# COVID-19-Related Abnormal Liver Enzymes Levels: A Retrospective Study

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**Research**

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# Abstract

**Background**: A new disease called Coronavirus disease (COVID-19) related to SARS-CoV-2 has brought serious attacks to the world. It causes damage to multiple organ systems of the body include liver. Here we intend to shed light on the clinical features its mechanism related to liver damage which caused by COVID-19.

**Methods**: Clinical records and laboratory results were obtained from 138 patients with laboratory-confirmed COVID-19 who were admitted to Tongji hospital, Wuhan, China from February 8, 2020 to February 18, 2020. Information on clinical features of patients with abnormal liver tests were collected for analysis.

**Results**: Fifty-four (39.1%) and eighty-three (60.1%) patients had abnormal liver enzyme levels on admission and during the course of disease. Hepatocyte type was more common than cholestatic type abnormal. 24(17.4%) patients reached the liver injury standard in the course of disease. Patients with abnormal liver enzyme levels were more likely to be male, had higher levels of inflammation indicators, lower pulse oxygen saturation and lymphocyte count. There is a significantly higher proportion of abnormal liver enzymes levels in the patients which administrated antibiotics during hospitalization, compared with that in the ones without antibiotics therapy (56.6% vs 32.7%). Patients with liver injury was an independent predictor of a poor prognosis ($p<0.0001$, OR 7.774, 95%CI 2.674-22.599).

**Conclusions**: Liver injury in COVID-19 patients was an independent predictor of a poor prognosis. The COVID-19-related abnormal liver enzymes levels may be considered as the result of secondary liver damage caused mainly by several factors. Hypoxia and disease severity account for the largest proportion.


# 1. Introduction

COVID-19 is a new coronavirus disease that broke out at the end of 2019. It has affected more than 180 countries around the world. As of May 28, a total of 5.80 million people was diagnosed. Currently, the number of SARS-CoV-2-infected patients is still rapidly increasing on a global scale. The pathogen of COVID-19 is SARS-CoV-2, which shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to Middle East respiratory syndrome coronavirus (MERS-CoV)—all three coronaviruses are known to cause severe respiratory symptoms, also lead to multiple organ failure(MOF) and even death in severe or critical cases[1–3]. Studies have shown that patients infected with SARS-CoV, MERS-CoV and SARS-CoV-2 may develop different degrees of liver injury[4]. Liver impairment has been reported in up to 60% of patients with SARS and has also been reported in patients infected with MERS-CoV[5]. The severe cases were more likely to have severe liver injury compared to mild cases[4]. Recent studies on COVID-19 have shown that the incidence of liver injury ranged from 14.8%-53%, mainly indicated by abnormal ALT/AST levels accompanied by slightly elevated bilirubin levels[6]. Similar to SARS and MERS, the proportion of developing liver injury in severe COVID-19 patients was significantly

higher than that in mild patients[7]. In death cases of COVID-19, the incidence of liver injury might reach as high as 58.06–78%.

It is currently uncertain whether the COVID-19-related liver dysfunction is due mainly to the viral infection per se or other coexisting conditions, such as the use of potentially hepatotoxic drugs and the coexistence of systemic inflammatory response, respiratory distress syndrome-induced hypoxia, multiple organ dysfunction, and angiotensin-converting enzyme (ACE)2-mediated liver dysfunction[8, 9].

Since COVID-19-related liver dysfunction is now attracting widespread attention,

We aim to describe the clinical course and liver test parameters in patients with COVID-19 admitted to the only referral hospital in Tongji hospital, Wuhan, China, and to compare the clinical features between liver dysfunction and non-liver dysfunction patients. Analyze the influence factors of liver dysfunction, which may help to prevent severe liver injury or failure in patients with COVID-19.

# 2. Methods

# 2.1 Study design and participants

From February 8, 2020 to February 18, 2020, a total of 138 consecutive patients were

admitted and treated in the ward of the Zhongfaxincheng campus of Tongji hospital, Tongji Medical College, Huazhong University of Science & Technology (the designated hospital for infectious disease by the Chinese CDC in the Wuhan area) who were cared for by the Peking University Medical Team, all of which were confirmed cases of COVID-19. Follow-up for this report ended on March 16, 2020. The clinical criteria of diagnosis, subtype and discharge were as per the standards for “Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia" (trial version 6)[10]. All patients were diagnosed after nasopharyngeal swab examination of SARS-CoV-2 RNA by RT-PCR, results showed as negative or positive. And all patients were classified into mild to critical cases based on results from chest radiography, clinical examination, and symptoms. As the patients admitted to our wards were all in serious condition, they were divided into severe and critical cases when admitted[11]. Severe pneumonia was defined by the presence of any of the following conditions: i) significantly increased respiration rate (RR): RR ≥ 30 times/minute; ii) hypoxia: oxygen saturation (resting state) < 93%; iii) blood gas analysis: partial pressure of oxygen/fraction of inspired oxygen (PaO2) /FiO2) ≤ 300 mmHg (millimeters of Mercury); or iv) chest imaging significantly progressed by more than 50% within 24–48 hours. Critical case was defined by respiratory failure and require mechanical ventilation, shock, combining other organ failure requires ICU monitoring treatment.

This study was approved by the Ethics Committee of the Peking University First Hospital (Number: 2020 − 271) and was exempted from the need for informed consent from patients.

### 2.2 Liver test parameters and abnormalities

Epidemiological, clinical, laboratory characteristics and treatment and outcomes data were acquired by the hospitalization management system. Liver test abnormalities were defined as the elevation of the following liver enzymes in serum: ALT > 41 U/L(≤ 41), AST > 40 U/L(≤ 40), gamma-glutamyl transferase (GGT) > 71 U/L(10–71), alkaline phosphatase (ALP) > 130 U/L(40–130), and total bilirubin (TBIL) > 26 μmol/L(≤ 26). As COVID-19 is a new, emerging infectious disease, guidance or consensus on liver injury classifications are lacking. Thus, we classified the abnormalities of liver dysfunction as ALT and/or AST, ALP and/or GGT or TBIL raised more than the upper limit unit of normal (ULN). We also classified the pattern of these abnormalities as hepatocellular, cholestatic, or mixed. Patients who had raised ALT and/or AST more than 3 × the ULN were classified as hepatocyte type; patients who had raised ALP or GGT twice the ULN were classified as cholestatic type; and patients who had a combination of both ALT/AST elevated more than 3 × the ULN and ALP/GGT twice the ULN were classified as mixed type. To further describe liver test characteristics, we defined ALT and/or AST over 3 × ULN, ALP, GGT, and/or TBIL over 2 × ULN as liver injury[12]. We also calculated the liver biochemistry activities by multiples of their ULN. Baseline was defined as the day of in-hospital in Tongji hospital, to ensure consistency of baseline, screenings the laboratory parameters were completed within 3 days. Then the laboratory examination was conducted every three to seven days, depending on the subject's specific conditions.

## 2.3 Therapeutic Strategies

All patients in our study were severe or critical cases, so all of them were given oxygen therapy, critical patients use mechanical ventilation. Vital signs and finger oxygen saturation were closely monitored. All patients rested in bed and received supportive treatments, including fluid supplementation and maintenance of electrolyte and acid-base homeostasis. 84% of patients received antiviral treatment, since there is no accepted antiviral treatment regimen, patients were treated with lopinavir/ritonavir, arbidol tablets, oseltamivir and ribavirin, 12.3% patients used two or more antiviral drugs at the same time. Some patients were treated with antibiotics according to their condition, moxifloxacin is the most commonly used drug. Some patients also used Chinese herbal medicine or nonsteroidal anti-inflammatory drugs (NSAID). Critical patients were treated with methylprednisolone pulse therapy, gamma globulin, or interleukin-6 antagonist if needed and this decision was based on healthcare providers' discretion.

## 2.4 Statistics

Tests for normal distribution were performed on continuous variables, and data following a normal distribution are presented as the means ± standard deviation (SD). The non-normally distributed data are presented as the median (interquartile range, IQR). Categorical variables are expressed as the number of subjects (or percentage). For the comparisons, the independent-samples t-test and the Mann– Whitney U test were used for normally distributed and non-normally distributed continuous variables, respectively. The chi-square test or Fisher's exact test was used for categorical variables, as appropriate. Comparisons among three groups or more were performed using independent-samples Kruskal-Wallis H analysis.

Univariate and multivariate regression analyses were performed to identify predictive variables, and the odd ratio (OR) was calculated in both univariate and multivariate analyses. All analyses were performed using SPSS 21.0. P values were two-sided, and $P < 0.05$ was considered significant.

# 3. Results

## 3.1 Baseline characteristics

138 patients with COVID were included in this study, including 67 (48.6%) females and 71 males (51.4%). The average age of the patients was 62.0 years (range 24–88). 122 patients were severe cases on admission, 16 were critical cases. 19 severe patients progressed to critical cases during hospitalization. By March 16, 64 of the 138 cases were discharged from the hospital, 13(9.4%) were relieved to mild cases, 24(17.4%) died. The prognosis of all patients was listed in Fig. 1. 119 patients were clustered. None of the patients were medical staff. 97 (70.8%) patients had chronic diseases, its composition and percentage were showed in Fig. 2. The underlying liver disease of three patients was chronic hepatitis B, steatohepatitis, and chronic hepatitis C, respectively.

## 3.2 Severity Of Covid-19 And Abnormal Liver Test

We were divided the patients into three groups according to the severity of the disease, group A was severe cases on admission(n = 103), group B was progression to critically ill cases during hospitalization(n = 19), group C was critically ill cases on admission(n = 16). The liver biochemistry of patients in different groups were shown in Table 1 and Table 2.

Table 1
Clinical characteristics of 138 patients with COVID-19 and liver test results on admission.

| | Total patients (n = 138) | Group A (n = 103) | Group B (n = 19) | Group C (n = 16) | *P* value |
|---|---|---|---|---|---|
| Age, years | 66 (54-71.25) | 65(50–70) | 68(59–77) | 67.5(62.5–76) | 0.118 |
| Female/male | 67/71 | 55/48 | 6/13 | 6/10 | 0.141 |
| Pulse oxygen saturation (%) ¶ | 95(88.5–97) | 96(93–97) | 87(80–95) | 78(72.3–94.8) | < 0.0001 |
| ALT, U/L | 22(15.8–40) | 22(14–40) | 30(18–43) | 30.5(19.3–45) | 0.267 |
| <ULN (n, %) | 105(76.1%) | 81(78.6%) | 13(68.4%) | 11(68.8%) | 0.318 |
| 1–2 ULN (n, %) | 26(18.8%) | 17(16.5%) | 5(26.3%) | 4(25%) | 0.107 |
| 2–3 ULN (n, %) | 2(1.4%) | 1(1%) | 1(5.3%) | 0 | 0.317 |
| ≥ 3 ULN (n, %) | 5(3.6%) | 4(3.9%) | 0 | 1(6.3%) | 0.480 |
| AST, U/L | 27.5(18–41) | 24(18–35) | 41(34–53) | 38(28.3–49.5) | < 0.0001 |
| <ULN (n, %) | 102(73.9%) | 85(82.5%) | 9(47.4%) | 8(50%) | 0.021 |
| 1–2 ULN (n, %) | 27(19.6%) | 12(11.7%) | 10(52.6%) | 5(31.3%) | 0.041 |
| 2–3 ULN (n, %) | 5(3.6%) | 4(3.9%) | 0 | 1(6.3%) | 0.48 |
| ≥ 3 ULN (n, %) | 4(2.9%) | 2(1.9%) | 0 | 2(12.5%) | 0.121 |
| ALB, g/l | 34.1(30.5–37.7) | 34.9(31.5–38.1) | 34(29.7–35.6) | 30.1(28.4–33.2) | < 0.0001 |
| ALP, U/L | 65(54-83.8) | 62(53–73) | 63(50–80) | 105(71.5-120.3) | < 0.0001 |
| <ULN (n, %) | 131(94.9%) | 99(96.1%) | 18(94.7%) | 14(87.5%) | < 0.0001 |

There was no statistical difference in age and gender between the three groups of patients. However, male was more likely to be or progressed to be critically ill. The pulse oxygen saturation gradually decreases as the disease progression ($P < 0.0001$).

The magnitude of the liver test elevations in our patients ranged from mild to moderate, 54(39.1%) patients had abnormalities of liver dysfunction on admission, only 13(9.4%) cases achieved liver injury level, among them 6 (46.2%) in group C ($P < 0.0001$). Regarding the patterns of abnormal liver test results, 6(4.3%) cases were hepatocyte type, 11(8.0%) were cholestatic type, and 4(2.9%) were mixed type. There was no patient TBIL level more than 2 ULN on admission. The level of AST, ALP, GGT and TBIL in critically ill patients was higher than that in severe patients on baseline, while critically ill patients had lower levels of ALB level (Table 1).

| | Total patients (n = 138) | Group A (n = 103) | Group B (n = 19) | Group C (n = 16) | *P* value |
|---|---|---|---|---|---|
| 1–2 ULN (n, %) | 6(4.3%) | 3(2.9%) | 1(5.3%) | 2(12.5%) | 0.538 |
| ≥ 2 ULN (n, %) | 1(0.7%) | 1(1%) | 0 | 0 | - |
| GGT, U/L | 28(18.8–55.3) | 25(18–45) | 36(20–58) | 77(21.3-159.3) | 0.019 |
| <ULN (n, %) | 114(82.6%) | 89(86.4%) | 17(89.5%) | 8(50%) | 0.249 |
| 1–2 ULN (n, %) | 14(10.1%) | 10(9.7%) | 1(5.3%) | 3(18.8%) | 0.925 |
| ≥ 2 ULN (n, %) | 10(7.2%) | 4(3.9%) | 1(5.3%) | 5(31.3%) | 0.62 |
| TBIL, μmol/L | 9.5(7-12.8) | 8.7(6.6–11.1) | 10.7(8.4–15.3) | 15.4(9.1–25.1) | 0.001 |
| <ULN (n, %) | 134(97.1%) | 102(99%) | 19(100%) | 13(81.3%) | 0.006 |
| 1–2 ULN (n, %) | 4(2.9%) | 1(1%) | 0 | 3(18.8%) | 0.665 |
| ≥ 2 ULN (n, %) | 0 | 0 | 0 | 0 | - |
| Liver abnormal | 54(39.1%) | 30(29.1%) | 12(63.2%) | 12(75%) | < 0.0001 |
| Hepatocellular | 6(4.3%) | 4(3.9%) | 0 | 2(12.5%) | 0.178 |
| Cholestatic | 11(8.0%) | 5(4.9%) | 1(5.3%) | 5(31.3%) | 0.001 |
| Mixed | 4(2.9%) | 3(2.9%) | 0 | 1(6.3%) | 0.55 |
| Liver injury | 13(9.4%) | 6(5.8%) | 1(5.3%) | 6(37.5%) | < 0.0001 |

¶ patient's fingertip oxygen saturation (oxygen inhalation or non-oxygen inhalation) on admission.

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine amino- transferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase, TBIL = total bilirubin, ULN = upper limit unit of normal.

There was no statistical difference in age and gender between the three groups of patients. However, male was more likely to be or progressed to be critically ill. The pulse oxygen saturation gradually decreases as the disease progression ($P < 0.0001$).

The magnitude of the liver test elevations in our patients ranged from mild to moderate, 54(39.1%) patients had abnormalities of liver dysfunction on admission, only 13(9.4%) cases achieved liver injury level, among them 6 (46.2%) in group C ($P < 0.0001$). Regarding the patterns of abnormal liver test results, 6(4.3%) cases were hepatocyte type, 11(8.0%) were cholestatic type, and 4(2.9%) were mixed type. There was no patient TBIL level more than 2 ULN on admission. The level of AST, ALP, GGT and TBIL in critically ill patients was higher than that in severe patients on baseline, while critically ill patients had lower levels of ALB level (Table 1).

Table 2 shows that 19 patients were progression to critical cases during hospitalization, liver test (ALT, AST, ALP, GGT and TBIL levels) in those 19 patients were higher than patients did not progression to critical cases ($P < 0.05$). 83(60.1%) patients had abnormalities of liver dysfunction. 15(10.9%) were hepatocyte type, 15(10.9%) were cholestatic type, and 8(5.8%) were mixed type. All cases progressed to critical illness had liver abnormal during the course of disease. The presence of liver injury became more pronounced during hospitalization, with 9(8.7%) and 5(26.3%) exhibiting in group A and group B, respectively($P < 0.0001$).

Table 2
Clinical characteristics of 138 patients with COVID-19 and liver test results (peak values) during hospitalization.

| | Total patients (n = 138) | Group A (n = 103) | Group B (n = 19) | Group C (n = 16) | *P* value |
|---|---|---|---|---|---|
| ALT, U/L | 40(21-63.3) | 29(18–57) | 61(38–114) | 53(29-82.8) | 0.002 |
| <ULN (n, %) | 70(50.7%) | 59(57.3%) | 5(26.3%) | 6(37.5%) | 0.266 |
| 1–2 ULN (n, %) | 46(33.3%) | 32(31.1%) | 8(42.1%) | 6(37.5%) | 0.204 |
| 2–3 ULN (n, %) | 8(5.8%) | 5(4.9%) | 2(10.5%) | 1(6.3%) | 0.354 |
| ≥ 3 ULN (n, %) | 14(10.1%) | 7(6.8%) | 4(21.1%) | 3(18.8%) | 0.997 |
| AST, U/L | 35(22.8–53.5) | 28(19–41) | 56(42–103) | 49.5(37.5–115) | < 0.0001 |
| <ULN (n, %) | 84(60.9%) | 77(74.8%) | 3(15.8%) | 4(25%) | 0.413 |
| 1–2 ULN (n, %) | 29(21%) | 13(12.6%) | 9(47.4%) | 7(43.8%) | 0.584 |
| 2–3 ULN (n, %) | 12(8.7%) | 8(7.8%) | 3(15.8%) | 1(6.3%) | 0.768 |
| ≥ 3 ULN (n, %) | 13(9.4%) | 5(4.9%) | 4(21.1%) | 4(25%) | 0.032 |
| ALP, U/L | 79(63.8-103.3) | 72(62–89) | 100(88–138) | 117(85-161.8) | < 0.0001 |
| <ULN (n, %) | 120(87%) | 97(94.2%) | 14(73.7%) | 9(56.3%) | 0.002 |
| 1–2 ULN (n, %) | 17(12.3%) | 5(4.9%) | 5(26.3%) | 7(43.8%) | 0.148 |
| ≥ 2 ULN (n, %) | 1(0.7%) | 1(1%) | 0 | 0 | - |
| GGT, U/L | 37.5(22.8–71.3) | 33(21–61) | 60(39–93) | 118(47.8-191.5) | < 0.0001 |
| <ULN (n, %) | 104(75.4%) | 85(82.5%) | 12(63.2%) | 7(43.8%) | 0.017 |
| 1–2 ULN (n, %) | 19(13.8%) | 13(12.6%) | 5(26.3%) | 1(6.3%) | 0.092 |
| ≥ 2 ULN (n, %) | 15(10.9%) | 13(12.6%) | 5(26.3%) | 1(6.3%) | 0.728 |
| TBIL, μmol/L | 11.2(8.7–20.8) | 9.9(7.8–13.6) | 24.9(21.3–32.5) | 25(17.2-46.73) | < 0.0001 |
| <ULN (n, %) | 117(84.8%) | 96(93.2%) | 12(63.2%) | 9(56.3%) | < 0.0001 |

| | Total patients (n = 138) | Group A (n = 103) | Group B (n = 19) | Group C (n = 16) | *P* value |
|---|---|---|---|---|---|
| 1–2 ULN (n, %) | 16(11.6%) | 7(6.8%) | 5(26.3%) | 4(25%) | 0.505 |
| ≥ 2 ULN (n, %) | 5(3.6%) | 0 | 2(10.5%) | 3(18.8%) | 0.564 |
| Liver abnormal | 83(60.1%) | 51(49.5%) | 19(100%) | 13(81.3%) | < 0.0001 |
| Hepatocellular | 15(10.9%) | 7(6.8%) | 4(21.1%) | 4(25%) | 0.03 |
| Cholestatic | 15(10.9%) | 5(4.9%) | 2(10.5%) | 8(50%) | < 0.0001 |
| Mixed | 8(5.8%) | 3(2.9%) | 2(10.5%) | 3(18.8%) | 0.027 |
| Liver injury | 24(17.4%) | 9(8.7%) | 5(26.3%) | 10(62.5%) | < 0.0001 |

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine amino- transferase, AST = aspartate aminotransferase, GGT = γ-glutamyl transpeptidase, TBIL = total bilirubin, ULN = upper limit unit of normal.

### 3.3 Clinical features of patients with COVID-19 and abnormal liver tests on admission and during hospitalization

Table 3 shows baseline and after hospitalization parameters which may related to the liver dysfunction. We divided patients into three groups based on whether liver test was abnormal on admission or hospitalization time, 55(39.9%) patients were normal from admission to discharge; 29(21.0%) patients normal on admission, but progressed to abnormal during hospitalization; 54(39.1%) patients abnormal on admission.

Table 3
Characteristics of 138 patients with COVID-19 on admission and during hospitalization by liver tests.

| | Total patients | Normal(n = 55) | Normal to abnormal (n = 29) | Abnormal (n = 54) | *P* value |
|---|---|---|---|---|---|
| Baseline parameters | | | | | |
| Age, years | 66(54-71.3) | 68(58–73) | 58(43-69.5) | 66(54.8–70.5) | 0.059 |
| Female/male | 67/71 | 38/17 | 11/18 | 18/36 | < 0.0001 |
| Pulse oxygen saturation (%) | 95(88.5–97) | 97(94–98) | 95(89–96) | 92(84–96) | < 0.0001 |
| Critical cases (n, %) | 16(11.6%) | 3(5.5%) | 1(3.4%) | 12(22.2%) | 0.008 |
| From diagnosis to admission, days | 14(10.8–18) | 14(10–18) | 13(9.5–17) | 14(11-17.3) | 0.666 |
| Water blood count, $\times 10^9$/L | 5.5(4.4–7.7) | 5.3(4.4–6.3) | 4.7(3.6–6.9) | 6.7(4.7–10.9) | 0.012 |
| Lymphocyte count, $\times 10^9$/L | 0.9(0.6–1.4) | 1.1(0.7–1.6) | 1.0(0.7–1.6) | 0.8(0.5–1.3) | 0.017 |
| Eosinophil count, $\times 10^9$/L | 0.02(0-0.06) | 0.03(0.01–0.07) | 0.03(0-0.08) | 0.005(0-0.04) | 0.003 |
| Lactate dehydrogenase, U/L | 290(234-407.3) | 239(205–274) | 290(226.5–329) | 409.5(311.3–583) | < 0.0001 |
| Serum creatinine, μmol/L | 74(58-91.3) | 70(52–93) | 75(58.5–88) | 78.5(64-93.8) | 0.22 |
| Serum glucose, mmol/L | 6.1(5.3–7.9) | 5.8(5.2-7.0) | 5.8(5.1–7.1) | 6.7(5.5–9.1) | 0.121 |
| hsCRP, mg/L | 36.5(6.3–85.6) | 8.8(2.2–35.3) | 36.8(5.9–63.3) | 68.3(38.1-155.9) | < 0.0001 |
| Prothrombin time, (s) | 14.1(13.5–14.7) | 13.9(13.5–14.3) | 14.1(13.2–14.6) | 14.4(13.6–15.3) | 0.026 |
| D-dimer, ug/mL | 1.3(0.5–2.5) | 0.63(0.4–1.8) | 1.0(0.5–2.1) | 1.9(1.1-4.0) | < 0.0001 |
| IL2R, U/mL | 714(462–1180) | 565(407–837) | 699(481-1189.8) | 917.5(632.8-1537.3) | 0.001 |
| IL-6, pg/mL | 18.8(4.3–50.8) | 7.8(2.1–20.6) | 15.9(6.5–54.6) | 42.3(13.8–75.3) | < 0.0001 |

| | Total patients | Normal(n = 55) | Normal to abnormal (n = 29) | Abnormal (n = 54) | *P* value |
|---|---|---|---|---|---|
| IL-8, pg/mL | 10(5.5–25) | 6.8(5-10.8) | 11(6-26.2) | 21.7(9.4–34.9) | < 0.0001 |
| IL-10, pg/mL | 5(5-7.5) | 5(5–5) | 5.5(5-10.1) | 5.8(5-9.5) | < 0.0001 |
| TNF-α, pg/mL | 8.3(5.7–12) | 7(4.4–10) | 7.6(5.2–12.3) | 9.9(7.4–13.5) | 0.001 |
| ESR, mm/h | 37(20.3–59.5) | 31.5(17.8–49) | 28(17–52) | 50(32–67) | 0.02 |
| Serum ferritin, ug/L | 681.9(387.5–1392) | 411.5(272.7-563.3) | 775.2(391.2-1369.4) | 1306.7(729.7-2014.2) | < 0.0001 |
| PCT, ng/mL | 0.05(0.03–0.15) | 0.03(0.02–0.05) | 0.06(0.03–0.12) | 0.15(0.05–0.4) | < 0.0001 |
| Parameters during hospitalization | | | | | |
| Maximum temperature (℃) | 38.5(38.0–39.0) | 38.2(37.8–38.8) | 38.7(38.0–39.0) | 38.7(38.4–39.5) | 0.003 |
| Antibiotic therapy | 65(47.1%) | 18(32.7%) | 16(55.2%) | 31(57.4%) | 0.023 |
| Chinese herbal medicine | 115(83.3%) | 50(90.0%) | 23(79.3%) | 42(77.8%) | 0.151 |
| Antiviral therapy | 118(85.5%) | 48(87.3%) | 27(93.1%) | 43(79.6%) | 0.226 |
| NSAIDs | 18(13%) | 4(7.3%) | 6(20.7%) | 8(14.8%) | 0.198 |
| Use of corticosteroid | 33(23.9%) | 6(10.9%) | 6(20.7%) | 21(38.9%) | 0.003 |
| Progressed to critical cases (n, %) | 35(25.4%) | 3(5.5%) | 8(44.4%) | 24(44.4%) | < 0.0001 |
| Non-invasive ventilation | 33(23.9%) | 2(3.6%) | 8(27.6%) | 23(42.6%) | < 0.0001 |
| Invasive ventilation | 10(7.2%) | 1(1.8%) | 1(3.4%) | 8(14.8%) | 0.023 |
| Death | 24(17.4%) | 2(3.6%) | 5(17.2%) | 17(31.5%) | 0.001 |
| Discharge | 64(46.4%) | 36(65.5%) | 14(48.3%) | 14(25.9%) | < 0.0001 |
| relief | 13(9.4%) | 3(5.5%) | 2(6.9%) | 8(14.8%) | 0.218 |
| IL: interleukin, hsCRP: hypersensitive c-reactive protein, PCT: procalcitonin, NSAIDs: non-steroidal anti-inflammatory drugs | | | | | |

We could see in Table 3 that male patients were more prone to liver abnormalities ($P < 0.0001$). Patients with abnormal liver biochemistry had lower pulse oxygen saturation on admission, and critically illness

percentage was higher than normal group ($P$ = 0.008). Liver biochemistry level was proportional to inflammation indicators, such as leukocytes, lactate dehydrogenase (LDH), hypersensitive c-reactive protein(hsCRP), interleukin (IL), tumor necrosis factor (TNF-α), erythrocyte sedimentation rate (ESR) and ferritin. Procalcitonin (PCT) and D-dimer was more likely higher in abnormal group too. Conversely, the levels of lymphocytes and eosinophils in patients with abnormal group was significantly lower than those in the other two groups.

The application of antibiotics (mostly moxifloxacin), corticosteroid, mechanical ventilation; maximum temperature and severity of disease were all related to abnormal liver biochemistry during the course of disease. 22(91.7%) died patients had liver dysfunction during the course of disease, and 11(45.8%) reached liver injury level. 50 (78.1%) cured patients' liver biochemistry returned to normal compared with 4 (30.8%) of uncured patients (P = 0.001) (Table not shown).

### 3.4 Related factors of abnormal liver function analyzed by univariable and multivariable

We used both univariate and multivariate analyses to identify the indicators related to abnormal liver function (Table 4). Divided into normal and abnormal two groups at baseline and after hospitalization, respectively. In univariate analysis, gender, severity of disease(reflected in use of non-invasive ventilation, maximum temperature, decrease in pulse oxygen saturation and lymphocyte count), inflammatory indexes (reflected in white blood cell count, hsCRP and serum ferritin levels), damage of other organ(heart) or system(coagulation), immunity(elevated of immunoglobulin G), decrease in eosinophil count, baseline liver test level (ALT and AST), drug (antibiotic, non-steroidal anti-inflammatory drugs) and death were all independent predictors of abnormal liver function. In the multivariate analysis, non-invasive ventilation (OR 103.142, 95%CI 7.314–1454.4), death (OR 15.756, 95%CI 2.006-123.755), pulse oxygen saturation < 93% (OR 3.236, 95%CI 1.351–7.752) and maximum temperature (OR 2.567, 95%CI 1.405–4.691) showed high odds ratio value related to liver abnormal. While serum ferritin, immunoglobulin G, baseline ALT and baseline AST were only at 1–2 folds odds of abnormal liver function.

Table 4
Univariable and multivariable analysis predictors of liver test abnormal.

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) | *P* value |
| Baseline parameters [a] | | | | |
| gender | 2.8(1.373–5.712) | 0.005 | - | |
| Non-invasive ventilation | 7.13(1.453–35.001) | 0.016 | 11.674(1.17-116.49) | 0.036 |
| Maximum temperature (℃) | 2.474(1.401–4.370) | 0.002 | 2.567(1.405–4.691) | 0.002 |
| Pulse oxygen saturation < 93% | 3.906(1.862–8.197) | < 0.0001 | 3.236(1.351–7.752) | 0.008 |
| White blood cell count, $\times 10^9$/L | 1.223(1.09–1.372) | 0.001 | - | |
| Lymphocyte count, $\times 10^9$/L | 0.443(0.219–0.899) | 0.024 | - | |
| Eosinophil count, $\times 10^9$/L | 0.001(0-1.369) | 0.061 | - | |
| CK-MB, ng/mL | 1.598(1.152–2.216) | 0.005 | - | |
| hsCRP, mg/L | 1.011(1.005–1.017) | < 0.0001 | - | |
| Serum ferritin, ug/L | 1.001(1.001–1.002) | < 0.0001 | 1.001(1-1.002) | 0.002 |
| d-dimer, ug/mL | 1.107(1.029–1.19) | 0.006 | | |
| Immunoglobulin G | 1.161(1.01–1.335) | 0.036 | 1.316(1.047–1.654) | 0.019 |
| Abnormal liver test during hospitalization [b] | | | | |
| Non-invasive ventilation | 6.913(1.297–36.851) | 0.024 | 103.142(7.314–1454.4) | 0.001 |
| ALT level on admission, U/L | 1.124(1.048–1.205) | 0.001 | 1.154(1.03–1.294) | 0.014 |
| AST level on admission, U/L | 1.162(1.076–1.255) | < 0.0001 | 1.13 (1.018–1.254) | 0.021 |
| antibiotic | 2.53(1.005–6.37) | 0.049 | - | |

### 3.5 Association of abnormal liver test results with COVID-19 severity

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *P* value | Odds ratio (95% CI) | *P* value |
| Non-steroidal anti-inflammatory drugs | 3.326(0.856–12.927) | 0.083 | - | |
| Death | 5.521(0.999–30.502) | 0.05 | 15.756(2.006-123.755) | 0.009 |

[a] Available in 138 patients. Neutrophil count was excluded due to collinearity with white blood cell count; lactate dehydrogenase, myoglobin and creatine kinase(CK) were excluded due to collinearity with CK-MB; Prothrombin time and activated partial thromboplastin time were excluded due to clinical correlation with d-dimer; Interleukin(IL), Erythrocyte sedimentation rate were excluded due to clinical correlation with hsCRP;

[b] Available in 84 patients, whose liver test were normal on admission. Non-invasive ventilation: patients whose disease progressed during hospitalization and should be used non-invasive ventilation, but do not use on admission.

### 3.5 Association of abnormal liver test results with COVID-19 severity

Table 5 shows that, after adjustment for age and sex, abnormality or injury as indicated by liver tests on admission was associated with mortality. Patients with abnormality of liver test were at almost 5-fold greater risk of mortality compared to those without liver test abnormalities (OR 4.602; 95%CI 1.691–12.528; p = 0.003). while using the definition of abnormality type, patients with hepatocellular, cholestatic and mixed type were only at 1–2 higher odds of decease disease.

After similar adjustment of peak value of liver test parameters during the course of disease, patients with liver injury were at almost 8-fold greater risk of mortality compared to those without liver test abnormalities (OR 7.774; 95% CI 2.674–22.599; p < 0.0001). Having hepatocyte, cholestatic or mixed type were increased only 1–2 folds of decease disease.

Table 5
Association of abnormal liver test results with COVID-19 severity (decease vs. non-decease).

| | Crude OR (95% CIs) | p value | Adjusted OR (95% CIs) † | p value |
|---|---|---|---|---|
| On admission | | | | |
| Abnormal | 5.504(1.928–13.247) | 0.001 | 4.602(1.691–12.528) | 0.003 |
| Hepatocellular | 2.50(0.431–14.502) | 0.307 | 1.044(1.004–1.086) | 0.03 |
| Cholestatic | 3.057(0.818–11.421) | 0.097 | 1.045(1.006–1.086) | 0.025 |
| Mixed | 1.609(0.16–16.16) | 0.686 | 1.043(1.003–1.084) | 0.036 |
| Injury | 3.487(1.03-11.803) | 0.045 | 1.046(1.006–1.087) | 0.023 |
| Peak values of liver test parameters during hospitalization | | | | |
| Abnormal | 9.557(2.146–42.559) | 0.003 | 1.054(1.011–1.098) | 0.013 |
| Hepatocellular | 3.889(1.234–12.253) | 0.02 | 1.048(1.007–1.09) | 0.020 |
| Cholestatic | 5.456(1.751–16.996) | 0.003 | 1.048(1.007–1.09) | 0.022 |
| Mixed | 5.5(1.27-23.814) | 0.023 | 1.05(1.01–1.093) | 0.015 |
| Injury | 6.574(2.445–17.67) | < 0.0001 | 7.774(2.674–22.599) | < 0.0001 |
| †Adjusted for age, sex. | | | | |

# 4. Discussion

Notably, 54(39.1%) of patients on admission had abnormal liver function. Similar to

previous studies, ALP elevation was the less common compared with abnormalities of

the other liver enzymes[6, 13]. It has been shown that SARS-CoV-2 also uses ACE2 as its entry receptor as SARS-CoV does. Previous article had found that both liver cells and bile duct cells express ACE2 too. However, the ACE2 expression of bile duct cells is at a concentration 20 times higher than that of liver cells, but to a comparable level of alveolar type 2 cells in the lung[14]. However, significant increases in circulating levels of serum ALP, bilirubin or GGT (that may reflect bile duct injury) have been rarely reported in COVID-19 patients, mainly indicated by abnormal ALT/AST levels[7]. Approximately 32.6% and 52.9% patients in this study had elevated ALT/AST on admission and after hospitalization respectively, significantly higher than elevated ALP/GGT (18.8% and 27.5% respectively). We found that liver injury was more common in men, this finding is consistent with the previous research[15], although the mechanism is unclear.

We also found that patients with abnormal liver test had higher inflammatory indexes, such as elevated hsCRP and serum ferritin, and more likely to have high fever, which may be related to the systemic

inflammatory response after virus infection. Table 2 in this article shows that patients who progress to critical illness during hospitalization were significantly more likely to have liver abnormal and injury than severe cases. Application of non-invasive ventilation and death were at almost 100- and 16-folds greater risk of liver abnormal than those non-severe patients in our study, and patients who had liver injury during hospitalization were at almost 8-fold greater risk of mortality compared to those without liver test abnormalities. All the above findings proved that liver abnormal or injury was proportional to the severity of the disease, which largely proves that liver injury was a secondary reaction of systemic injury[15, 16]. As almost all patients had liver tests on admission and hospitalization, liver test abnormality can be used as an indicator of disease progress, attention should be paid to the changing trend of liver function in patients especially severe cases.

Because no effective and accepted antiviral treatment regimen for COVID-19, symptomatic and supportive treatments are crucial. Many patients were treated with antiviral, NSAIDS, corticosteroid and antibiotics. However, both antiviral drugs (lopinavir/ritonavir, arbidol tablets), antibiotics (moxifloxacin) and acetaminophen have adverse reactions, including liver injury. A recent study reported that moderate microvascular steatosis and mild lobular and portal activity were present in liver biopsy specimens, indicating that the liver injury could be caused by either SARS-CoV-2 infection or drug-induced liver injury[17, 18]. In our study, the drugs used by patients before admission are mainly antibiotics, antiviral, Chinese herbal medicine and NSAID drugs. We analyzed the prehospital medications and found that there was no statistical difference between liver abnormal and normal groups. However, several patients with normal liver function developed liver abnormal function during hospitalization, the proportion of antibiotics application in patients with those patients in our study was significantly higher than that without liver abnormal, which supporting the diagnosis of drug-induced liver injury.

Our study still presented some limitations. This study was retrospective, and some cases had incomplete documentation for the history of prehospital. Moreover, all data were collected from a single center at a certain timepoint. So, the sample size is relatively limited, and these findings cannot be generalized to rural communities or other regions of varying epidemiological characteristics. In addition, statistical errors cannot be fully excluded because of the small sample size. Furthermore, as very few patients had underlying liver disease (only 3 patients), the potential influence of underlying liver disease on COIVD-19 liver abnormality or injury cannot be assessed. As new cases are emerging globally, further studies in large patient series are warranted to corroborate the pathogenic mechanism.

# 5. Conclusion

In conclusion, we estimated the clinical characteristics of COVID-19 in patients with abnormal liver test results. Liver injury in COVID-19 patients was an independent predictor of a poor prognosis. The COVID-19-related liver damage may be considered as the result of secondary liver damage caused mainly by several factors, such as the use of potentially hepatotoxic drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, and liver response to disease severity. Hypoxia and

disease severity account for the largest proportion. Attention should be paid to monitor the occurrence of liver injury in clinical practice, especially in severe cases.

# Abbreviations

Middle East respiratory syndrome coronavirus(MERS-CoV)

multiple organ failure(MOF)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

gamma-glutamyl transferase (GGT)

alkaline phosphatase (ALP)

angiotensin-converting enzyme (ACE)

upper limit unit of normal (ULN)

nonsteroidal anti-inflammatory drugs (NSAID)

lactate dehydrogenase (LDH)

hypersensitive c-reactive protein(hsCRP)

interleukin (IL)

tumor necrosis factor (TNF-α)

erythrocyte sedimentation rate (ESR)

procalcitonin (PCT)

# Declarations

**Ethics approval and consent to participate:**

This study was approved by the Ethics Committee of the Peking University First Hospital(Number: 2020-271) and was exempted from the need for informed consent from patients.

**Consent for publication:**

Not applicable.

**Availability of data and materials:**

All data generated or analyzed during this study are included in this published article.

**Competing interests:**

All authors confirm that there are no conflicts of interest.

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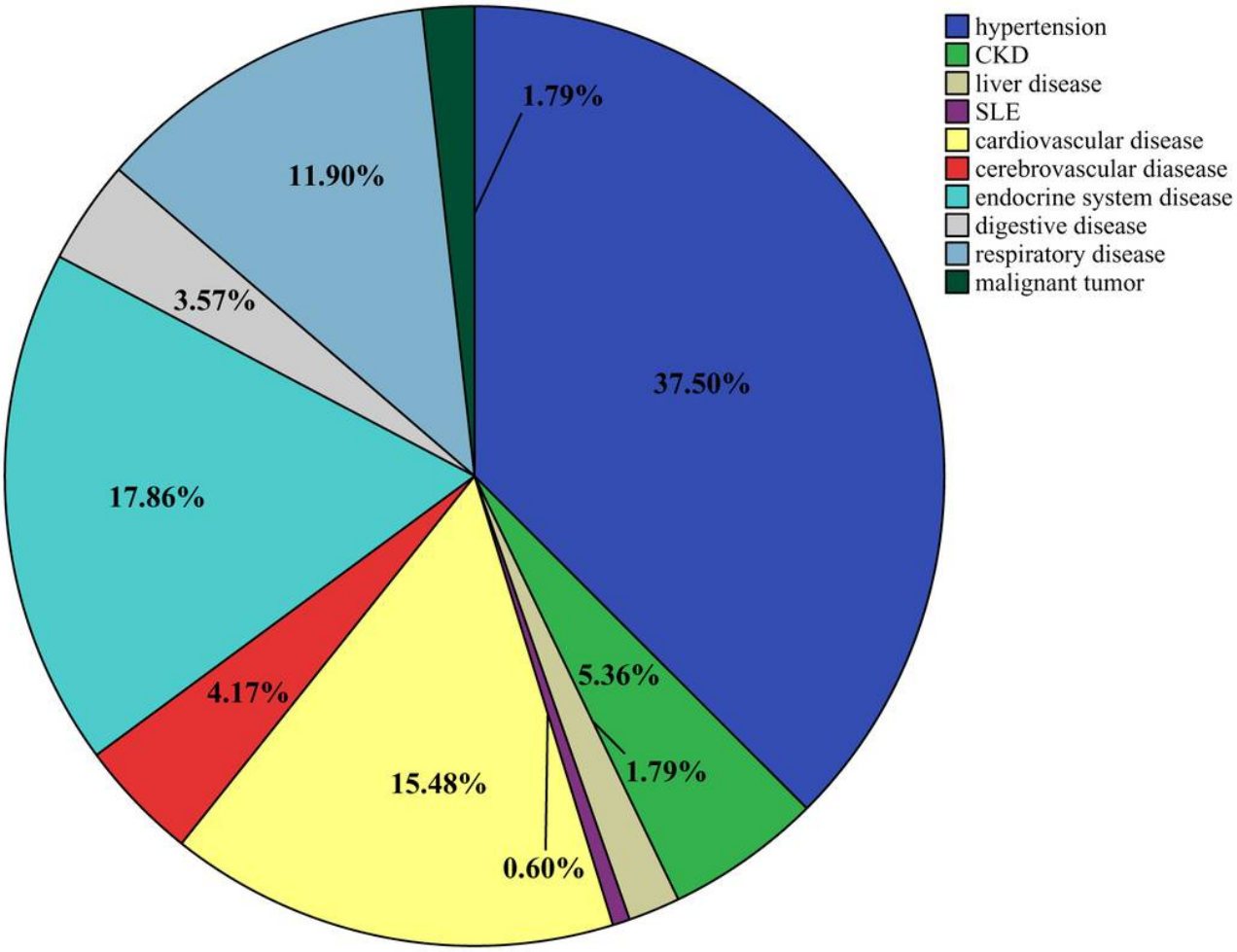
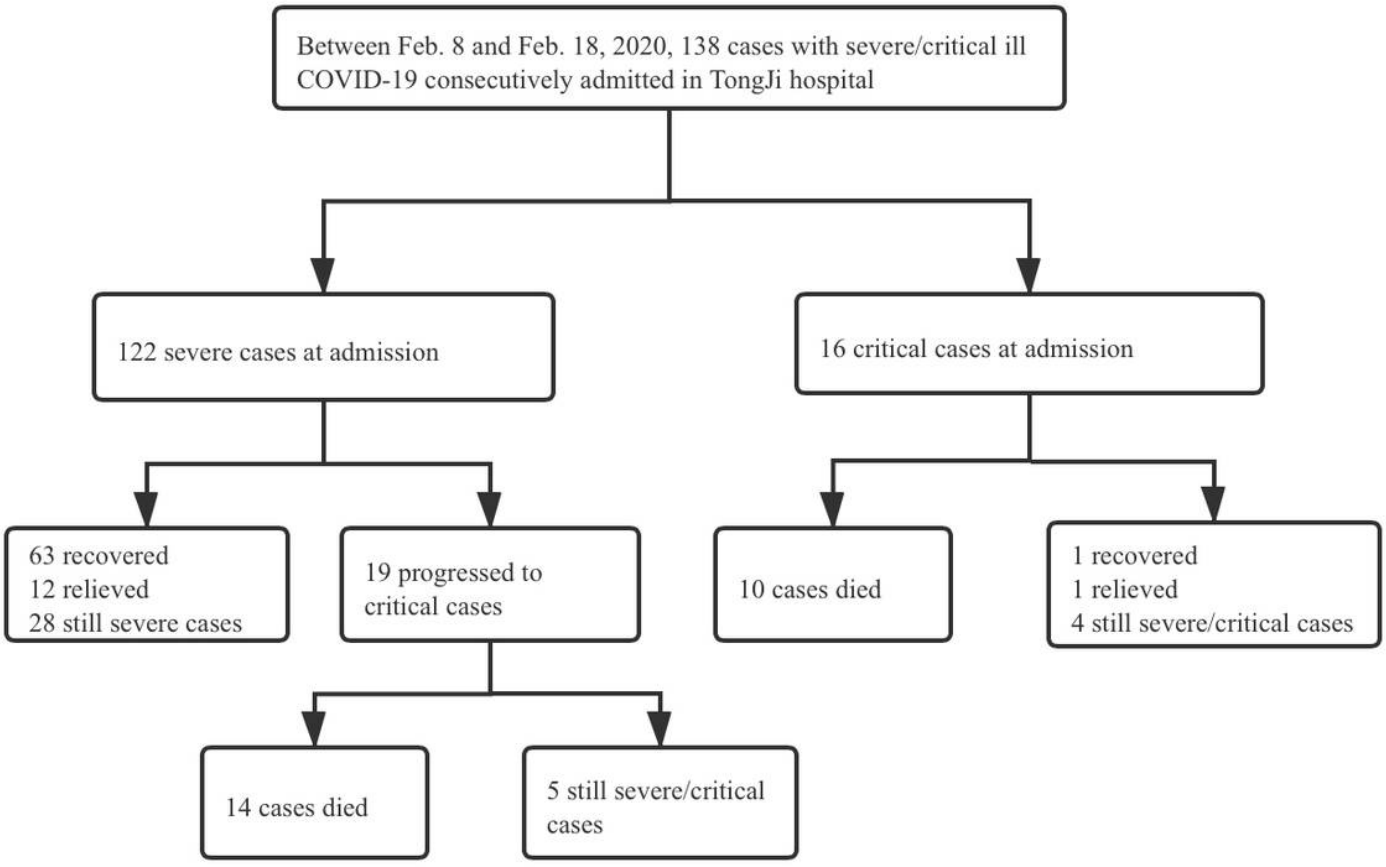
# Figures




## Figure 1

The composition and percentage of underlying diseases. CKD: chronic kidney disease, SLE: systemic lupus erythematosus.




## Figure 2

The flow sheet reflecting the patient cohort including those patient's prognosis.