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Association of liver abnormalities with in-hospital mortality in patients with COVID-19

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Background & Aims: The evolution and clinical significance of abnormal liver chemistries and the impact of hepatitis B infection on outcome in patients with COVID-19 is not well characterized. This study aimed to explore these issues.

Methods: This large retrospective cohort study included 2,073 patients with coronavirus disease 2019 (COVID-19) and definite outcomes in Wuhan, China. Longitudinal liver function tests were conducted, with associated factors and risk of death determined by multivariate regression analyses. A prognostic nomogram was formulated to predict the survival of patients with COVID-19. The characteristics of liver abnormalities and outcomes of patients with COVID-19, with and without hepatitis B, were compared after 1:3 propensity score matching.

Results: Of the 2,073 patients, 1,282 (61.8%) had abnormal liver chemistries during hospitalization, and 297 (14.3%) had a liver injury. The mean levels of aspartate aminotransferase (AST) and direct bilirubin (D-Bil) increased early after symptom onset in deceased patients and showed disparity compared to levels in discharged patients throughout the clinical course of the disease. Abnormal AST (adjusted hazard ratio [HR] 1.39; 95% CI 1.04–1.86, p = 0.027) and D-Bil (adjusted HR 1.66; 95% CI 1.22–2.26; p = 0.001) levels at admission were independent risk factors for mortality due to COVID-19. A nomogram was established based on the results of multivariate analysis and showed sufficient discriminatory power and good consistency between the prediction and the observation. HBV infection in patients did not increase the risk of poor COVID-19-associated outcomes.

Conclusions: Abnormal AST and D-Bil levels at admission were independent predictors of COVID-19-related mortality. Therefore, monitoring liver chemistries, especially AST and D-Bil levels, is necessary in hospitalized patients with COVID-19.

Keywords: COVID-19; Aspartate aminotransferase; Direct bilirubin; Hepatitis B; Liver injury.
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Lay summary: Liver test abnormalities (in particular elevations in the levels of aspartate aminotransferase [AST] and direct bilirubin [D-Bil]) were observed after symptom onset in patients who went on to die of coronavirus disease 2019 (COVID-19). Abnormal levels of AST and D-Bil at admission were independent predictors of COVID-19-related mortality. HBV infection in patients did not increase the risk of poor COVID-19-associated outcomes.

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has spread rapidly worldwide.[1] As a new, highly contagious disease, COVID-19 was first reported with characteristics of viral pneumonia, such as fever, dry cough, and lymphopenia, with ground-glass opacities on chest CT imaging. In addition, alterations in liver chemistries were found in patients with COVID-19.[2] A previous study revealed that liver abnormalities occurred more frequently in severely or critically ill patients with COVID-19.[3] Pathological examination of liver tissues from deceased patients with COVID-19 confirmed that liver involvement of COVID-19 was characterized by microvesicular steatosis, focal necrosis with infiltration of lymphocytes, and microthrombosis in the portal area.[4] Given the alterations in liver function tests and liver impairment in pathological findings in patients with COVID-19, the clinical course and outcome of patients with COVID-19 and liver abnormalities needed to be explored. In addition, the relationship between liver chemistries and in-hospital deaths due to COVID-19 remains controversial.

This large, retrospective cohort study conducted at 3 centers of a designated hospital for treating COVID-19 in Wuhan, China, reported the dynamic characteristics of alteration in liver chemistries in patients with COVID-19. In addition, the association between liver abnormalities and in-hospital outcomes of patients with COVID-19 was investigated. The present study established a predictive model based on the baseline characteristics at admission in patients with COVID-19, including liver abnormalities. Moreover, the characteristics and outcomes of patients with COVID-19 and hepatitis B, as well as other liver diseases, were described and investigated.

Patients and methods

Study design, participants, and data collection

This retrospective study (TJ-COVID19-LI) was conducted on patients with COVID-19 discharged or deceased in 3 centers (Main District, Sino-French Branch, and Optical Valley Branch) of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) from January 18 to April 25, 2020. The diagnosis of COVID-19 was made according to the interim guidance of the World Health Organization.[5] The hospitalization of the patients was based on the criteria proposed by the National Health Commission of China guidelines for the management of COVID-19. In detail, hospitalized patients were laboratory-confirmed patients with symptoms of fever, or respiratory symptoms such as cough or dyspnea, showing the radiologic features of viral pneumonia.[4] The inclusion and exclusion criteria of this study are listed in Table S1. This study was approved by the Institutional Review Board (IRB) of Tongji Hospital (Approval No.: TJ-IRB20200342). Written informed consent was waived by the IRB of Tongji Hospital for the rapidly emerging infectious disease and because of the retrospective nature of the study.

The electronic medical records of all patients from the Tongji Cloud Hospital Information System were reviewed. The data were collected using a standardized data collection form and analyzed by the authors under the Data Process & Application Platform (DPAP, Yidu Cloud). A de-identified patient identification was assigned to each patient in the DPAP to protect confidentiality. A team of experienced clinicians who had been treating patients with COVID-19 reviewed and cross-checked the data. The attending clinicians were approached when the core data in the patients' medical records were unavailable or if any clarifications were needed.

The laboratory testing of patients during hospitalization was conducted in the clinical laboratory of Tongji Hospital. The real-time PCR of nasal and pharyngeal swab specimens was used to test for SARS-CoV-2 RNA as described previously.[6] The laboratory tests included a complete blood count, coagulation profile, serum biochemical tests (including liver and renal function tests, cardiac troponin I [cTnI], lactate dehydrogenase [LDH], high-sensitivity C-reactive protein [CRP], procalcitonin, and cytokines), hepatitis B-related antigen or antibodies, and hepatitis C-related antibodies. Chest CT scans of every patient were performed. The frequency of laboratory tests and examinations was determined by the clinicians treating COVID-19, and serial laboratory data were collected until the discharge or death of every patient.

Definition

The upper limit of the normal range of liver chemistries was determined at the clinical laboratory of Tongji Hospital and is listed in Table S2. Definitions of liver abnormalities, mild liver abnormalities, types of liver abnormalities, liver injury, acute liver injury (ALI), acute liver failure (ALF), acute-on-chronic liver failure (ACLF), the severity of the disease (severe pneumonia or not), complications such as acute respiratory distress syndrome (ARDS) and septic shock, excessive alcohol assumption, diagnosis of cirrhosis and decompensated cirrhosis, metabolic dysfunction-associated fatty liver disease (MAFLD), hepatitis B, and hepatitis C viral infection are listed in Table 1 and Table S3.

Statistical analysis

Detailed statistical analyses are described in supplementary methods. All statistical analyses were performed using R software, version 3.5.1 (R Foundation for Statistical Computing), and statistical significance was determined at p <0.05.

Results

Dynamic characteristics of liver chemistries in patients with COVID-19

A total of 2,073 patients with COVID-19 were included in the analysis of liver function test abnormalities (Fig. S1). At admission, 1,013 (48.9%) patients were diagnosed with severe COVID-19, of whom 200 (9.7% total) died after a median (IQR) interval from symptom onset to death of 22.38 (16.72–32.66) days (Table S4). In the remaining 1,873 patients who survived, the median (IQR) interval from symptom onset to discharge was 39.46 (30.48–52.54) days.

Serial liver chemistries of patients were collected and analyzed. Any liver abnormality was documented in 1,282 (61.8%

Table 1. Clinical classification and definitions of alterations of liver chemistries in this study.

Terminology	Definitions
Liver abnormalities	Liver abnormalities were defined as serum levels of ALT, AST, ALP, GGT, T-Bil, or D-Bil exceeding the ULN.
Liver injury	Liver injury was defined according to clinical guidelines of ACG and BSG in evaluation of abnormal liver blood tests[7,8] and the definition used in previous studies in COVID-19 patients.[7] In detail, liver injury was considered in patients with an increase in ALT or AST of at least 3× ULN, or an increase in ALP, T-Bil or D-Bil of at least 2× ULN.
Mild liver abnormalities	Patients with abnormal ALT, AST, ALP, GGT, T-Bil, or D-Bil serum levels, but symptoms and serologic abnormalities that did not meet the criteria for injury, acute injury or acute failure.
Types of liver abnormalities	Classification of liver abnormalities was based on clinical guidelines of ACG and BSG in evaluation of abnormal liver blood tests.[8,9] Hepatocellular type: if the hepatocellular-related indices including ALT or AST levels were above ULN and ALP level was in the normal range; Cholestatic type: if ALP levels were increased but with normal AST and ALT levels; Mixed type: in the presence of elevation of both ALP and ALT/AST levels; Others: if patterns of liver abnormalities were not matched with types of liver abnormalities mentioned above such as isolated elevation of GGT or bilirubin.
Acute liver injury	Acute liver injury was measured in patients without chronic liver diseases according to the EASL CPGs[10] and the definition used in previous studies in COVID-19 patients.[11] Acute liver injury was considered if patients with liver injury and showing disorder of coagulation (INR ≥1.5) and jaundice (T-Bil level of ≥51 μmol/L (3 mg/dl)) within 26 weeks of the onset of illness.
Acute liver failure	Acute liver injury was measured in patients without chronic liver diseases. Acute liver failure was diagnosed in patients with acute liver injury and manifestations of hepatic encephalopathy (grade ≥2, according to the West Haven criteria[12]).
Acute-on-chronic liver failure	In patients with chronic liver diseases, liver failure was defined according to the acute-on-chronic liver failure consensus recommendations of APASL.[13] Acute-on-chronic liver failure is manifested as an acute (within 4 weeks) increase of serum T-Bil ≥85 μmol/L (5 mg/dl) and disorder of coagulation (INR ≥1.5), as well as clinical ascites or encephalopathy (grade ≥2) in a patient with chronic liver disease.

ALP, alkaline phosphatase; ALT, alanine aminotransferases; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; D-Bil, direct bilirubin; GGT, gamma-glutamyltransferase; INR, international normalized ratio; T-Bil, total bilirubin; ULN, upper limit of normal.

total) patients during their hospitalization, of whom 958 (46.2%) had these at admission. Mild liver abnormalities were documented in 985 (47.5%) patients during hospitalization, of whom 853 (41.1%) had these at admission. Liver injury was documented in 297 (14.3%) patients during hospitalization, of whom 105 (5.1%) already had this at admission (Table 2).

The types of liver abnormalities were hepatocellular in 614 (29.6%) patients at admission and 535 (25.8%) during hospitalization; cholestatic in 57 (2.7%) at admission and 126 (6.1%) during hospitalization; and mixed in 108 (5.2%) at admission and 533 (25.7%) during hospitalization. When referring to specific liver indices, the elevation of alanine aminotransferase (ALT) (43.3% during hospitalization and 24.2% at admission), aspartate aminotransferase (AST) (38.9% during hospitalization and 26.3% at baseline levels), and gamma-glutamyltransferase (GGT) (31.8% during hospitalization and 21.4% at admission) levels was pronounced in patients with COVID-19 (Table 1), whereas the elevation of total bilirubin (T-Bil), direct bilirubin (D-Bil), and alkaline phosphatase (ALP) was less common. Only 7 patients had an isolated elevation of T-Bil. Consistently, kernel density estimates using Gaussian kernels depicted the baseline distributions (tested at admission) and peak values of ALT, AST, ALP, GGT, T-Bil, and D-Bil in patients. The widest separation of distribution between baseline and peak values were observed for ALT, AST, and GGT levels (Fig. S2).

Notably, 73.0% (146/200) of deceased patients had liver abnormalities at admission, and this incidence of liver abnormalities was higher than that in discharged patients (73.0% *vs.* 43.4%, p <0.001). In addition, during hospitalization, the prevalence of liver abnormalities (92.5% *vs.* 58.6%, p <0.001) and liver injury (31.5% *vs.* 3.6%, p <0.001) was also higher in deceased patients. Both baseline and peak values of liver indices were higher in the deceased group, except for the incidence of abnormalities in baseline ALT levels. In addition, abnormal AST and D-Bil levels were most commonly found in liver tests of deceased patients at admission and during hospitalization (Table 2).

In the last liver function tests of 1,873 discharged patients during hospitalization, 594 (31.7%) still showed liver abnormalities, and liver injury was not found. The results of detailed liver chemistries showed that elevated ALT (349 patients, 18.6%) and GGT (323 patients, 17.2%) levels were most commonly seen in patients approaching discharge (Table S5). However, in 200 deceased patients, 85% (170/200) showed liver abnormalities, and 35.5% (77/200) showed liver injury in their last liver function tests before succumbing. In detail, the elevation of AST (117 patients, 58.5%) and D-Bil (104 patients, 52%) were most commonly seen in deceased patients before succumbing (Table S5).

Generalized additive models illustrated the changes in liver chemistries in deceased and discharged patients (Fig. 1). In detail, the mean AST and D-Bil levels in the deceased group increased early after symptom onset and were higher than those in the discharged group throughout the clinical course of COVID-19. Also, the mean levels of ALP, T-Bil, and GGT in the deceased group were comparable with those in the discharged group at symptom onset but then increased and peaked in the late stage of the disease. In addition, the changes in mean ALT levels fluctuated, and the values were close in the deceased and discharged groups.

ALI was found in 10 (0.5%) of 1,869 patients without chronic liver diseases during their hospitalization (Table S4); ultimately, all 10 of these patients died. ALI occurred on day 18.5 (IQR 16.25–30.75) after symptom onset. The occurrence of hepatic encephalopathy and ALF could not be assessed because 8 of the 10 patients with ALI received invasive mechanical ventilation

Table 2. Characteristics of liver abnormalities in patients with COVID-19.

Variables	Total (N = 2,073)	Deceased (n = 200)	Discharged (n = 1,873)	*p* value
Age, years	62.00 [50.00, 70.00]	70.00 [63.75, 78.00]	61.00 [48.00, 69.00]	<0.001
Male	1,024 (49.4)	134 (67.0)	890 (47.5)	<0.001
BMI	23.88 [22.12, 25.66]	24.06 [22.85, 25.51]	23.86 [22.04, 25.69]	0.068
Severe pneumonia	1,013 (48.9)	162 (81.0)	851 (45.4)	<0.001
Hospitalization	13.00 [9.00, 21.00]	11.00 [7.75, 16.00]	14.00 [9.00, 21.00]	<0.001
Liver indices tested at admission				
Liver abnormalities	958 (46.2)	146 (73.0)	812 (43.4)	<0.001
Liver injury	105 (5.1)	26 (13.0)	79 (4.2)	<0.001
Type of liver abnormalities				
Hepatocellular type	614 (29.6)	94 (47.0)	520 (27.8)	<0.001
Cholestatic type	57 (2.7)	9 (4.5)	48 (2.6)	0.172
Mixed type	108 (5.2)	27 (13.5)	81 (4.3)	<0.001
Others	179 (8.6)	16 (8.0)	163 (8.7)	0.838
Elevated ALT	501 (24.2)	56 (28.0)	445 (23.8)	0.213
Elevated AST	545 (26.3)	113 (56.5)	432 (23.1)	<0.001
Elevated ALP	165 (8.0)	36 (18.0)	129 (6.9)	<0.001
Elevated GGT	443 (21.4)	57 (28.5)	386 (20.6)	0.013
Elevated T-Bil	71 (3.4)	22 (11.0)	49 (2.6)	<0.001
Elevated D-Bil	186 (9.0)	66 (33.0)	120 (6.4)	<0.001
ALT, U/L	23.00 [15.00, 37.00]	28.00 [18.75, 42.00]	22.00 [14.00, 37.00]	<0.001
AST, U/L	25.00 [19.00, 38.00]	41.50 [28.00, 59.00]	24.00 [18.00, 35.00]	<0.001
ALP, U/L	67.00 [55.00, 82.00]	75.00 [58.00, 101.00]	66.00 [55.00, 80.00]	<0.001
GGT, U/L	28.00 [18.00, 51.00]	37.00 [25.00, 66.75]	28.00 [18.00, 49.00]	<0.001
T-Bil, μmol/L	8.90 [6.50, 12.40]	11.80 [8.47, 18.72]	8.60 [6.30, 12.00]	<0.001
D-Bil, μmol/L	3.80 [2.80, 5.30]	5.75 [4.30, 9.30]	3.60 [2.70, 5.00]	<0.001
Peak values of liver indices during hospitalization				
Liver abnormalities	1,282 (61.8)	185 (92.5)	1,097 (58.6)	<0.001
Liver injury	297 (14.3)	103 (51.5)	194 (10.4)	<0.001
Type of liver abnormalities				
Hepatocellular type	828 (39.9)	80 (40.0)	748 (39.9)	1
Cholestatic type	58 (2.8)	6 (3.0)	52 (2.8)	1
Mixed type	240 (11.6)	89 (44.5)	151 (8.1)	<0.001
Others	156 (7.5)	10 (5.0)	146 (7.8)	0.199
Elevated ALT	897 (43.3)	122 (61.0)	775 (41.4)	<0.001
Elevated AST	807 (38.9)	165 (82.5)	642 (34.3)	<0.001
Elevated ALP	298 (14.4)	95 (47.5)	203 (10.8)	<0.001
Elevated GGT	659 (31.8)	108 (54.0)	551 (29.4)	<0.001
Elevated T-Bil	228 (11.0)	88 (44.0)	140 (7.5)	<0.001
Elevated D-Bil	372 (17.9)	143 (71.5)	229 (12.2)	<0.001
ALT, U/L	33.00 [20.00, 58.00]	48.00 [28.00, 85.25]	32.00 [19.00, 56.00]	<0.001
AST, U/L	30.00 [21.00, 48.00]	68.00 [43.00, 144.25]	28.00 [20.00, 43.00]	<0.001
ALP, U/L	76.00 [62.00, 95.00]	116.00 [85.75, 176.25]	74.00 [61.00, 90.00]	<0.001
GGT, U/L	37.00 [22.00, 69.00]	69.50 [37.75, 120.25]	35.00 [21.00, 64.00]	<0.001
T-Bil, μmol/L	11.40 [8.50, 16.20]	22.05 [14.55, 33.75]	11.00 [8.20, 15.00]	<0.001
D-Bil, μmol/L	4.60 [3.50, 6.70]	11.95 [7.40, 22.82]	4.40 [3.30, 6.10]	<0.001

Data are presented as medians [IQR], or n/N (%). For group comparisons of continuous variables, Mann-Whitney test was used. In addition, comparison of categorical variables was done using the chi-square test or the Fisher exact test, as appropriate.
ALP, alkaline phosphatase; ALT, alanine aminotransferases; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; D-Bil, direct bilirubin; GGT, gamma-glutamyltransferase; T-Bil, total bilirubin.

under sedation. We then noticed that isolated ALI was not found in patients with COVID-19. ARDS, septic shock, acute kidney injury, and cardiac injury were the most common conditions simultaneously occurring with ALI in patients with COVID-19 (Fig. S3).

Association of alterations of liver chemistries with in-hospital mortality of COVID-19 patients

The association of liver abnormalities with in-hospital death in patients with COVID-19 was explored using Cox proportional hazards model (Tables S6 and S7). After adjustment for age, gender, high BMI, severe pneumonia at admission, metabolic cardio-cerebrovascular disease, liver disease, chronic pulmonary disease, chronic kidney disease, reduced lymphocyte, and platelet counts and albumin levels, and prolonged prothrombin time, elevated interleukin-6, D-dimer, CRP, LDH, procalcitonin, creatinine, and cTnI levels at admission, liver injury during hospitalization was associated with in-hospital mortality (hazard ratio [HR] 4.63; 95% CI 2.34–9.14; p <0.001). Among the types of liver abnormalities, cholestatic (HR 3.99; 95% CI 1.43–11.14; p = 0.008) and mixed types (HR 4.77; 95% CI 2.41–9.41; p <0.001) of liver abnormalities during hospitalization were independently associated with in-hospital death (Table S7). In addition, adjusted HRs for the associations between specific liver indices and all-cause mortality were also analyzed. Table S7 shows that patients with abnormal AST, ALP, GGT, T-Bil, or D-Bil levels during hospitalization had a higher mortality risk compared to patients with normal levels of these liver indices.

We further explored the value of abnormal admission levels of liver chemistries in predicting in-hospital mortality. After

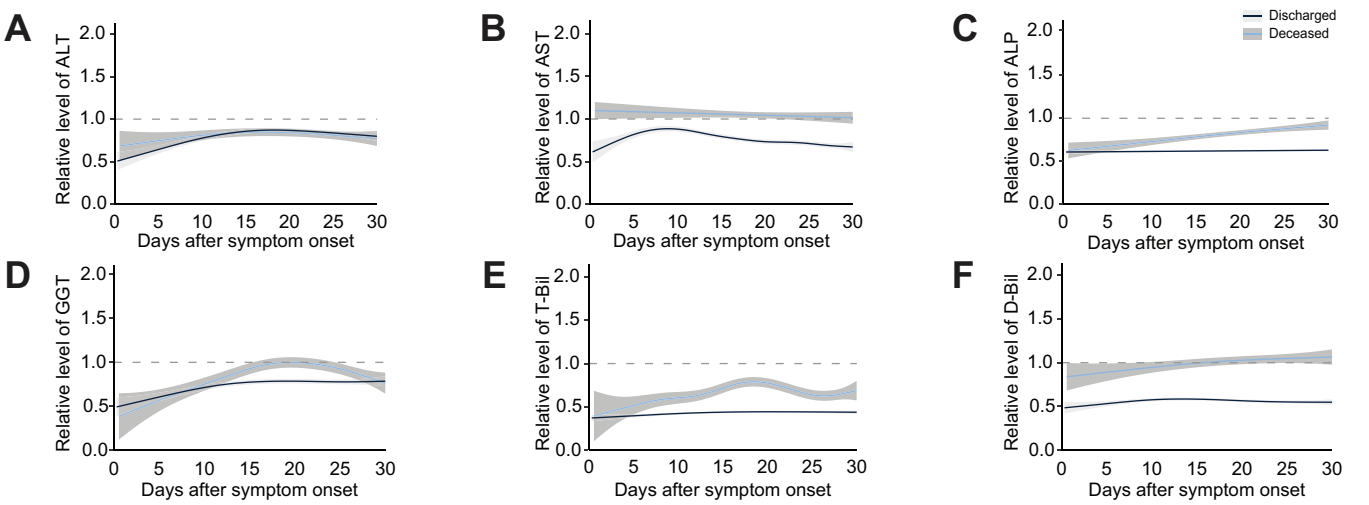

Fig. 1. Temporal changes of liver chemistries in the clinical course of patients with COVID-19. Trajectories of mean (A) ALT, (B) AST, (C) ALP, (D) GGT, (E) T-Bil and (F) D-Bil in the clinical course of deceased and discharged patients with COVID-19, with 95% confidence band (grey) based on generalized additive model. ALP, alkaline phosphatase; ALT, alanine aminotransferases; AST, aspartate aminotransferase; D-Bil, direct bilirubin; GGT, gamma-glutamyltransferase; T-Bil, total bilirubin.

similar adjustment, liver injury at admission was also associated with in-hospital death due to COVID-19 (HR 2.08; 95% CI 1.25–3.44; $p = 0.005$). In addition, abnormal AST and D-Bil levels at admission showed predictive potential for in-hospital death in COVID-19, with HRs of 1.61 (95% CI 1.20–2.15, $p = 0.001$) and 1.57 (95% CI 1.14–2.16, $p = 0.006$), respectively. Even among patients without severe pneumonia at admission, those with liver injury (5.9% *vs.* 2.0%, $p = 0.002$) or abnormal AST (9.8% *vs.* 2.0%, $p < 0.001$) or D-Bil levels (14.3% *vs.* 3.0%, $p < 0.001$) were more likely to die (Table S8).

Based on a backward stepwise selection with Akaike information criterion of multivariate Cox regression analyses and to avoid multicollinearity among liver chemistries, 2 prognostic models were selected (Fig. 2). In model 1, liver injury at admission was independently associated with the risk of in-hospital death (HR 1.87; 95% CI 1.23–2.85; $p = 0.003$). In the second model, abnormal AST (HR 1.39; 95% CI 1.04–1.86; $p = 0.027$) and D-Bil (HR 1.66; 95% CI 1.22–2.26; $p = 0.001$) levels at admission were independent risk factors for in-hospital death. The goodness of fit was similar across these models, with a C-index value of 0.876 (95% CI 0.833-0.918, model 1) and 0.887 (95% CI 0.844-0.929, model 2).

Next, we visualized the second regression model with a higher C-index using a nomogram. Each prognostic factor was assigned a score based on the top scale of the nomogram. By adding up these scores to the total on the bottom scale, the 14-, 21-, and 28-day overall survival of patients with COVID-19 were predicted (Fig. 3). The calibration plots on bootstrap resampling validation showed good consistency (Fig. S4).

Clinical characteristics and outcomes of patients with COVID-19 accompanied by hepatitis B and other pre-existing liver diseases

A total of 204 patients among the included 2,073 patients had pre-existing liver diseases, including hepatitis B (134 patients), HCV infection (39 patients), MAFLD (20 patients), and compensated cirrhosis (11 patients; etiology: HBV infection [n = 5], HCV infection [n = 1], HBV/HCV co-infection [n = 1], alcohol abuse [n = 1], schistosomiasis [n = 2], unknown [n = 1]). In addition, the initial cohort comprised 3 patients with decompensated cirrhosis (etiology: HBV infection [n = 3]), who were excluded from the final cohort of 2,073 patients. The characteristics of the patients with COVID-19 and hepatitis B (HBV group) *vs.* patients without liver diseases (normal group) are listed in Table S9. All patients in the HBV group had available hepatitis B e-antigen status, and 119 (88.8%) had negative hepatitis B e-antigen. The in-hospital mortality was 6.0% (8/134) in the HBV group. Only 4 patients showed peak ALT levels ≥5x the upper limit of normal (ULN) (hepatitis flare) during hospitalization. ACLF was found in 1 of 134 patients with hepatitis B during hospitalization. In this patient, ACLF developed on the 10th day after symptom onset, accompanied by ARDS with mechanical ventilation for 3 days; the patient died on the 8th day after ACLF development (Fig. S5).

In addition, we performed propensity score matching (3:1) for baseline confounders that could possibly interfere with the association of hepatitis B and all-cause mortality. There was no difference in the mortality between patients with HBV and those without liver disease (6.0% *vs.* 6.2%, $p > 0.99$). The Kaplan-Meier curves of the matched HBV and normal groups further confirmed that the survival rates and curves of these groups were similar (Fig. 4). Further, no statistically significant difference in the baseline levels and peak values of liver chemistries were found between the matched HBV and normal groups. The trajectories of liver chemistries in the matched HBV and normal groups were close to each other throughout the clinical course of COVID-19 (Fig. S6).

The characteristics of patients with HCV infection, MAFLD, and cirrhosis in this study are shown in Table S10. Three patients with decompensated cirrhosis, who were in the initial cohort of 2,601 patients but were excluded from the cohort of 2,073 patients, were included in the analysis on liver abnormalities in COVID-19 to investigate the impact of COVID-19 on patients with decompensated cirrhosis. The prevalence of liver abnormalities in these patients was higher than that in patients without liver diseases, whereas the prevalence of liver injury in patients without decompensated liver function was comparable with that

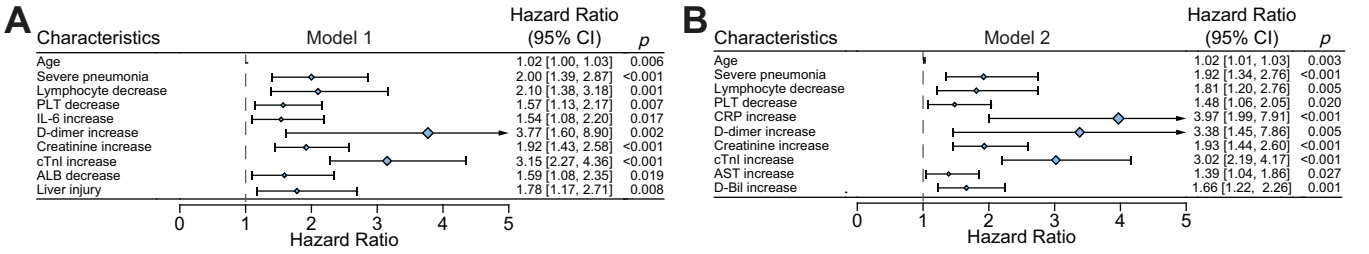

Fig. 2. Prognostic models for the fatal outcome in COVID-19. Two prognostic models, based on multivariable cox regression analyses, which included (A) liver injury at admission, or (B) abnormal AST and D-Bil levels at admission, and other baseline findings, were obtained after backward stepwise selection with Akaike information criterion. The hazard ratios and the 95% CIs associated with COVID-19 mortality in each model were presented. ALB, albumin; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; cTnI, cardiac troponin I; D-Bil, direct bilirubin; PLT, platelet count; PT, prothrombin time.

in patients without liver diseases. Notably, none of the 3 patients with COVID-19 and decompensated cirrhosis were diagnosed as having severe pneumonia at admission, whereas ACLF developed in 2 (66.7%) patients with a time interval from admission to ACLF of 6 and 7 days. Jaundice and ascites were found in both of these patients, and finally, 1 patient died on the 14th day after the diagnosis of ACLF (Fig. S7).

Discussion

This study is one of the largest studies evaluating the prevalence and impact of abnormal liver blood tests in patients with COVID-19. It provides robust evidence about the prevalence, pattern, severity, and dynamic changes in liver abnormalities, as well as associated clinical outcomes, in patients with COVID-19 in Wuhan, China. In addition, the clinical characteristics and outcomes of COVID-19 in patients with pre-existing liver diseases, especially in those with hepatitis B, were analyzed.

This study shows that a mild elevation of liver chemistries is most commonly found in patients with COVID-19, whereas liver injury is relatively rare. However, liver injury determined either at admission or during hospitalization is independently associated with in-hospital death after adjusting for baseline confounders. The prevalence and prognostic value of abnormal liver chemistries in COVID-19 varies across different studies[14,15] and are influenced by the baseline characteristics of patients such as age, severity of pneumonia, pre-existing comorbidities, and the presence of multi-organ failure. Moreover, due to the different prognostic power of predicting COVID-19 mortality in different liver indices, even in the same study, different definitions of liver abnormalities and liver injury showed different prognostic power for COVID-19 mortality. For example, a previous study enrolled 417 patients with COVID-19 and used 2 different definitions to classify the patterns of liver abnormalities in COVID-19; the associations between liver abnormalities and COVID-19 severity were significantly different under different definitions.[7] These results suggest that varied definitions of COVID-19-associated liver abnormalities and liver injury limited the possible comparisons of different studies. Therefore, in the absence of any consensus on liver abnormalities or liver injury in patients with COVID infection, we elected to evaluate the impact of specific liver chemistry parameters.

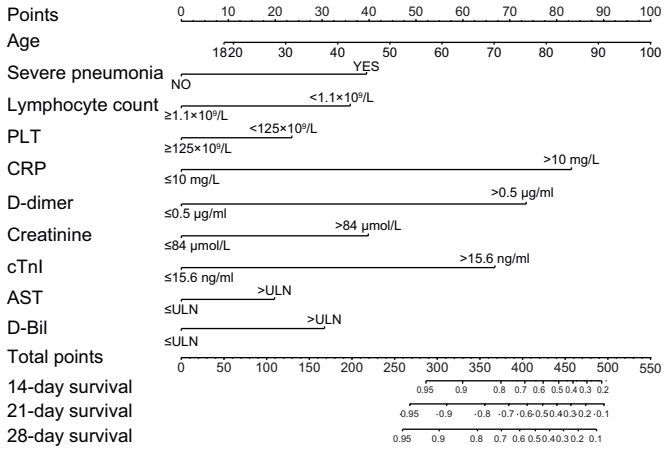

Fig. 3. Prognostic nomogram for predicting the overall survival probability of patients with COVID-19. To use the nomogram, based on the multivariable cox regression model, an individual patient's value (all values of variables are measured at admission) is located on each value axis, and a line is drawn upward to determine the number of points and to predict the overall survival probability of patients with COVID-19. The sum of these numbers is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the likelihood of 14-day, 21-day, and 28-day survival. AST, aspartate aminotransferase; CRP, C-reactive protein; cTnI, cardiac troponin I; D-Bil, direct bilirubin; PLT, platelet count.

This study investigated liver chemistries separately. Our results show that liver abnormalities in COVID-19 are featured by the elevation of AST, ALT, and GGT levels, whereas the alterations in ALP and bilirubin levels are relatively uncommon. These characteristics of abnormalities are consistent with those in previous reports from other cities of China,[7,16] Europe,[17,18] and the United States.[19] In addition, we first report trajectories of liver chemistries in the clinical course of deceased patients with COVID-19 and found that the mean levels of AST and D-Bil increase early after symptom onset in deceased patients and show disparity compared to those in discharged patients throughout the clinical course of the disease. Moreover, we observed that abnormal D-Bil is commonly found during the hospital stay of deceased patients with COVID-19, with its prevalence second only to that of abnormal AST level in liver chemistries, despite the fact that abnormal D-Bil levels are not commonly found in patients with COVID-19. Both baseline and peak abnormal AST and D-Bil levels are independently associated with in-hospital death in patients with COVID-19. Future studies should evaluate the observed association between early AST and D-Bil elevation and mortality in patients with COVID-19.

Due to the retrospective design of this study, the causality of liver abnormalities and fatal outcome in COVID-19 cannot be explored. However, this study reports that liver outcomes, including ALI and ACLF, are rarely found in patients with COVID-

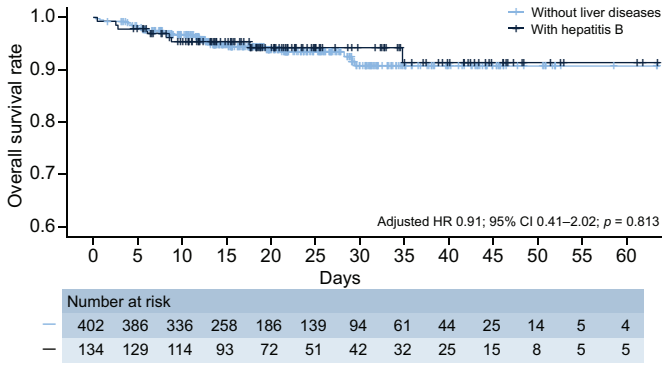

Fig. 4. Kaplan-Meier survival curve for in-hospital mortality of COVID-19 patients with hepatitis B and without liver diseases after propensity score matching. COVID-19, coronavirus disease 2019; HR, hazard ratio.

19. ALI and ACLF develop in the late stage of the disease and are always accompanied by acute multi-organ injuries, such as ARDS and acute kidney injury. These results suggest that the liver is unlikely a key organ driving the mortality due to COVID-19, although liver abnormalities are commonly found in COVID-19.

The present study reports the largest cohort of patients with COVID-19 and hepatitis B. The prevalence of hepatitis B in patients with COVID-19 is similar to that in the general Chinese population[20] and is much higher than that in previous reports.[21] This disparity might be because the serological tests of hepatitis B surface antigen were not performed in all enrolled patients in previous studies, and the results of the present study do not support the hypothesis that HBV has an impact on the susceptibility to SARS-CoV-2 infection. In addition, after adjusting baseline characteristics by propensity score matching between groups, in-hospital mortality in patients with hepatitis B is similar to that in patients without liver diseases. These results suggest that HBV infection does not increase the risk of COVID-19-associated poor outcomes. In addition, SARS-CoV-2 infections might not increase the risk of severe liver impairment in patients with hepatitis B and compensated liver function.

In this study, we do not report increased mortality in patients with liver diseases and with compensated liver function. In contrast, a high prevalence of ACLF and in-hospital mortality is reported in 3 patients with COVID-19 and decompensated cirrhosis. These results are consistent with previous findings that patients with COVID-19 and Child-Pugh B and C cirrhosis show a significantly higher prevalence of hepatic decompensation events and in-hospital mortality compared with those with Child-Pugh A cirrhosis.[19,22] Given the high mortality caused by COVID-19 in patients with decompensated cirrhosis, the present study conforms with the suggestion from the EASL-ESCMID position paper that measures should be taken to protect patients with decompensated cirrhosis from SARS-CoV-2 infection.[23]

This study has several limitations. Firstly, selection bias might be inevitable because the study enrolled only inpatients with COVID-19, and 48.9% of patients in the cohort were diagnosed with severe pneumonia at admission, which is not consistent with the real-world situation that most COVID-19 cases are mild or moderate. Secondly, repeated liver function tests were performed by clinicians at different time intervals for each patient. Therefore, patients with severe pneumonia and liver test derangements might undergo a higher number of tests, leading to bias. Thirdly, liver abnormalities at admission might be influenced by pre-existing liver diseases or other basic conditions of patients, but the pre-hospital status of liver function tests of patients could not be retrieved from the present cohort. Finally, this is a retrospective and observational study, and hence a validation cohort could not be set up to assess the accuracy of the predictive model due to the urgent circumstances of the pandemic. However, the bootstrap resampling cohort was used, and the ideal C-index of the model was presented. Moreover, the calibration curves for survival probability also showed good consistency between the prediction and the observation.

In conclusion, the early onset of elevated AST and D-Bil in patients following hospitalization with COVID-19 was an independent predictor of in-hospital mortality. The proposed nomogram based on abnormal AST and D-Bil levels at admission and other individual characteristics accurately predict the prognosis of patients with COVID-19. Therefore, monitoring liver chemistries, especially AST and D-Bil levels, is necessary in hospitalized patients with COVID-19.

Abbreviations

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; ALI, acute liver injury; ALP, alkaline phosphatase; ALT, alanine aminotransferases; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CRP, C-reaction protein; cTnI, cardiac troponin I; D-Bil, direct bilirubin; GGT, gamma-glutamyltransferase; HR, hazard ratio; LDH, lactate dehydrogenase; MAFLD, metabolic dysfunction-associated fatty liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T-Bil, total bilirubin; ULN, upper limit of normal.

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Conflict of interests

All authors declare no conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

BZ, XC, ZD, and PY designed the study and obtained funding. JH and JL supervised the whole study process and coordinated all the work. ZD, GL, LC, WW, YW, and JS collected the data and prepared the figures and tables. CS, GL, and HF contributed to analytical tools. QC, GJ, TL, PZ, WZ, YL, and BhZ analyzed and interpreted data. WgZ, ZY, WY, YY, HZ, ZT, and HW reviewed and cross-checked the data. ZD wrote the manuscript. All authors critically reviewed and approved the manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found at https://doi.org/10.1016/j.jhep.2020.12.012.

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Author names in bold designate shared co-first authorship

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