

# Dynamic Changes in Liver Function Tests and Their Correlation with Illness Severity and Mortality in Patients with COVID-19: A Retrospective Cohort Study

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**Objective:** To describe the longitudinal changes in liver function tests, and their association with illness severity and mortality in patients with COVID-19.

**Methods:** A retrospective cohort study of 1003 hospitalized patients with COVID-19 was conducted. Longitudinal liver function tests and clinical outcomes were analyzed.

**Results:** Abnormal liver function parameters were observed, both at admission (ALT 13.2%, AST 8.5%, ALP 2.0%, GGT 7.4%, LDH 37.6%, TBIL 4.0%, DBIL 7.8%, Albumin 10.1%) and peak hospitalization (ALT 29.4%, AST 17.5%, ALP 2.6%, GGT 13.4%, LDH 49.4%, TBIL 10.1%, DBIL 18.0%, Albumin 30.6%) in patients with COVID-19. Compared with non-severe patients, severe patients had markedly higher liver function parameters from baseline to 30 days after hospital admission. Abnormal ALT and LDH at hospital admission and some medications use (Hydroxychloroquine, Lopinavir/Ritonavir, and Traditional Chinese medicines) were associated with peak hospitalization ALT > 5× the upper limit unit of normal (ULN). On multivariate analysis, age >60 years, male, obesity, comorbidity, abnormal LDH and albumin at hospital admission and peak hospitalization were associated with progression to severe COVID-19 (OR > 1;  $p < 0.05$ ). COX analysis revealed that ALT > 2 ULN (HR=7.0,  $p=0.011$ ), AST > 2 ULN (HR=34.7,  $p < 0.001$ ), and TBIL > 2 ULN (HR=54.6,  $p < 0.001$ ) were associated with a higher mortality.

**Conclusion:** Dynamic abnormalities of liver function parameters are common in hospitalized patients with COVID-19, and associated with illness severity and mortality.

**Keywords:** COVID-19, SARS-CoV-2, liver function parameters, liver injury, clinical outcomes

## Introduction

Since November 2019, the outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has influenced over 200 countries, areas or territories worldwide.<sup>1</sup> The evidence that human-to-human transmission has been reported among close contacts of patients with COVID-19.<sup>2</sup> Although considerable efforts have been made to reduce transmission, the overall upward trend of COVID-19 is continuing around the world. As of 17 January 2021, the outbreak of COVID-19 brings the cumulative numbers to over 93 million reported cases and over 2 million deaths globally.<sup>3</sup>

Although patients with COVID-19 present most commonly with respiratory symptoms, multiple extrapulmonary organ dysfunctions have also been reported.<sup>4</sup>

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Previous studies have reported the prevalence of abnormal liver function parameters in patients with COVID-19, primarily alanine aminotransferase (ALT) (12.9–41.6%) and aspartate aminotransferase (AST) (18.2–66.9%).<sup>5–7</sup> Furthermore, some studies have reported abnormal liver function parameters were associated with clinical outcomes of patients with COVID-19, including longer hospital stays,<sup>7</sup> higher risk for severe COVID-19,<sup>6,8</sup> and death.<sup>9</sup>

Different from previous reports, the severity rate and mortality rate of COVID-19 is relatively low in Shanghai, China, owing to the “Four Early Principle” (early detection, early diagnosis, early isolation, and early treatment). Data remain limited about the incidence and clinical value of liver injury in patients with COVID-19 from areas with low severity rate and mortality rate. In this cohort of 1003 hospitalized patients with COVID-19 in Shanghai, China, we aim to report the incidence of liver injury, describe the longitudinal changes in liver function parameters during the hospitalization, and evaluate the association between liver injury and illness severity and mortality.

## Methods

### Participants

A total of 1003 confirmed patients with COVID-19 admitted to Shanghai Public Health Clinical Center, Shanghai, China, between January 20th 2020 and October 20th 2020, were retrospectively analyzed. Patients with COVID-19 were confirmed according to the positive results of SARS-CoV-2 RNA tests in nasopharyngeal or throat swab specimens using the polymerase chain reaction (PCR) method.<sup>10</sup> Severe COVID-19 was diagnosed according to at least one of the following standards:<sup>10</sup> (1) Respiratory frequency  $\geq 30$  breath/min; (2) Resting oxygen saturation  $\leq 93\%$ ; (3) Oxygenation index  $\leq 300$  mmHg; (4) Mechanical ventilation; (5) shock; (6) Other organ failures and the intensive care unit (ICU) admission.

### SARS-CoV-2 RNA Extraction Method and PCR Protocol

SARS-CoV-2 nucleic acids were detected using automatic magnetic extraction device and accompanying kit (Bio-Germ Medical Technology Co., Ltd, Shanghai, China) and screened with an RT-PCR kits (Bio-Germ Medical Technology Co., Ltd., Shanghai, China) with amplification targeting the ORF1a/b and N gene. The RT-PCR with 5  $\mu$ L RNA was used to target the nucleocapsid gene and open

reading frame lab gene using a SARS-CoV-2 nucleic acid detection reagent (Bio-Germ Medical Technology Co., Ltd., Shanghai, China). The final reaction mixture concentration was 500 nm for primer, and 200 nm for probe, respectively. Conditions for the amplifications were 50°C for 15 minutes, 95°C for 3 minutes, followed by 45 cycles of 95°C for 15 seconds and 60°C for 30 seconds.

### Data Collection

In this retrospective study, all data were extracted from the electronic medical records of Shanghai Public Health Clinical Center. Demographic data including age, sex, body mass index (BMI), and comorbidity were obtained. Clinical data including epidemiological histories, clinical manifestations, laboratory parameters, chest CT scans, hospital stays, and clinical outcomes were collected. Liver function tests including serum ALT, AST, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin (TBIL), direct bilirubin (DBIL), and albumin, were performed using fully-auto-biochemistry-analysis-instruments (ARCHITECT C16000; ABBOTT LABORATORIES; SHANGHAI; CHINA).

### Liver Function Tests Abnormalities and Liver Injury Classifications

Liver function test abnormalities were defined as the elevation of the following parameters in serum referring to Shanghai Public Health Clinical Center laboratory reference range standards: ALT > 44 U/L, AST > 38 U/L, ALP > 338 U/L, GGT > 73 U/L, LDH > 211 U/L, TBIL > 21  $\mu$ mol/L, DBIL > 7  $\mu$ mol/L, albumin <38 g/L. As of now, the guidance or consensus on liver injury classifications are lacking for COVID-19 patients. However, as the magnitude of the liver function test elevations in our patients ranged from mild elevations to severe elevations. To describe the severity of liver injury, in this study, patients who had raised liver function parameters more than 5 $\times$  the upper limit unit of normal (ULN) were classified as significant liver injury; patients who had raised liver function parameters 2–5 ULN were classified as moderate liver injury; and patients who had raised liver function parameters 1–2 ULN were classified as mild liver injury.

### Statistical Analysis

Normally distributed data, non-normal distribution data, and categorical data were presented as mean  $\pm$  standard

deviation, median (interquartile range, IQR), and frequency, respectively. The statistical differences were compared using the Student's *t*-test for normally distributed data, non-parametric Mann–Whitney-test for non-normal distribution data, and Chi-square test for categorical data. Clinical outcomes were modeled using liver function test results at admission and at their peak during hospitalization. Multivariate logistic regression analysis was used to adjust for age, gender, obesity, comorbidity, and liver function parameters. The Kaplan–Meier curves and estimates of survival data have become a familiar way of dealing with differing survival times (times-to-event).<sup>11</sup> In this study, we performed the survival estimates using the Kaplan–Meier method, comparing the death rates according to the liver function parameters between the groups. All statistical analyses were performed in SPSS (version 16.0) and GraphPad Prism (version 6.0), and  $p < 0.05$  was considered statistically significant.

## Results

### Baseline Characteristics of Patients

Baseline characteristics of patients are summarized in Table 1. Of 1003 patients with COVID-19, the median age was 36 years (IQR, 25–51), 602 patients (60.0%) were male, 288 patients (28.7%) had obesity, and 183 patients (18.2%) had comorbidity, mainly including hypertension (11.5%) and diabetes mellitus (5.1%). In this study, twenty-three patients had chronic liver diseases, including chronic hepatitis B (n=15), alcoholic or nonalcoholic fatty liver disease (n=9), and autoimmune liver disease (n=1). Two patients had both chronic hepatitis B and fatty liver disease. Twenty-four patients had chronic heart diseases, including coronary artery disease (n=20), chronic cardiac dysfunction (n=4), and cardiomyopathy (n=3). Three patients had both coronary artery disease and chronic cardiac dysfunction. Sixteen patients had chronic pulmonary diseases, including asthma (n=10), chronic obstructive pulmonary disease (n=4), and interstitial pneumonia (n=2).

**Table 1** Baseline Characteristics of the Study Population

	Total	Non-Severe Group	Severe Group	p-value
Number	1003	968	35	-
Age (years)	36 (25–51)	35 (25–50)	64 (49–74)	<0.001
Male gender, n (%)	602 (60.0%)	574 (59.3%)	28 (80%)	0.014
BMI (kg/m <sup>2</sup> )	26.3 ± 6.5	26.2 ± 6.2	27.9 ± 7.8	<0.001
Obesity, n (%)	288 (28.7%)	270 (27.9%)	18 (51.4%)	0.003
Comorbidity, n (%)	183 (18.2%)	159 (16.4%)	24 (68.6%)	<0.001
Hypertension	115 (11.5%)	97 (10.0%)	18 (51.4%)	<0.001
Diabetes mellitus	51 (5.1%)	44 (4.5%)	7 (20%)	<0.001
CHD	24 (2.4%)	18 (1.9%)	6 (17.1%)	<0.001
CLD	23 (2.3%)	22 (2.3%)	1 (2.9%)	0.821
CPD	16 (1.6%)	12 (1.2%)	4 (11.4%)	<0.001
CKD	5 (0.5%)	4 (0.4%)	1 (2.9%)	0.044
Antiviral therapy				
TCM	511 (50.9%)	505 (52.2%)	6 (17.1%)	<0.001
Hydroxychloroquine	278 (27.7%)	274 (28.3%)	4 (11.4%)	0.028
Lopinavir/Ritonavir	124 (12.4%)	111 (11.5%)	13 (37.1%)	<0.001
Laboratory findings				
WBC (10 <sup>9</sup> /L)	5.7 (4.4–7.0)	5.7 (4.5–7.0)	5.9 (3.6–7.9)	0.668
Lymphocyte (10 <sup>9</sup> /L)	1.5 (1.1–2.0)	1.5 (1.1–2.0)	0.7 (0.5–1.0)	<0.001
Platelet (10 <sup>9</sup> /L)	217 (172–262)	220 (175–265)	172 (121–209)	<0.001
PCT (ng/mL)	0.05 (0.02–0.10)	0.05 (0.02–0.10)	0.10 (0.06–0.15)	<0.001
CRP (mg/L)	0.5 (0.5–6.0)	0.5 (0.5–4.7)	37.6 (12.9–78.7)	<0.001
ESR (mm/h)	27 (10–53)	26 (10–50)	52 (38–89)	<0.001

**Note:** The p values indicate differences between severe group and non-severe group.

**Abbreviations:** CHD, chronic heart diseases; CLD, chronic liver diseases; CPD, chronic pulmonary diseases; CKD, chronic kidney diseases; TCM, Traditional Chinese medicines; WBC, white blood count; PCT, procaltitonin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Five patients had chronic kidney diseases, including chronic renal dysfunction (n=4) and nephrotic syndrome (n=1). The median levels of white blood count (WBC), lymphocyte, platelet, procalcitonin (PCT), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were  $5.7 \times 10^9/L$  (IQR, 4.4–7.0),  $1.5 \times 10^9/L$  (IQR, 1.1–2.0),  $217 \times 10^9/L$  (IQR, 172–262), 0.05 ng/mL (IQR, 0.02–0.10), 0.5 mg/L (IQR, 0.5–6.0), and 27 mm/h (IQR, 10–53), respectively.

Severe patients with COVID-19 had higher age (median, 64 vs 35 years,  $p < 0.001$ ) and BMI (mean, 27.9 vs 26.2 kg/m<sup>2</sup>,  $p < 0.001$ ), more common male gender (80% vs 59.3%,  $p = 0.014$ ), obesity (51.4% vs 27.9%,  $p = 0.003$ ), and comorbidity (68.6% vs 16.4%,  $p < 0.001$ ) than non-severe patients (Table 1). Compared with non-severe patients with COVID-19, severe patients had significantly higher PCT (0.10 vs 0.05 ng/mL,  $p < 0.001$ ), CRP (37.6 vs 0.5 mg/L,  $p < 0.001$ ), ESR (52 vs 26 mm/h,  $p < 0.001$ ), but significantly lower lymphocyte count ( $0.7$  vs  $1.5 \times 10^9/L$ ,  $p < 0.001$ ) and platelet count ( $172$  vs  $220 \times 10^9/L$ ,  $p < 0.001$ ) (Table 1).

### Antiviral Medications Use During Hospitalization

Antiviral medications were assessed, including Traditional Chinese medicines (TCM) (50.9%), hydroxychloroquine (27.7%), and lopinavir/ritonavir (12.4%). In this retrospective study, TCM included Ganlu Xiaodu Micropills,

Yinqiao Powder, Xiangsu Powder, Shengjiang Powder, Agastache, Pinellia and Poria Decoction, Sanren Decoction, Moxing Shigan Decoction, Little Bupleurum Decoction, Qingfeipaidu decoction, Baihu Decoction, Dachengqi Decoction, LungCleansing and Detoxifying Decoction, Jinhua Qinggan Granule, Lianhua Qingwen Capsule, Huoxiang Zhengqi capsules, Shufengjiedu capsules, Huashibaidu Formula, Xuanfeibaidu Granule, and Xuebijing Injection.

### Liver Function Parameters of 1003 Patients on Hospital Admission

Liver function parameters of 1003 patients on hospital admission are summarized in Table 2. The median levels of ALT, AST, ALP, GGT, LDH, TBIL, DBIL, and albumin were 20 U/L (IQR, 14–31), 20 U/L (IQR, 17–26), 75 U/L (IQR, 55–193), 21 U/L (IQR, 14–36), 198 U/L (IQR, 172–232), 8.4 umol/L (IQR, 6.5–11.3), 3.4 umol/L (IQR, 2.3–4.6), and 45 g/L (IQR, 41–47), respectively. Severe patients had significantly higher levels of ALT (26 vs 20 U/L,  $p = 0.015$ ), AST (31 vs 20 U/L,  $p < 0.001$ ), GGT (30 vs 21 U/L,  $p < 0.001$ ), LDH (334 vs 197 U/L,  $p < 0.001$ ), TBIL (10.2 vs 8.3 umol/L,  $p = 0.026$ ), DBIL (4.9 vs 3.3 umol/L,  $p < 0.001$ ), but significantly lower albumin (37 vs 45 g/L,  $p < 0.001$ ) than non-severe patients. Abnormal AST (42.9% vs 7.2%,  $p < 0.001$ ), LDH (88.6% vs 35.7%,  $p < 0.001$ ),

**Table 2** Liver Function Tests of 1003 Patients with COVID-19 on Hospital Admission

Characteristic	Total	Non-Severe	Severe	p-value
Number	1003	968	35	-
ALT (U/L)	20 (14–31)	20 (14–31)	26 (16–36)	0.015
ALT, abnormal (> 44 U/L)	132 (13.2%)	125 (12.9%)	7 (20%)	0.223
AST (U/L)	20 (17–26)	20 (17–26)	31 (24–51)	< 0.001
AST, abnormal (> 38 U/L)	85 (8.5%)	70 (7.2%)	15 (42.9%)	< 0.001
ALP (U/L)	75 (55–193)	75 (55–196)	69 (49–177)	0.486
ALP, abnormal (> 338 U/L)	20 (2.0%)	20 (2.1%)	0	0.930
GGT (U/L)	21 (14–36)	21 (14–35)	30 (21–60)	< 0.001
GGT, abnormal (> 73 U/L)	74 (7.4%)	69 (7.1%)	5 (14.3%)	0.112
LDH (U/L)	198 (172–232)	197 (171–229)	334 (264–452)	< 0.001
LDH, abnormal (> 211 U/L)	377 (37.6%)	346 (35.7%)	31 (88.6%)	< 0.001
TBIL (umol/L)	8.4 (6.5–11.3)	8.3 (6.5–11.2)	10.2 (7.9–14.9)	0.026
TBIL, abnormal (> 21 umol/L)	40 (4.0%)	38 (3.9%)	2 (5.7%)	0.959
DBIL (umol/L)	3.4 (2.3–4.6)	3.3 (2.3–4.5)	4.9 (3.7–7.0)	< 0.001
DBIL, abnormal (> 7 umol/L)	78 (7.8%)	70 (7.2%)	8 (22.9%)	< 0.001
Albumin (g/L)	45 (41–47)	45 (42–47)	37 (33–40)	< 0.001
Albumin, abnormal (< 38 g/L)	101 (10.1%)	83 (8.6%)	18 (51.4%)	< 0.001

**Notes:** The p values indicate differences between severe group and non-severe group.  $p < 0.05$  was considered statistically significant.

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin.

DBIL (22.9% vs 7.2%,  $p < 0.001$ ), and albumin (51.4% vs 8.6%,  $p < 0.001$ ) were commonly observed in severe patients, compared with non-severe patients.

## Hospital Admission vs Peak Hospitalization Liver Function Parameters in 1003 Patients

Hospital admission vs peak hospitalization liver function tests in 1003 patients with COVID-19 are shown in Table 3. Abnormal liver function parameters were observed at admission (ALT 13.2%, AST 8.5%, ALP 2.0%, GGT 7.4%, LDH

37.6%, TBIL 4.0%, DBIL 7.8%, albumin 10.1%) and peak hospitalization (ALT 29.4%, AST 17.5%, ALP 2.6%, GGT 13.4%, LDH 49.4%, TBIL 10.1%, DBIL 18.0%, albumin 30.6%) in hospitalized patients with COVID-19. Most patients with abnormal liver function parameters had minimal elevations 1–2 ULN at admission (ALT 84.8%, AST 84.7%, ALP 85%, GGT 78.4%, LDH 94.2%, TBIL 95.0%, DBIL 93.6%), as well as peak hospitalization (ALT 68.1%, AST 77.8%, ALP 88.5%, GGT 72.4%, LDH 89.1%, TBIL 90.1%, DBIL 86.7%). The significant elevations of liver function tests (>5 ULN) were rarely observed (ALT 4.7%, AST 2.3%, ALP 0, GGT 3.0%, LDH 0, TBIL 3.0%, DBIL 0.6%) during

**Table 3** Hospital Admission vs Peak Hospitalization Liver Tests in 1003 Patients with COVID-19

		Hospital Admission	Peak Hospitalization
ALT (U/L)	Abnormal (> 44 U/L)	132 (13.2%)	295 (29.4%)
	1–2 ULN	112 (84.8%)	201 (68.1%)
	2–5 ULN	19 (14.4%)	80 (27.1%)
	> 5 ULN	1 (0.8%)	14 (4.7%)
AST (U/L)	Abnormal (> 38 U/L)	85 (8.5%)	176 (17.5%)
	1–2 ULN	72 (84.7%)	137 (77.8%)
	2–5 ULN	12 (14.1%)	35 (19.9%)
	> 5 ULN	1 (1.2%)	4 (2.3%)
ALP (U/L)	Abnormal (> 338 U/L)	20 (2.0%)	26 (2.6%)
	1–2 ULN	17 (85%)	23 (88.5%)
	2–5 ULN	3 (15%)	3 (11.5%)
	> 5 ULN	0	0
GGT (U/L)	Abnormal (> 73 U/L)	74 (7.4%)	134 (13.4%)
	1–2 ULN	58 (78.4%)	97 (72.4%)
	2–5 ULN	14 (18.9%)	33 (24.6%)
	> 5 ULN	2 (2.7%)	4 (3.0%)
LDH (U/L)	Abnormal (> 211 U/L)	377 (37.6%)	495 (49.4%)
	1–2 ULN	355 (94.2%)	441 (89.1%)
	2–5 ULN	22 (5.8%)	54 (10.9%)
	> 5 ULN	0	0
TBIL (umol/L)	Abnormal (> 21 umol/L)	40 (4.0%)	101 (10.1%)
	1–2 ULN	38 (95%)	91 (90.1%)
	2–5 ULN	1 (2.5%)	7 (6.9%)
	> 5 ULN	1 (2.5%)	3 (3.0%)
DBIL (umol/L)	Abnormal (> 7 umol/L)	78 (7.8%)	180 (18.0%)
	1–2 ULN	73 (93.6%)	156 (86.7%)
	2–5 ULN	5 (6.4%)	23 (12.8%)
	> 5 ULN	0	1 (0.6%)
Albumin (g/L)	Abnormal (< 38 g/L)	101 (10.1%)	307 (30.6%)
	32–38 (g/L)	91 (90.1%)	238 (77.5%)
	< 32 (g/L)	10 (9.9%)	69 (22.5%)

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin; ULN, upper limit of normal.

hospitalization. Most patients with abnormal liver function parameters had minimal reduction of albumin (32–38g/L) at admission (90.1%), as well as peak hospitalization (77.5%), and a small subset of patients had significant reduction of albumin (<32g/L) at admission (9.9%), as well as peak hospitalization (22.5%).

### Predictors of Peak Hospitalization ALT > 5 ULN

Predictors of ALT > 5 ULN at time of peak liver test value during hospitalization are summarized in Table 4, including abnormal ALT and LDH on hospital admission, and medications use (Hydroxychloroquine, Lopinavir/Ritonavir, and TCM) during hospitalization. Compared to patients with ALT ≤ 5 ULN, those with ALT > 5 ULN had more common abnormal ALT (35.7% vs 12.8%, *p*=0.012) and LDH (78.6% vs 31.0%, *p*=0.001) on hospital admission, and more Hydroxychloroquine (57.1% vs 27.3%, *p*=0.013), Lopinavir/Ritonavir (42.9% vs 11.9%, *p* < 0.001), and TCM (78.6% vs 50.6%, *p*=0.037) use.

### Association Between Liver Function Parameters and Clinical Outcomes

The association between liver function parameters and clinical outcomes is shown in Table 5. On multivariate analysis, age >60 years, male gender, BMI > 30 kg/m<sup>2</sup>, comorbidity, abnormal LDH and albumin on hospital admission, and abnormal peak hospitalization LDH and albumin were associated with

progression to severe COVID-19 (OR > 1; *p* < 0.05). The dynamic profile of liver function parameters in patients by severity of COVID-19 is illustrated in Figure 1. Severe COVID-19 patients had markedly higher levels of ALT, AST, GGT, LDH, TBIL, DBIL, but significantly lower levels of albumin than non-severe patients from baseline to 30 days after admission (*p* < 0.05) (Figure 1). The peak of ALT, LDH, TBIL, DBIL value, and the trough of albumin was observed on 6–10 day of hospitalization. The peak of ALP and GGT value was observed on 11–15 day of hospitalization (Figure 1).

On multivariate analysis, age >60 years (OR=6.44; 95% CI 2.24–14.77; *p* < 0.005), BMI > 30 kg/m<sup>2</sup> (OR=1.78; 95% CI 1.23–4.35; *p*=0.024), comorbidity (OR=6.74; 95% CI 2.93–21.85; *p* < 0.001), and abnormal peak hospitalization ALT (OR=3.37; 95% CI 1.25–8.16; *p*=0.008), AST (OR=4.82; 95% CI 1.28–16.16; *p* < 0.001), and TBIL (OR=5.65; 95% CI 1.87–18.20; *p* < 0.001) were associated with death. Kaplan-Meier curves for cumulative rate of death in patients with different level of ALT (a), AST (b), and TBIL (c) are illustrated in Figure 2. ALT > 2 ULN (HR=7.0; CI%= 1.6–31.4; *p* = 0.011), AST > 2 ULN (HR=34.7; CI%= 7.8–155.3; *p* < 0.001), and TBIL > 2 ULN (HR=54.6; CI%= 6.6–453.8; *p* < 0.001) were associated with a higher mortality.

### Discussion

Although COVID-19 is well known for causing respiratory symptoms, it can also cause extrapulmonary manifestations, including hepatocellular injury.<sup>12</sup> In this study of

**Table 4** Predictors of ALT > 5 ULN at Time of Peak Liver Test Value During Hospitalization

Characteristic	ALT at Time of Peak Liver Test Value		
	< 5 ULN (n=989)	> 5 ULN (n=14)	p value
Age (years)	36 (25–51)	30 (26–55)	0.707
Male gender, n (%)	593 (60%)	9 (64.3%)	0.743
BMI (kg/m <sup>2</sup> )	26.2 ± 6.4	27.0 ± 6.6	0.889
Diabetes mellitus, n (%)	50 (5.1%)	1 (7.1%)	0.716
Hypertension, n (%)	114 (11.5%)	1 (7.1%)	0.609
Chronic liver disease, n (%)	23 (2.3%)	0	0.566
Abnormal ALT on hospital admission, n (%)	127 (12.8%)	5 (35.7%)	0.012
Abnormal AST on hospital admission, n (%)	82 (8.3%)	3 (21.4%)	0.08
Abnormal GGT on hospital admission, n (%)	73 (7.4%)	1 (7.1%)	0.973
Abnormal LDH on hospital admission, n (%)	366 (37.0%)	11 (78.6%)	0.001
Abnormal TBIL on hospital admission, n (%)	40 (4.0%)	0	0.443
Hydroxychloroquine use, n (%)	270 (27.3%)	8 (57.1%)	0.013
Lopinavir/Ritonavir use, n (%)	118 (11.9%)	6 (42.9%)	< 0.001
Traditional Chinese Medicine use, n (%)	500 (50.6%)	11 (78.6%)	0.037

**Abbreviations:** ALT, alanine aminotransferase; ULN, upper limit of normal; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; TBIL, total bilirubin.

**Table 5** Association Between Admission and Peak Hospitalization Liver Tests and Clinical Outcomes

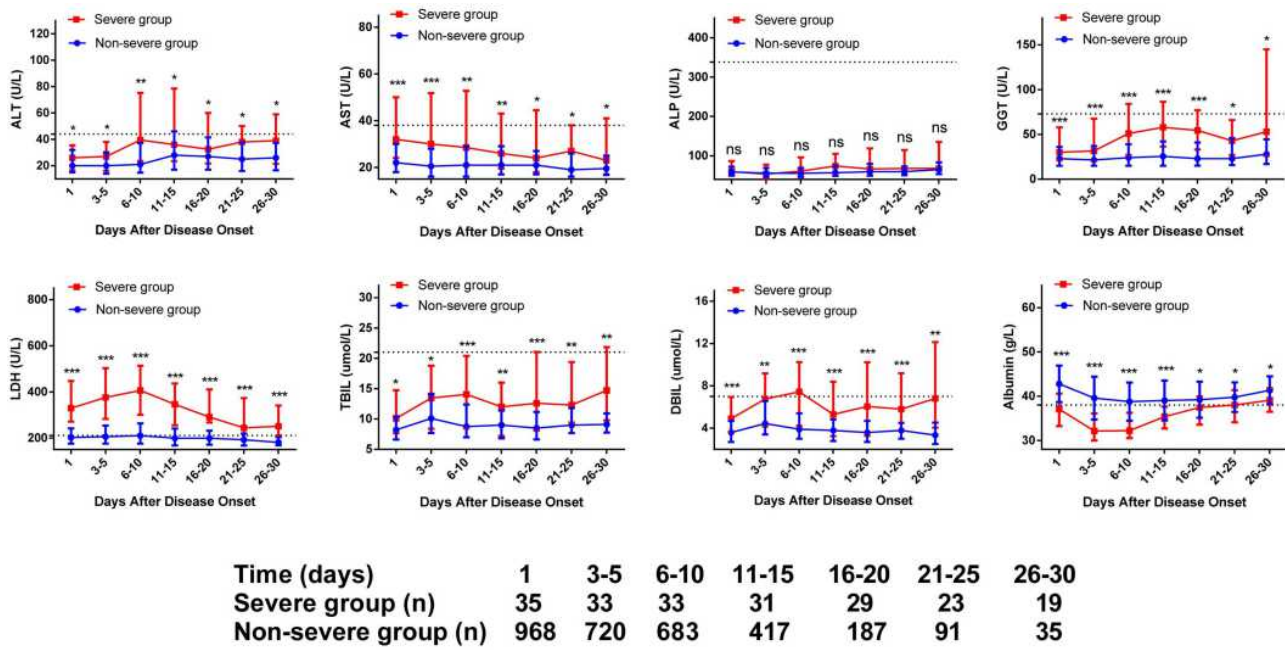
	Severe COVID-19 (Multivariate Model)		Death (Multivariate Model)	
	OR (90% CI)	p-value	OR (90% CI)	p-value
Age > 60 years	4.02 (1.58–10.20)	0.003	6.44 (2.24–14.77)	0.005
Male gender	2.71 (1.27–8.79)	0.019	1.46 (0.28–6.35)	0.368
BMI > 30 kg/m <sup>2</sup>	3.46 (1.32–9.43)	0.012	1.78 (1.23–4.35)	0.024
Comorbidity	6.08 (2.45–15.10)	<0.001	6.74 (2.93–21.85)	<0.001
Hospital Admission				
Abnormal ALT	0.37 (0.07–1.90)	0.234	0.99 (0.04–26.30)	0.994
Abnormal AST	3.01 (0.70–13.03)	0.141	1.50 (0.16–14.47)	0.725
Abnormal ALP	0.22 (0.01–5.86)	0.218	0.85 (0.12–18.95)	0.799
Abnormal GGT	0.67 (0.12–1.19)	0.951	0.58 (0.07–4.55)	0.601
Abnormal LDH	3.36 (1.41–8.78)	0.002	2.11 (0.29–15.48)	0.464
Abnormal TBIL	0.49 (0.01–17.06)	0.696	1.02 (0.07–14.73)	0.986
Abnormal DBIL	1.85 (0.14–6.31)	0.325	4.62 (0.45–47.39)	0.197
Abnormal Albumin	2.45 (1.16–7.51)	0.026	4.74 (0.70–31.95)	0.110
Peak Hospitalization				
Abnormal ALT	2.28 (0.96–6.46)	0.139	3.37 (1.25–8.16)	0.008
Abnormal AST	3.92 (0.56–11.25)	0.141	4.82 (1.28–16.16)	<0.001
Abnormal ALP	0.29 (0.01–7.21)	0.453	1.45 (0.07–30.66)	0.811
Abnormal GGT	2.15 (0.98–7.86)	0.088	3.79 (0.60–57.87)	0.117
Abnormal LDH	3.84 (1.67–9.88)	<0.001	0.89 (0.01–47.85)	0.558
Abnormal TBIL	0.21 (0.03–1.66)	0.139	5.65 (1.87–18.20)	<0.001
Abnormal DBIL	0.49 (0.01–17.06)	0.696	1.39 (0.05–35.27)	0.806
Abnormal Albumin	3.94 (1.36–11.43)	0.002	2.16 (0.87–5.59)	0.747

**Abbreviations:** OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin.

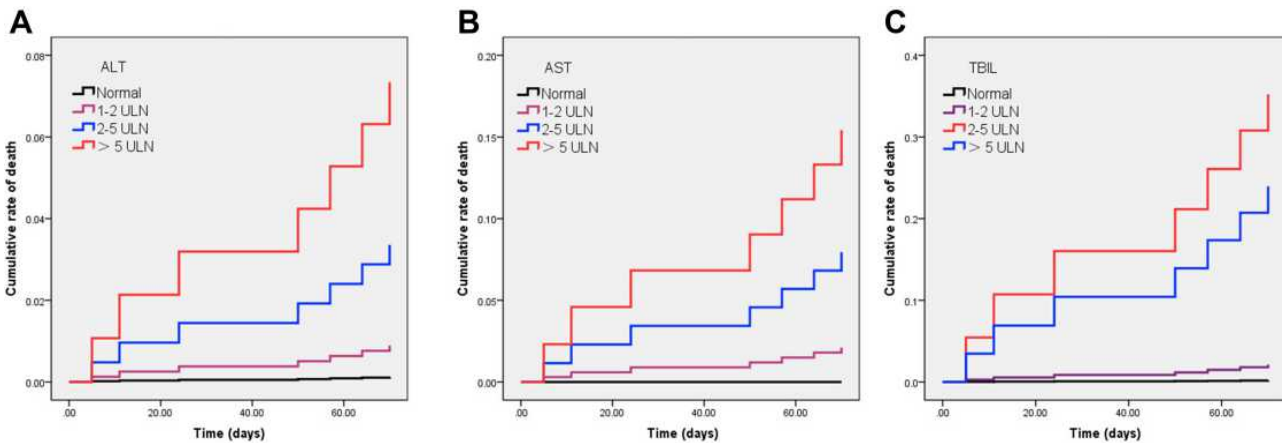
1003 patients with COVID-19, ALT and AST abnormalities were observed in 13.2% and 8.5% of patients at admission, respectively, and in 29.4% and 17.5% of patients at peak hospitalization, respectively. Based on a meta-analysis, the pooled prevalence estimates of elevated liver function abnormalities in China were as follows: ALT 15.0% and AST 15.0%.<sup>13</sup> However, some studies from America showed higher prevalence ranging between 40–50.6% in cohorts ranging from 116 to 2780 patients.<sup>14–16</sup> Obviously, abnormal liver function parameters are less common in Chinese patients than that reported in the U.S.<sup>5,13,15,16</sup> The differences in baseline factors (chronic liver diseases, obesity, alcohol consumption) and hospital management (antiviral medication use) may potentially account for some of this disparity. Moreover, the different laboratory references of liver function parameters in different health-care systems might lead to the different definitions of liver injury, which may be one of the reasons for the disparity in the prevalence of

liver injury between Chinese patients and the US patients. For example, the ULN of ALT ranges from 40 U/L to 50 U/L in the studies from China,<sup>6,8,9</sup> but ranges from 33 U/L to 50 U/L in the studies from the US.<sup>5,16,17</sup>

This study showed that the pattern of abnormal liver function tests is predominantly hepatocellular (at admission: ALT 13.2%, AST 8.5%; at peak hospitalization: ALT 29.4%, AST 17.5%) rather than cholestatic, although less common elevations in ALP (2.0% at admission, and 2.6% at peak hospitalization), GGT (7.4% at admission, and 13.4% at peak hospitalization), and TBIL (4.0% at admission, and 10.1% at peak hospitalization) can be observed. Given that angiotensin converting enzyme-2 (ACE2), the entry receptor for SARS-CoV-2, is much more heavily expressed in cholangiocytes than in hepatocytes,<sup>18</sup> therefore our findings suggest that the direct cytopathic effect of the SARS-CoV-2 may not be the main mechanism of COVID-19-related liver damage. Hepatic dysfunction in COVID-19 could be related to an uncontrolled immune



**Figure 1** Dynamic profile of liver function tests in patients by severity of COVID-19. The liver function tests in non-severe group (blue line) and severe group (red line) were analyzed at different time points after hospital admission. The liver function tests are shown using median and IQR. “\*” means  $p < 0.05$ ; “\*\*” means  $p < 0.01$ ; “\*\*\*” means  $p < 0.001$ . Severe group had markedly higher levels of ALT, AST, GGT, LDH, TBIL, DBIL, but significantly lower levels of albumin compared with non-severe group from baseline to 30 days after admission ( $p < 0.05$ ).



**Figure 2** Kaplan-Meier curves for cumulative rate of death during hospitalization in patients with different level of ALT (A), AST (B), and TBIL (C). ALT > 2 ULN (HR=7.0; CI%= 1.6–31.4;  $p = 0.011$ ), AST > 2 ULN (HR=34.7; CI%= 7.8–155.3;  $p < 0.001$ ), and TBIL > 2 ULN (HR=54.6; CI%= 6.6–453.8;  $p < 0.001$ ) were associated with a higher mortality.

reaction, sepsis or drug-induced liver injury, besides the direct cytopathic effect of the virus.<sup>19</sup>

Abnormal liver parameters are usually minimally elevated, although some significant abnormal liver function parameters (>5 ULN) (ALT 4.7%, AST 2.3%, GGT 3.0%, TBIL 3.0%, DBIL 0.6%) may be observed at peak hospitalization. The current results are consistent with prior observations.<sup>5,6</sup> An American study reported that only 5.9% and 6.0% of ALT and AST elevations, respectively,

were beyond 5 ULN at hospital admission, and 20.6% and 16.6% of ALT and AST elevations, respectively, were beyond 5 ULN at peak hospitalization.<sup>5</sup> A Hong Kong study of 1040 COVID-19 patients reported that only 4.9% and 1.3% of ALT and AST elevations, respectively, were beyond 5 ULN during hospitalization.<sup>20</sup>

This study shows an association between antiviral medications use (Hydroxychloroquine, Lopinavir/Ritonavir, and TCM) and peak hospitalization ALT > 5



ULN in patients with COVID-19. Previous studies also showed that the use of certain drugs showed an association with the progression of liver damage in patients with COVID-19.<sup>5,7,20</sup> An American study reported that Hydroxychloroquine and Lopinavir/Ritonavir use was the predictor of peak hospitalization liver parameters >5 ULN.<sup>5</sup> A Chinese study reported that a significantly higher proportion of patients with abnormal liver function (57.8%) had received Lopinavir/Ritonavir after admission compared to patients with normal liver function (31.3%).<sup>7</sup> Another Chinese study reported that the use of Lopinavir/Ritonavir ± Ribavirin + interferon beta (OR 1.94,  $p=0.006$ ) was independently associated with ALT/AST elevation.<sup>20</sup> Based on previous studies and our results, we suggested Hydroxychloroquine, Lopinavir/Ritonavir, and TCM should be used with caution in patients with abnormal ALT and LDH at hospital admission.

In a Chinese cohort of 675 patients with COVID-19, compared to patients with normal AST levels, mortality and risk of mechanical ventilation significantly increased 19.27-fold and 116.72-fold, respectively, in patients with AST above 3-fold ULN.<sup>21</sup> In another Chinese cohort, Cai et al found that the presence of abnormal liver tests and liver injury were associated with the progression to severe COVID-19.<sup>6</sup> In a large Hong Kong cohort of 1040 COVID-19 patients, Yip et al found ALT/AST elevation and acute liver injury are independently associated with adverse clinical outcomes including admission to intensive care unit, use of invasive mechanical ventilation and/or death in COVID-19 patients.<sup>20</sup> Saini et al retrospectively analysed liver function tests of 170 patients with confirmed COVID-19, and also found number of patients with raised levels of any of the liver enzymes were 89 (58.5%), out of which 43 (48.31%) had liver injury, which manifested as increased severity in terms of ICU requirement ( $p=0.0005$ ).<sup>22</sup> In this study, abnormal liver parameters during hospitalization are associated with illness severity and mortality of COVID-19, with the strongest associations observed between peak liver tests and severe COVID-19, as well as peak liver tests and death. Based on previous studies and our results, we suggested monitoring levels of liver function parameters, which could assist in the optimum management of patients with COVID-19.

Many TCM were used in patients with COVID-19 in our cohort; therefore, the effect of TCM on liver functions should not be neglected in COVID-19 patients.<sup>23</sup> In fact, the TCM-related liver injury is not uncommon in patients with COVID-19.<sup>24</sup> A meta-analysis showed that the TCM

as a complementary therapy for treating COVID-19 may not be beneficial for improving liver function based on the current evidence.<sup>23</sup> In this study, we found that the TCM use is one of the predictors of peak hospitalization ALT > 5 ULN. Based on previous studies and our results, we suggested that prevention and management of TCM-induced liver injury should be concerned in COVID-19 patients who received TCM therapy.

Besides liver injury, other gastrointestinal manifestations were also concerned in COVID-19 patients. At the age of COVID-19 crisis, gastrointestinal physicians may face rare gastrointestinal symptoms such as dysentery, pure hyperbilirubinemia, and so on. For example, Hormati et al have reported the clinical data in details as well as the result of chest CT of a COVID-19 patient with dysentery.<sup>25</sup> In a case series, Hormati et al also have reported pure hyperbilirubinemia may be considered as rare gastrointestinal symptom of COVID-19.<sup>26</sup> Therefore, it is necessary that all gastrointestinal physicians should be aware of the possible occurrence of these gastrointestinal symptoms (hepatic involvement, pure hyperbilirubinemia, dysentery) as an important prognosis of COVID-19 pneumonia and it should be exactly addressed in new referred patients to gastrointestinal clinic. In addition, Hormati et al address preventive strategies that may significantly reduce close contact between patients and gastrointestinal physicians for successful control of COVID-19 infection.<sup>27</sup> Preventive strategies should be performed to prevent transmission of COVID-19 infection from infected patients to uninfected gastrointestinal physicians and staff members during the performance of high-risk procedures.<sup>27</sup>

This study has several limitations. First, retrospective observational cohort study design with inclusion restricted to patients who were hospitalized within a single hospital, and limited access to laboratory, and medication variables, which may influence clinical outcomes. Second, this study did not elucidate the etiology of liver function test elevations in hospitalized patients with COVID-19. However, based on previous studies, we have reasons to believe that the drug's effects, possible viral inclusion in liver cells, systemic inflammation, and hypoxia are potential causes of liver injury in patients with COVID-19.<sup>28</sup> Third, in our hospital, the qualitative analysis (positive or negative) of SARS-CoV-2 RNA is used to guide the diagnosis and treatment of COVID-19 patients. Although CT (cycle-threshold)-value for viral load can support in the better interpretation of clinical decisions, in this retrospective study, the quantification of SARS-CoV-2 viral load is not available.

In conclusion, in this large sample retrospective cohort study, we described the longitudinal changes of liver function parameters in patients with COVID-19. In addition, we confirmed patients with abnormal liver function parameters were at increased risk of severe COVID-19 and death. The COVID-19-related liver injury is related to antiviral medication use.

## Ethics Approval and Consent to Participate

Although this is a retrospective study, at hospital admission, all patients provided verbal consent for their clinical data might be used for further medical study. Shanghai Public Health Clinical Center Ethics Committee approved this study, including the verbal informed consent process. When we performed the study, all personal information of patients was de-identified to protect privacy. The procedures followed were in accordance with the ethical standards of the Helsinki Declaration (1964, amended most recently in 2008) of the World Medical Association.

## Consent for Publication

All authors read and approved the manuscript.

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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; took part in drafting, revising or critically reviewing the article; 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.

## Role of the Sponsor

The funding organization is a public institution and had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

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## Disclosure

The authors reported no conflicts of interest for this work.

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