatory indicators (CRP, PCT, TNF, IL-2r, IL-6), as well as decreased lymphocytes and its stratification according to CD antibody recognition. However, patients with low-

Table 2
Treatment and prognosis of COVID-19 patients with elevated liver enzymes/normal liver enzymes.

Items	All ($n=649$)	Elevated liver enzymes group ($n=200$)	Normal liver enzymes group ($n=449$)	χ^2 values	P values
Disease severity					
Severe/critical	194/632 (30.7)	89/198 (44.9)	105/434 (24.2)	27.535	<0.001
Therapy					
Early antiviral therapy*	329/649 (50.7)	92/200 (46.0)	237/449 (52.8)	2.548	0.110
Antibiotic treatment	431/649 (66.4)	155/200 (77.5)	276/449 (61.5)	15.939	<0.001
Glucocorticoid therapy	145/563 (25.8)	67/169 (39.6)	78/394 (19.8)	24.366	<0.001
Oxygen therapy					
High-flow nasal cannula	56/609 (9.2)	24/188 (12.8)	32/421 (7.6)	4.152	0.042
Mechanical ventilation	77/609 (12.6)	41/188 (21.8)	36/421 (8.6)	20.681	<0.001
Prognosis					
Discharge from hospital	530/647 (81.9)	144/198 (72.7)	386/449 (86.0)	16.264	<0.001
Death	72/647 (11.1)	37/198 (18.7)	35/449 (7.8)	16.482	<0.001
Remained in hospital	33/647 (5.1)	10/198 (5.1)	23/449 (5.1)	0.001	0.969

Data are presented as No./total No. (%). *Early antiviral therapy refers to any antiviral drug usage in 4 days before admission. COVID-19: Coronavirus disease 2019.

Table 3
Treatment and prognosis of COVID-19 patients with elevated bilirubin/normal bilirubin.

Items	All ($n=649$)	Elevated bilirubin group ($n=69$)	Normal bilirubin group ($n=580$)	χ^2 values	P values
Disease severity					
Severe/critical	194/632 (30.7)	35/69 (50.7)	159/563 (28.2)	14.605	<0.001
Therapy					
Early antiviral therapy*	329/649 (50.7)	36/69 (52.2)	293/580 (50.5)	0.068	0.795
Antibiotic treatment	431/649 (66.4)	54/69 (78.3)	377/580 (65.0)	4.861	0.027
Glucocorticoid therapy	145/563 (25.8)	21/56 (37.5)	124/507 (24.5)	4.486	0.034
Oxygen therapy					
High-flow nasal cannula	56/609 (9.2)	6/65 (9.2)	50/544 (9.2)	0	0.992
Mechanical ventilation	77/609 (12.6)	13/65 (20.0)	64/544 (11.8)	3.565	0.059
Prognosis					
Discharge from hospital	530/647 (81.9)	48/69 (69.6)	482/578 (83.4)	7.954	0.005
Death	72/647 (11.1)	14/69 (20.3)	58/578 (10.0)	6.555	0.010
Remained in hospital	33/647 (5.1)	7/69 (10.1)	26/578 (4.5)	2.978	0.084

Data are presented as No./total No. (%). *Early antiviral therapy refers to any antiviral drug usage in 4 days before admission. COVID-19: Coronavirus disease 2019.

level albumin also had increased anti-inflammatory mediators IL-10 and decreased hemoglobin, which were not observed in elevated bilirubin group. Alike patients with elevated liver enzymes, patients in elevated bilirubin group and low-level albumin group also manifested a higher incidence of multiple-organs injury, with increased level of urea nitrogen, myohemoglobin, cTnI, and D-dimer. Meantime, elevated concentration of brain natriuretic peptide (BNP) and fibrinogen were also found in subjects with low-level albumin. However, according to chest CT findings, pleural thickening seemed less common in patients with elevated bilirubin. But higher proportions of bilateral involvement, linear opacity, and pleural effusion were seen in the low-level albumin group, as well as the increased number of involved pulmonary lobes.

Treatment and prognosis in COVID-19 patients with liver dysfunction and normal liver function

As for therapeutic strategy, patients with elevated liver enzymes received more antibiotic treatment (155/200 [77.5%] *vs.* 276/449 [61.5%]; $P < 0.001$; Table 2) and systematic glucocorticoid therapy (67/169 [39.6%] *vs.* 78/394 [19.8%]; $P < 0.001$). In the choice of oxygen therapy, patients in elevated liver enzymes groups showed increased proportion of high-flow nasal cannula (24/188 [12.8%] *vs.* 32/421 [7.6%]; $P = 0.042$), and more patients needed mechanical ventilation (41/188 [21.8%] *vs.* 36/421 [8.6%]; $P < 0.001$). Compared with normal liver enzymes group, patients with elevated liver enzymes were more prone to developing into severe/critical types (89/198 [44.9%] *vs.* 105/434 [24.2%]; $P < 0.001$). For prognosis, with a lower proportion of discharge (144/198 [72.7%] *vs.* 386/449 [86.0%]; $P < 0.001$), in-hospital mortality of elevated liver enzymes group was much higher than that in normal liver enzymes group (37/198 [18.7%] *vs.* 35/449 [7.8%]; $P < 0.001$).

Tables 3 and 4 summarize the treatment and prognosis for patients with abnormal level of bilirubin and albumin, respectively. Alike the higher percentage of antibiotic and glucocorticoid treatment which occurred in elevated bilirubin group, patients in low-level albumin group also manifested decreased administration of early antiviral therapy. In terms of respiratory support, patients with low-level albumin also showed the same tendency as those who had elevated liver enzymes, while no significant difference was found between elevated and normal bilirubin group. Consistent with the evaluation of liver enzymes, low-level albumin group and elevated bilirubin group showed greater proportion of severe/critical type (both $P < 0.001$) and significant higher mortality ($P < 0.001$; $P = 0.010$) as compared with their counterparts.

Association between liver dysfunction and poor prognosis

To determine the adverse effect of liver dysfunction on the prognosis, we conducted multiple logistic regression analysis on each important outcome adjusted for age, sex, and comorbidity. The data revealed that patients with elevated liver enzymes had increased risk of developing severe/critical type (2.55 [95% CI, 1.76–3.69]; $P < 0.001$; Fig. 1A) and requiring mechanical ventilation (2.50 [95% CI, 1.50–4.18]; $P < 0.001$). Different from elevated bilirubin, which only had influence on disease severity (2.72 [95% CI, 1.62–4.56]; $P < 0.001$), low-level albumin contributed to the elevated hazard of severe/critical type (3.15 [95% CI, 2.02–4.93]; $P < 0.001$) and need of mechanical ventilation (3.29 [95% CI, 1.88–5.74]; $P < 0.001$) of different degrees. Importantly, abnormal liver enzymes, elevated bilirubin, and low-level albumin all were associated with increased mortality risk, with adjusted ORs presented as 2.89 (95% CI, 1.74–4.81; $P < 0.001$), 2.17 (95% CI, 1.12–4.21; $P = 0.022$), and 3.70 (95% CI, 2.14–6.41; $P < 0.001$), respectively. In addition, survival curves, as illustrated in Fig. 1B–D, confirmed liver dysfunction on admission increased risk of death in COVID-19.

Table 4
Treatment and prognosis of COVID-19 patients with low-level albumin/normal-level albumin.

Items	All ($n=649$)	Low-level albumin group ($n=267$)	Normal-level albumin group ($n=382$)	χ^2 values	P values
Disease severity					
Severe/critical	194/632 (30.7)	133/267 (49.8)	61/365 (16.7)	79.417	<0.001
Therapy					
Early antiviral therapy*	329/649 (50.7)	118/267 (44.2)	211/382 (55.2)	7.664	0.006
Antibiotic treatment	431/649 (66.4)	216/267 (80.9)	215/382 (56.3)	42.690	<0.001
Glucocorticoid therapy	145/563 (25.8)	89/213 (41.8)	56/350 (16.0)	46.038	<0.001
Oxygen therapy					
High-flow nasal cannula	56/609 (9.2)	31/246 (12.6)	25/363 (6.9)	5.735	0.017
Mechanical ventilation	77/609 (12.6)	55/246 (22.4)	22/363 (6.1)	35.260	<0.001
Prognosis					
Discharge from hospital	530/647 (81.9)	178/265 (67.2)	352/382 (92.1)	65.891	<0.001
Death	72/647 (11.1)	56/265 (21.1)	16/382 (4.2)	45.418	<0.001
Remained in hospital	33/647 (5.1)	22/265 (8.3)	11/382 (2.9)	9.504	0.002

Data are presented as No./total No. (%). *Early antiviral therapy refers to any antiviral drug usage in 4 days before administration. COVID-19: Coronavirus disease 2019.

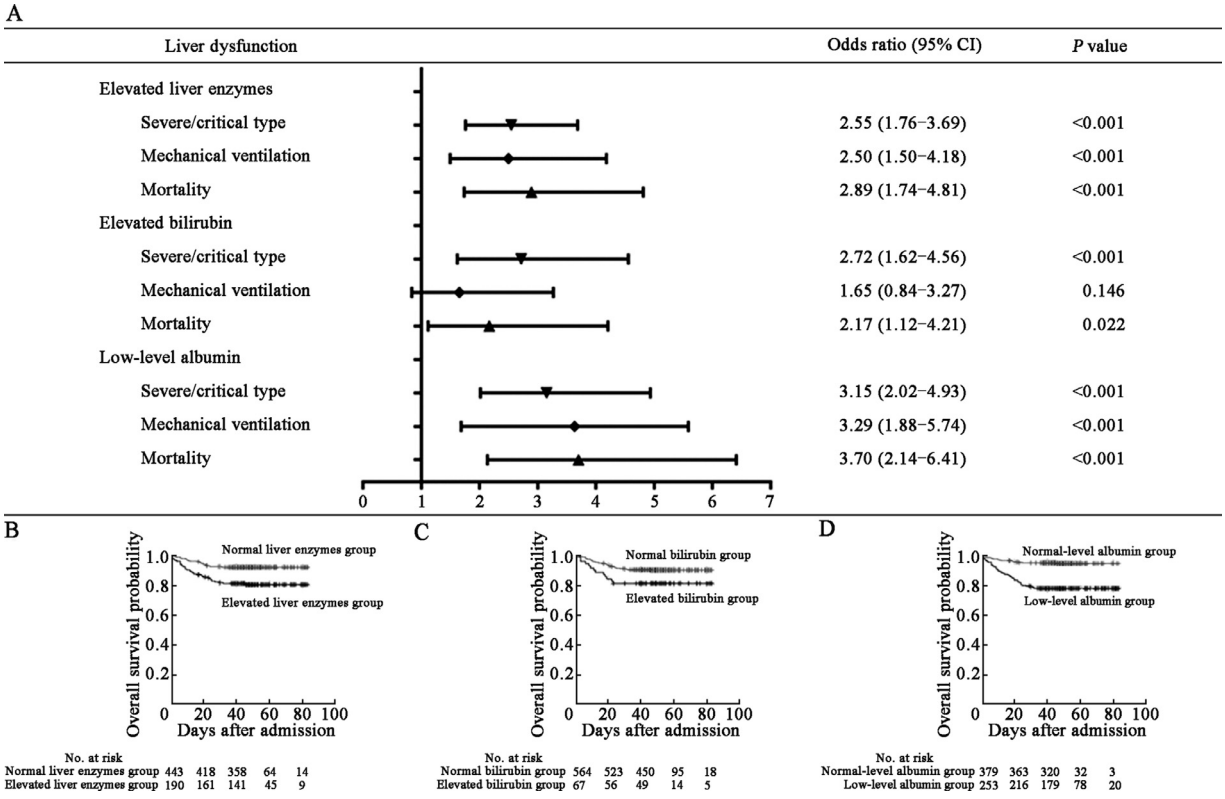

Fig. 1. Odds ratio for clinical outcomes and survival curves in COVID-19 patients with normal or abnormal liver function. Odds ratio of abnormal liver function indicators on admission for clinical outcomes in COVID-19 patients; adjusted by sex, age, and comorbidity; scale bar represents the odds ratios and 95% CI (A). Survival curve in COVID-19 patients with elevated liver enzymes *vs.* normal liver enzymes ($P < 0.001$) (B); elevated bilirubin *vs.* normal bilirubin ($P = 0.019$) (C); low-level albumin *vs.* normal-level albumin ($P < 0.001$) (D) on admission. CI: Confidence interval.

Considering the poor prognosis in elevated liver enzymes group, we performed univariable logistic regression in this subgroup and found that age ≥65 years (2.37 [95% CI, 1.14–4.93]; $P = 0.021$) and cTnI ≥1.5 ng/mL (3.13 [95% CI, 1.18–8.31]; $P = 0.022$) were associated with the high rate of death [Table 5]. Furthermore, according to the multivariable regression analysis, cTnI ≥1.5 ng/mL (2.88 [95% CI, 1.07–7.74]; $P = 0.036$) was identified as an independent predictor for in-hospital mortality.

Discussion

This large-scale, multicenter retrospective study performed comprehensive comparison on clinical manifestations and outcomes between COVID-19 patients with normal liver function and liver dysfunction and focused on the influence of liver dysfunction on poor endpoints. We demonstrated a high incidence of abnormalities in liver enzyme, bilirubin, and albumin on admission in COVID-19. Accompanied by the higher proportion of male patients and probability of dyspnea, patients with liver dysfunction on admission manifested decreased lymphocytes, increased level of inflammatory, kidney function and cardiac indicators, as well as elevated inclination to develop into bilateral, multi-lobular lesions on chest images. Importantly, associated with poorer outcomes, liver dysfunction also resulted in higher hazard to exacerbate into severe/critical type, needing mechanical ventilation and death. Moreover, cTnI ≥1.5 ng/mL was an independent predictor for in-hospital mortality in patients with elevated liver enzymes.

Alike severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), liver dysfunction often occurred in COVID-

Table 5
Univariable and multivariable logistic regression analysis of mortality risk factors in COVID-19 patients with elevated liver enzymes.

	Univariable analysis		Multivariable analysis	
Items	OR (95% CI)	*P* values	OR (95% CI)	*P* values
Age ≥ 65 years	2.37 (1.14–4.93)	0.021	1.79 (0.74–4.32)	0.196
Male	1.31 (0.58–2.97)	0.522		
Comorbidities	1.30 (0.62–2.71)	0.486		
Lymphocyte ≤ 0.8×10^9/L	1.32 (0.64–2.71)	0.453		
Albumin ≤ 30 g/L	1.80 (0.84–3.83)	0.130		
D-dimer ≥ 0.5 μg/mL	2.20 (0.80–6.03)	0.128		
CK ≥ 200 U/L	0.62 (0.25–1.56)	0.312		
LDH > 245 U/L	2.36 (0.67–8.25)	0.180		
cTnI ≥ 1.5 ng/mL	3.13 (1.18–8.31)	0.022	2.88 (1.07–7.74)	0.036

CI: Confidence interval; CK: Creatine kinase; COVID-19: Coronavirus disease 2019; cTnI: Cardiac troponin I; LDH: Lactate dehydrogenase; OR: Odds ratio.

19 patients and presented higher rate in severe and critical cases.[6,11–13] But its pathophysiologic mechanisms are still unclear.[7,14] Highly homologous to severe acute respiratory syndrome-coronavirus (SARS-CoV), SARS-CoV-2 shares the same manner to enter and infect target cells, with angiotensin-converting enzyme II (ACE2) as the main receptor.[15] ACE2 was expressed at low levels in hepatocytes, but enriched in cholangiocytes, which participated in the repair of liver injury.[16] Meanwhile, cytokine storm was associated with COVID-19, and with the attack on multiple organs, it could cause a series of abnormal indicators.[6] Moreover, the use of hepatotoxic drugs, such as antiviral drugs and acetaminophen, may also contribute to liver impairment.[17] As a result, the high incidence of liver dysfunction on admission in our research might be attributed to the reasons mentioned above to some extent. In addition, albumin was also included as a classification indicator, which can comprehensively reflect the liver's synthetic function and systematic intake and consumption of nutrition.

In the present study, we found that patients with liver dysfunction showed increased ratio of male, which was consistent with the result of Xie et al.[8] However, it deserved further research to identify whether the sex inclination was related to the differences in the distribution of ACE2 receptor on hepatocytes. In line with recent reports, fever, cough, and dyspnea were the most common symptoms for COVID-19 patients.[5,6] Meanwhile, incidence of dyspnea was significantly higher in patients with liver dysfunction, which might be partly explained by hypoxia-induced liver injury.[18] When hypoxia occurred, oxygen reduction, increased lipid accumulation, and peroxidation products in hepatocytes can result in necrocytosis and inflammatory cell infiltration.[19,20]

With reference to laboratory test, previous studies have reported that patients with liver injury presented higher level of white blood cell counts, neutrophils, and CRP.[8] And as shown in Zhang's study, ALT, AST, total bilirubin, and albumin were positively correlated with CRP and neutrophil-to-lymphocyte ratio.[9] Similarly, increased leukocytes and neutrophils were verified in our research. As we all know, lymphopenia was the most common feature of COVID-19 and associated with poor prognosis; and $CD4^+$ T cells and $CD8^+$ T cells played an important role in affecting viral replication or clearance.[21] Importantly, we also found a significant decrease in lymphocytes among liver dysfunction group, accompanied with lower count and proportion of T lymphocytes. In addition, according to our findings, not only CRP showed elevated levels in liver dysfunction group, but other inflammatory mediators, cytokines, cardiac biomarkers, and kidney function indicators as well as coagulation function factors also increased. It should be stressed that cytokine storm has been identified as the occurrence in critical cases of SARS-CoV-2 infection; while enormous pro-inflammatory signals could contribute to necrosis and apoptosis of hepatocytes and initiate a feedforward cycle of high hepatotoxicity, further aggravating liver and systemic multiple organ injury.[4,22]

As for radiological findings, bilateral, multi-lobular ground-glass opacities were the most common lesion in COVID-19, especially for severe patients.[6,23] Similarly, increased proportion of bilateral involvement was found in elevated liver enzymes group and low-level albumin group. Moreover, our research manifested more lobes involved in liver dysfunction groups, which was consistent with Xie et al,[8] who revealed that liver injury patients had a greater extent of pulmonary lesions.

Without specific drugs, the management of COVID-19 was based on previous beneficial experiences in treating influenza, SARS, MERS, etc.[24] Different from Fan et al,[17] who reported liver injury was associated with lopinavir/ritonavir, antiviral agents did not present higher usage rates in abnormal liver enzyme group and elevated bilirubin group according to our study, which needs to be confirmed by further research. However, our findings revealed higher proportion of antibiotic and systematic glucocorticoid treatment in all groups with abnormal liver indicators. Up to now, glucocorticoid therapy is still controversial, and WHO has not classified it as priority treatment choices. But in the case of severe COVID-19, it cannot be ignored that glucocorticoid can effectively alleviate the inflammation, prevent progression into acute respiratory distress syndrome, and reduce mortality risk.[24]

Previous studies have reported that increased incidences of elevated ALT, AST, bilirubin, and hypoalbuminemia occurred in severe COVID-19 patients.[6,21] In Cai's research, patients classified as hepatocellular and/or cholestatic type of abnormal liver tests were at about three times higher odds of severe disease.[25] Correspondingly, our study revealed that with greater proportion of severity type, elevated liver enzymes, increased bilirubin, and low-level albumin increased the risk of developing into severe/critical types in 2.55, 2.72, and 3.15 times, respectively. Respiratory support is crucial for COVID-19 patient.[14] And when refractory respiratory distress and hypoxia cannot be alleviated by routine oxygen therapy, mechanical ventilation is considered as necessary.[24] As one of the composite outcomes, higher percentage of mechanical ventilation was shown in the group with elevated liver enzymes and low-level albumin according to our results. On the other hand, these abnormal parameters on admission also increased the requirement of mechanical ventilation.

Importantly, our findings also suggested that patients with abnormal liver function indicators on admission had increased mortality, accompanied by the significant differences in survival curve when compared with the subjects with normal corresponding liver test parameters. Similarly, Yang et al[26] and Ruan et al[27] have demonstrated the different levels of liver enzymes, bilirubin, and albumin between survivors and no-survivors with COVID-19. Mortality risk factors of COVID-19 have been identified by some research, including old age, lymphopenia, D-dimer, etc.[27,28] For the first time, after the adjustment of sex, age, and comorbidities, we reported that ALT, AST, bilirubin, and albumin on admission indeed affected in-hospital mortality of COVID-19. Therefore, more attention and better protection should be given to the COVID-19 patients who had liver dysfunction on admission. With the highest in-hospital mortality, elevated liver enzymes group was further analyzed separately and cTnI ≥1.5 ng/mL was identified as an inde-

pendent mortality risk factor in this subgroup. Similarly, a recent meta-analysis also concluded that the level of cTnI was significantly higher in non-survivors.[29] The high expression of ACE2 in cardiovascular system might exacerbate myocardial impairment and subsequent multiple organ failure, which would cause poor prognosis.[28,30]

Our study has some limitations that need to be pointed out. Firstly, due to liver non-specificity and loss of clinical data, some parameters (such as LDH, glutamyltransferase, and cholinesterase) were not included for the subgroup analysis. Secondly, stratified analysis of liver function indicators and comparison between admission and post-treatment were not conducted in this study. In addition, underlying liver diseases and detailed treatment before admission were based on self-reported information, which may have a certain degree of underreporting and bias.

In conclusion, COVID-19 patients with liver dysfunction on admission were older, and of more serious symptoms, worse laboratory, and radiological findings. Abnormal liver function indicators were associated with more severe diseased condition, more requirement of mechanical ventilation support, and increased mortality. Moreover, cTnI ≥1.5 ng/mL was an independent risk factor of death in elevated liver enzymes group. It is necessary to monitor liver function parameters and pay more attention to patients with liver dysfunction.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pccm.2023.08.004.

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