Progressive liver injury and increased mortality risk in COVID-19 patients: a retrospective cohort study in China

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Abstract

Background: Liver injury is common and also can be fatal, particularly in severe or critical patients with coronavirus disease 2019 (COVID-19). However, there is lack of an in-depth investigation into the risk factors of liver injury and into the effective measures to prevent subsequent mortality risk. Methods: A retrospective cohort study of 440 consecutive patients with relatively severe COVID-19 between January 28 and March 9, 2020 in Tongji Hospital, Wuhan, China was performed. Data on clinical features, laboratory parameters, medications and prognosis were collected. Results: COVID-19-associated liver injury more frequently occurred in patients aged [?]65 years, or female, or with other comorbidities, decreased lymphocyte count, elevated D-dimer or serum ferritin (all p values<0.05). The disease severity of COVID-19 was an independent risk factors of livery injury (OR 2.86; 95% CI 1.78 to 4.59 in severe patients and 13.44; 95% CI, 7.21 to 25.97 in critical patients). The elevated levels of on-admission aspartate aminotransferase (AST) and total bilirubin (TBIL) indicated the increased mortality risk (both p values <0.001). Using intravenous nutrition or antibiotics increased risk of COVID-19-associated liver injury. Hepatoprotective drugs tended to be of assistance to treat the liver injury and improve the prognosis of patients with COVID-19-associated liver injury. Conclusions: More intensive monitoring with AST or TBIL is recommended for COVID-19 patients, especially aged [?]65 years, or female, or with other comorbidities. Drug hepatotoxicity of antibiotics and intravenous nutrition should be alert for COVID-19 patients.

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Results : COVID-19-associated liver injury more frequently occurred in patients aged [?]65 years, or female, or with other comorbidities, decreased lymphocyte count, elevated D-dimer or serum ferritin (all p values<0.05). The disease severity of COVID-19 was an independent risk factors of livery injury (OR 2.86; 95% CI 1.78 to 4.59 in severe patients and 13.44; 95% CI, 7.21 to 25.97 in critical patients). The elevated levels of on-admission aspartate aminotransferase (AST) and total bilirubin (TBIL) indicated the increased mortality risk (both p values <0.001). Using intravenous nutrition or antibiotics increased risk of COVID-19-associated liver injury. Hepatoprotective drugs tended to be of assistance to treat the liver injury and improve the prognosis of patients with COVID-19-associated liver injury.

Conclusions : More intensive monitoring with AST or TBIL is recommended for COVID-19 patients, especially aged [?]65 years, or female, or with other comorbidities. Drug hepatotoxicity of antibiotics and

intravenous nutrition should be alert for COVID-19 patients.

Keywords : COVID-19; Liver injury; Prognosis; Risk factors; Hepatoprotective drugs;

Introduction

The World Health Organization declared the coronavirus disease 2019 (COVID-19) outbreak on March 11, 2020, and the number of cases and deaths of COVID-19 globally is soaring[1]. On July 11, 2020, more than 10,000,000 confirmed cases of novel coronavirus infection and more than 500,000 deaths had been reported worldwide. The global spread of COVID-19 is an enormous threat to humanity.

Liver impairment has been reported as a common clinical manifestation in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2, 3]. Between 14% and 53% of patients have elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST)[4-7], and a recent study reported that patients with abnormal liver tests were more likely to progress to severe disease[8]. It becomes extremely emergent to treat severe patients and reduce mortality. However, most of the current studies aimed at patients with mild illness, and lacked survival data, leading to the erroneous conclusion that abnormal liver function is not an important issue. Comprehensive and detailed studies on the clinical features, risk factors, and prognosis of patients with liver injury are still lacking, and it is urgent to clarify predictive factors and therapeutic approaches for liver injury.

Here we conducted a retrospective cohort study to identify the risk factors related to liver injury in COVID-19 patients, to evaluate the impact of liver injury on prognosis and to determine whether it is a reliable and independent predictor of disease prognosis, to investigate the efficacy of hepatoprotective drugs in patients with liver injury to provide references for clinical management and treatment. Our results provide relatively comprehensive and reliable references for clinical decisions, thus improving outcomes for COVID-19 patients.

Methods

Study participants

This study was a retrospective observational study. All patients with COVID-19 consecutively admitted to six wards in the Sino-French New City Branch of Tongji Hospital, Huazhong University of Science and Technology, from January 28 to March 9, 2020, were enrolled. Tongji Hospital was designated to treat severe and critical COVID-19 patients by the Wuhan government in January 2020. Follow-up of the clinical outcomes of all patients was censored on March 27, 2020.

Data collection

Sociodemographic characteristics, clinical symptoms, laboratory parameters, chest CT scanning features, outcomes, and medications were extracted from the electronic medical records. We followed laboratory-specific thresholds for all laboratory parameters and categorized each into two or three strata. To quantify the severity of pneumonia, we utilized two scores, i.e., confusion, uremia, respiratory rate, blood pressure, and age [?]65 (CURB-65)[9], and the quick Sequential Organ Failure Assessment (qSOFA)[10].

Definition

COVID-19 patients and disease severity

We included all patients with confirmed COVID-19 according to*Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (trial seventh edition)* by the Chinese National Health Commission[11]. Severity of COVID-19 was categorized into three stages: Severe cases were defined as (i) respiratory rate [?] 30 breaths/min, (ii) oxygen saturation [?] 93%, or (iii) PaO2/FiO2 ratio [?] 300 mmHg. Critical cases were defined as including one or more of the following criteria: shock, respiratory failure requiring mechanical ventilation, in combination with other organ failures, or admission to ICU. Or else, other COVID patients were general cases. In-hospital disease severity were the severest grade during hospitalization.

Liver biochemistry abnormality or injury (LBAI) and acute liver injury (ALI)

COVID-19-related liver injury was divided into three stages as per the Chinese Guideline for COVID-19-related liver injury[12]. Stage 0, normal liver biochemistry (LB), was defined as markers indicating liver function i.e. ALT, AST, TBIL within normal limits. Stage 1, liver biochemistry abnormality (LBA), was defined as liver function markers outside the normal limits but not reaching the thresholds for stage 2. Stage 2, ALI, was defined as an ALT or AST increase of [?]3 times the upper limit of normal, or TBIL increase of [?]2 times the upper limit of normal. In our study, LBAI was defined as either stage 1 or stage 2. Worsening of LB was defined as any stage elevation during hospitalization. Cases were excluded from the study if no data on ALT, AST and total bilirubin (TBIL) were available.

Other terms

We discriminated liver injury associated with COVID-19 by temporal patterns, e.g., admission to the hospital, in-hospital, and cumulative incidence that took both time points into account. We also linked the time of illness onset that refers to the onset of symptoms. Hepatoprotective drugs used in the study included magnesium isoglycyrrhizinate, diammonium glycyrrhizinate, and polyene phosphatidylcholine.

Ethics approval

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from the patients. This study was approved by the ethics committee of Peking University Third Hospital (IRB00006761-M2020060).

Statistical analysis

Categorical variables are summarized as counts (percentages) and continuous variables are presented as the median with interquartile range (IQR). Univariate binary logistic regression was used to explore the factors correlating with cumulative LBAI. The cumulative incidence rates of mortality were assessed using the Kaplan-Meier method and significant differences between the subgroups were determined using the standard log-rank test. Univariable and multivariable Cox proportional hazard regression was used for the survival analysis associated with liver injury markers and other risk factors for mortality. All descriptive statistical analyses were conducted with SPSS version 23.0 (IBM Corp, USA) and analytical analyses were done using R version 4.0.0 (R Foundation for Statistical Computing, Austria). We judged a two-sided p less than 0.05 statistically significant.

Results

Demographic and clinical characteristics associated with LBAI

A total of 440 patients with COVID-19 were included in the final analysis. The median age was 63 years (IQR 18) and 233 (53%) were female. Median follow-up time was 17 days (IQR 21). The total incidence rate of cumulative LBAI was 57.7%, including 15.7% with ALI. The different incidence rates of cumulative LBAI stratified by sociodemographic and clinical characteristics were shown in table 1. The likelihood of cumulative LBAI increased with age of patients, with a 2-fold risk in patients aged [?]65 years compared with those aged 50 years or younger (OR 1.83; 95% CI 1.03 to 3.26). Female patients were at higher risk of cumulative LBAI (OR 2.09; 95% CI 1.46 to 3.06) than males.

Additional significant associated risk factors with LBAI included comorbidities, especially diabetes, vital signs on admission (including temperature, respiratory rate, pulse oximeter O2 saturation, and heart rate), and severity of illness (qSOFA and CURB-65 scores). Compared to general COVID-19 patients, LBAI occurred more often in severe and critical patients with 2-fold (OR 2.86; 95% CI 1.78 to 4.59) and 13-fold (OR 13.44; 95% CI 7.21 to 25.07) higher likelihood, respectively.

Laboratory and imaging features associated with LBAI

The likelihood of cumulative LBAI among COVID-19 patients varied with the laboratory parameters and chest CT imaging features, as shown in table 1. Patients with abnormal counts of blood cells at admission were more prone to later develop cumulative LBAI, especially decreased lymphocyte count (OR 4.10; 95% CI 2.74 to 6.12) and elevated neutrophil count (OR 2.29; 95% CI 1.50 to 3.49). Most biochemical indices at admission indicated the subsequent incidence of cumulative LBAI, such as elevated γ-Glutamyl transferase (GGT), decreased albumin, elevated C-reactive protein. Abnormal coagulation parameters were strongly associated with cumulative LBAI, especially the increase of D-dimer levels, which suggested a 5-fold increase in the likelihood of cumulative LBAI. Serum ferritin, an index of inflammation, also showed a positive association with cumulative incidence of LBAI (OR 6.91; 95% CI 3.8 to 12.57). The presence of bilateral lesions, ground-glass shadows, consolidation, or pleural effusion on CT images all suggested an increased risk of cumulative LBAI (all p values < 0.05).

On-admission LBAI associated with cumulative ALI

Liver function on admission predicted the subsequent risk of cumulative occurrence of ALI among COVID-19 patients to a great extent, as shown in figure 1. The cumulative incidence of ALI over two months was 41.9% (95% CI 31.4 to 51.9%) in patients with on-admission LBAI, dramatically higher than the 9.6% (95% CI 4.7 to 16.5%) in patients with on-admission normal LB ($p < 0.0001$); the risk was 8-fold higher in the LBAI group than that in the normal LB group (HR 8.07; 95% CI 4.23 to 5.37). We also observed similar patterns albeit with moderately reduced effect (HR 4.83; 95% CI 2.45 to 9.54) when on-admission LBA associated with the subsequent risk of in-hospital incidence of ALI was analyzed (supplementary figure 1).

Drugs and treatment associated with LBAI

To address the issue of whether liver dysfunction was caused by drugs commonly used to treat COVID-19, such as antibiotics, antivirus, traditional Chinese medicine/Chinese patent drug, and intravenous nutrition (IVN), we analyzed the association of drugs with subsequent incidence of ALI or LBAI or worsening LB (figure 2 and supplementary figure 2). The results showed that patients who received IVN either on admission or in hospital were associated with cumulative LBAI or ALI; a similar association was found between in-hospital use of antibiotics with subsequent ALI or worsening LB.

Treatment with oxygen therapy by mask, high-flow nasal cannula, or mechanical ventilation were used approximately 6-fold more in patients with cumulative LBAI than those with normal cumulative LB, indicating hypoxia was an important risk factor of LBAI (supplementary table 1).

On-admission and cumulative LBAI associated with increased risk of in-hospital mortality

In this cohort predominated by severe or critically COVID patients, a mortality of 22.3% (98/440) was observed from admission to thereafter two months with substantial differences between mortality in patients with cumulative LBAI and normal cumulative LB (34.3% vs. 5.9%, $p<0.0001$) (table 2). With the worsening status of liver function on-admission, the mortality risk significantly increased from double in on-admission LBA (adjusted HR 1.78; 95% CI 1.03 to 3.06) to up to four times the risk in on-admission ALI (adjusted HR 4.00; 95% CI 1.68 to 9.50; figure 3a and supplementary table 2). Even stronger association were noticed when cumulative liver injury instead of that of on-admission was used (figure 3b).

In-depth analysis into single marker indicating liver function revealed that the levels of AST and TBIL but not ALT at admission or at peak were strong risk indicators of mortality (figure 3c-e; supplementary figure 3; supplementary table 2). To clarify the potential impact of existing chronic liver disease on the prognosis, such as hepatitis, fatty liver or cirrhosis, we conducted the sensitivity analysis by removing 12 cases with chronic liver diseases, and found similar results (supplementary table 2). Meanwhile, to clarify the effects of 38 censored patients on the survival analysis, we also conducted another sensitivity analysis and confirmed similar conclusions (supplementary table 2).

In addition, shorter intervals between illness onset to hospital admission (12 days vs. 19 days, $p<0.0001$), longer hospital stays (19 days vs. 12 days, $p<0.0010$), and prolonged time from illness onset to death (25 days vs. 19 days, $p=0.037$) were observed in the patients with cumulative LBAI compared to the patients with normal cumulative LB (table 2).

Dynamics variations of liver function monitoring the risk of in-hospital mortality

The temporal patterns of liver biochemistry parameters over time from illness onset differed by different survival outcomes of COVID-19 patients (figure 4). In general, the levels of ALT, AST, and TBIL varied in a wider range over time in the non-survivors than in the survivors. Although no pronounced elevation of ALT levels was observed especially at the time of admission, there was a smooth decrease over time in the survivors compared to a sharp elevation in the fourth week in the non-survivors. AST and TBIL levels at the time of admission tended to be higher in the non-survivors and showed sharp elevation in the fourth and sixth weeks or continuous elevation until the fifth week, respectively,contrast with almost no variation over time in survivors (figure 4). The peak of ALT, AST, and TBIL happened in the fourth, sixth and fifth week from illness onset, respectively. Additional liver biochemistry markers such as GGT, direct bilirubin, and albumin also presented different time-varying tendency in the non-survivors from that of survivors (supplementary figure 4).

Hepatoprotective drugs associated with a reduced risk of in-hospital mortality

The use of hepatoprotective drugs in the patients with cumulative LBAI tended to attenuate the risk of in-hospital mortality by 38% in the univariate model (crude HR 0.62; 95% CI 0.41 to 0.96; figure 3f; supplementary table 2) compared to their normal LB counterparts, although this association was not significant after adjustment for confounding risk factors such as age, sex, comorbidities, disease severity, lymphocyte count, D-dimer, serum ferritin (adjusted HR 0.67; 95% CI 0.4 to 1.08).

Discussion

In the present retrospective cohort study, we observed a high LBAI prevalence of up to 57.7% and a high mortality of 22.3% in patients hospitalized with relatively severe COVID-19. Some key demographics, clinical features, and lab parameters, e.g., age [?] 65 years, female, comorbidities, the severity of disease, depleted lymphocyte count, abnormal D-dimer and elevated serum ferritin levels were found to be significantly associated with liver injury. On-admission liver function is a reliable predictor of subsequent liver injury. Patients with liver injury had up to four times the risk of mortality. AST and TBIL are factors most strongly related to prognosis and therefore could aid in prognosis monitoring. The use of antibiotics and IVN were associated with liver injury and therefore should be used with caution among COIVD-19 patients. Hepatoprotective drugs tended to favor survival, and their uses deserve recommendations for patients with abnormal liver function.

In some recent studies, elevated levels of ALT and AST were reported in patients with COVID-19, with rates ranging from 14% to 53%[4-7]. The prevalence of liver injury in the present study was higher, partly due to the high proportion of severe and critical COVID-19. Previous studies found that liver injury was common in critically ill patients with COVID-19[4, 6]. Several indices of liver function, including ALT, AST, and TBIL, were significantly elevated in severe COVID-19 cases compared with mild cases[1]. These results were coincident with ours. Besides this, we found some key demographics, e.g., age 65 years or above, female, and comorbidities were significant indicators of liver injury. These demographic characteristics and comorbidities are wind vanes for liver injury and are cue signals which are helpful for intensive care and individualized tailored surveillance.

Multiple explanations for the mechanism of liver injury were proposed to date [13]. It is now thought that COVID-19 itself is a likely cause of liver injury. Liver biopsy specimens of patients who died from COVID-19 show degeneration of hepatocytes and focal necrosis[8]. Abundant SARS-CoV-2 viral particles were observed in hepatocytes[14]. Angiotensin-converting enzyme 2 (ACE2) receptor is the cell entry receptor of SARS-CoV-2, and according to a recent study using single-cell RNA sequencing, ACE2 was highly expressed not only in type II alveolar epithelial cells, but also in bile duct cells[15]. Hence it is hypothesized that SARS-CoV-2 may infect the liver and cause abnormal liver function in these patients[16]. Our findings that the elevated GGT, a cholangiocyte-related enzyme, was strongly associated the increased risk of liver injury, may provide supportive evidence for the hypothesis.

Other causes of ALI may be systemic inflammatory response, hypoxemia, and drug usage [17]. During the course of COVID-19, immune cells can release a group of inflammatory cytokines[18], which cause systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS). SIRS and ARDS can lead to more cell damage and necrosis. This vicious cycle can lead not only to lung damage but also liver damage [19]. Our study observed that depleted lymphocytes, elevated procalcitonin, elevated IL-6, and elevated serum ferritin levels are significant indicators of liver injury, and these markers should be monitored. Many COVID-19 patients who experience different degrees of hypoxemia need to receive oxygen therapy. In theory, hypoxemia in severe COVID-19 pneumonia may lead to hypoxia of liver tissue and abnormalities of liver function[5].

Many COVID-19 patients, especially those who are severe and critically severe, are treated with multiple drugs. Liver injury emerging during the course of disease could be the side effect of drugs or drug interactions. In the present study, we explored the effect of drugs on liver function, and found two commonly used drugs, IVN and antibiotics related with increased risk of LBAI. This indicated that IVN and antibiotics should be given with great caution in patients with COVID-19.

The patients included in the present study were severely ill and the overall mortality was high. The studied wards were rebuilt during the epidemic for severe or critical patients, although in the later part of the study period, we received some general patients. In addition, patients were sometimes transferred to the studied wards late in their illness, contributing to the high rate of poor clinical outcomes. Protecting high-risk individuals to reduce the mortality of COVID-19 patients is a fundamental challenge in managing the pandemic. In addition to old age and underlying comorbidities as the well-established predictors of high risk[20], we found that patients with liver abnormalities were at high risk. In particular, acute liver injury was an independent risk factor with a mortality four times higher than normal liver function. Moreover, progressive liver injury, indicated by liver function markers which were continuously abnormal over the course of disease, strongly predicted mortality in COVID-19. Our findings were supported by a recent study in which AST abnormality was found strongly associated with risk of mortality[21]. However, the design of our study, which included more complete baseline clinical characteristics to effectively adjust for bias, leads to more extensive findings than in previous studies. For instance, TBIL abnormality, not a significant indicator in the earlier study at admission or peak, sensitively indicated subsequent mortality risk in our study; liver injury panel results rather than single indices such as AST were more informative for evaluating both the severity of liver injury and the mortality risk.

To manage the liver injury and thereafter reduced the mortality risk, several tips might be of great assistance. First, treat the underlying liver diseases properly. Second, the therapeutic regimen, e.g. abovementioned antibiotics, with respect to the varieties, doses, and duration should be used cautiously and moderately for the reduced risk of drug-induced liver injury. Third, all COVID-19 patients, particularly at severe or critical stage, were advised to meticulous monitoring of liver associated biochemical indications, such as AST and TBIL, so as to catch liver injury in time. Fourth, for COVID-19 patients, any prophylactic use of drugs to protect the liver is not mandatory. But for patients with LBAI, as the evidence of this present study, the commonly used hepatoprotective drugs could improve survival to some degree.

Our study, which is among the first studies of survival analysis associated with liver injury in COVID-19, provided valuable information on the effective prevention, intensive monitoring, and individualized treatment for COVID-19 patients. However, there are several limitations to be addressed. First, any retrospective single-center study could have selection biases in identifying and recruiting participants. Second, the population size was relatively small. Third, we found that comorbidities were related to liver injury, but a small fraction of patients had various degrees of consciousness disorders at admission which made it difficult to collect detailed medical history.

In conclusion, liver injury is highly prevalent among COVID-19 patients and also can be fatal, particularly in severe or critical patients. More intensive monitoring with AST or TBIL and individualized tailored therapeutics are highly recommended for COVID-19 patients with liver injury, especially in those age [?]65 years, or female, or with other comorbidities. Drug hepatotoxicity should be alert for the use of antibiotics and IVN for COVID-19 patients. When severe liver damage occurs, liver protective drugs are favorable for improved prognosis. Further research should focus on the mechanism of liver injury in COVID-19 and more effective measures to prevent progressive liver injury and mortality risks of COVID-19.

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Figure legends

Fig 1. Cumulative incidence rate of ALI stratified by on-admission LB. Shadows indicate the 95% confidence intervals of the corresponding estimates cumulative incidence rate. ALI, acute liver injury; LB, liver biochemistry; LBAI, liver biochemical abnormality or injury.

Fig 2. Association between drugs and liver injury. **(a)** cumulative incidence of LBAI and drugs used during the whole course. **(b)**cumulative incidence of ALI and drugs used during the whole course.**(c)** in-hospital incidence of ALI and drugs used after admission. (**d**) in-hospital worsening liver biochemistry and drugs used after admission. Univariate model refers to univariate binary logistic regression model. Multivariate model refers to multivariate binary logistic regression model adjusted by age, sex, comorbidities (defined as history of at least one disease out of hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic renal disease, chronic respiratory disease and chronic liver disease), in-hospital disease severity status, lymphocyte count, D-dimer, serum ferritin. OR, odds ratio. CI, confidence interval. ALI, acute liver injury; LB, liver biochemistry; LBAI, liver biochemical abnormality or injury; Antivirus include oseltamivir, arbidol, lopinavir/ritonavir, and some other uncommonly used antiviral drugs.

Fig 3. Cumulative incidence of in-hospital mortality of patients with COVID-19, stratified by liver disease indicators or hepatoprotective drugs . Shadows indicate the 95% confidence intervals of the corresponding estimates: **(a)** stages of on-admission liver injury. **(b)** stages of cumulative liver injury.**(c)** on-admission ALT. **(d)** on-admission AST.**(e)** on-admission TBIL. **(f)** HPD uses in patients with abnormal liver function. LB, liver biochemistry. LBA, liver biochemical abnormality; ALI, acute liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; HPD, hepatoprotective drugs.

Fig 4. Dynamic variations of liver biochemistry from illness onset. Shadows indicate the 95% confidence intervals of the corresponding estimates: **(a)** ALT. **(b)** AST.**(c)** TBIL. ALT, alanine aminotransferase;

AST, aspartate aminotransferase; TBIL, total bilirubin.

Table legends

Table 1 Sociodemographic, clinical characteristics, laboratory parameters, and CT imaging features of 440 patients with COVID-19, stratified by severity of cumulative liver abnormality or injury

Table 2 Outcomes for 440 patients of COVID-19, stratified by severity of cumulative liver abnormality or injury

Table 1Sociodemographic, clinical characteristics, laboratory parameters, and CT imaging features of 440 patients with COVID-19, stratified by severity of cumulative liver abnormality or injury

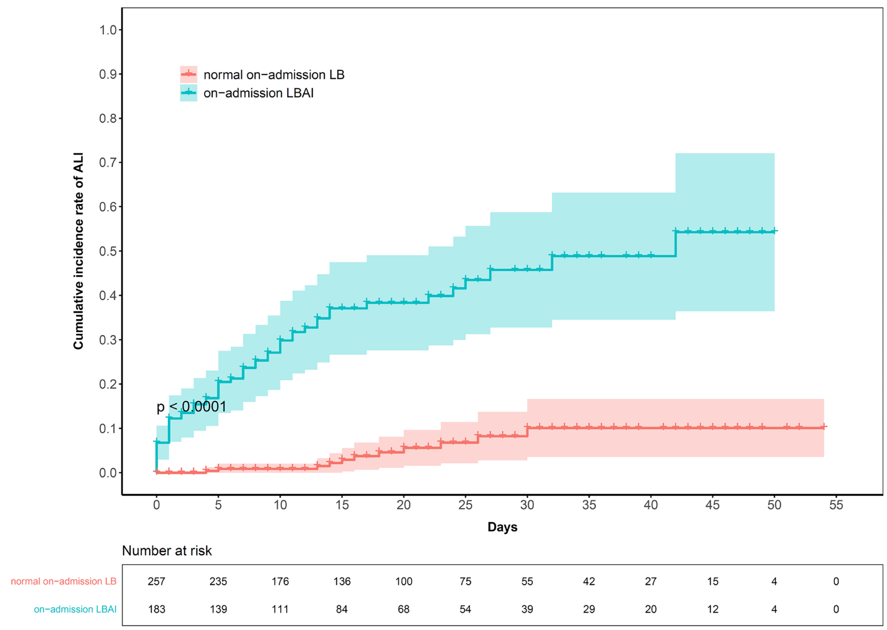
	All patients (n=440)	Normal cumulative LB (n=186)	Cumulative LBA (n=185)	Cumulative ALI (n=69)	Cumulative LBAI (n=254)	p value*
Outcomes						
Discharge	304 (69.1%)	166 (54.6%)	117 (38.5%)	21 (6.9%)	138 (45.4%)	<0.0001[§]
Death	98 (22.3%)	11 (11.2%)	45 (45.9%)	42 (42.9%)	87 (88.8%)	
Still in hospital	38 (8.6%)	9 (23.7%)	23 (60.5%)	6 (15.8%)	29 (76.3%)	
ICU admission	91 (20.7%)	11 (12.1%)	45 (49.5%)	35 (38.5%)	80 (88.0%)	<0.0001
Time from illness onset to hospital admission (median, IQR), days	438	19 (11 to 35)	13 (9 to 19)	11 (8 to 16)	12 (9 to 18)	<0.0001
Hospital stay time (median, IQR), days	402	12 (6 to 22)	19 (11 to 29)	17 (8 to 28)	19 (10 to 29)	<0.0001
Time from illness onset to death (median, IQR), days	93	19 (9 to 26)	23 (16 to 33)	28 (18 to 33)	25 (17 to 33)	0.037
Time from illness onset to discharge (median, IQR), days	303	40 (32 to 49)	40 (34 to 51)	42 (31 to 51)	40 (34 to 50)	0.088
Time from illness onset to last day of follow-up (median, IQR), days	37	61 (52 to 66)	59 (49 to 64)	58 (52 to 67)	59 (51 to 65)	0.689
Time from illness onset to ICU admission (median, IQR), days	90	15 (13 to 25)	18 (11 to 30)	19 (14 to 26)	18 (12 to 26)	0.478
Duration of viral shedding after illness onset (median, IQR), days	298	33 (24 to 42)	30 (25 to 38)	26 (21 to 36)	30 (24 to 38)	0.172

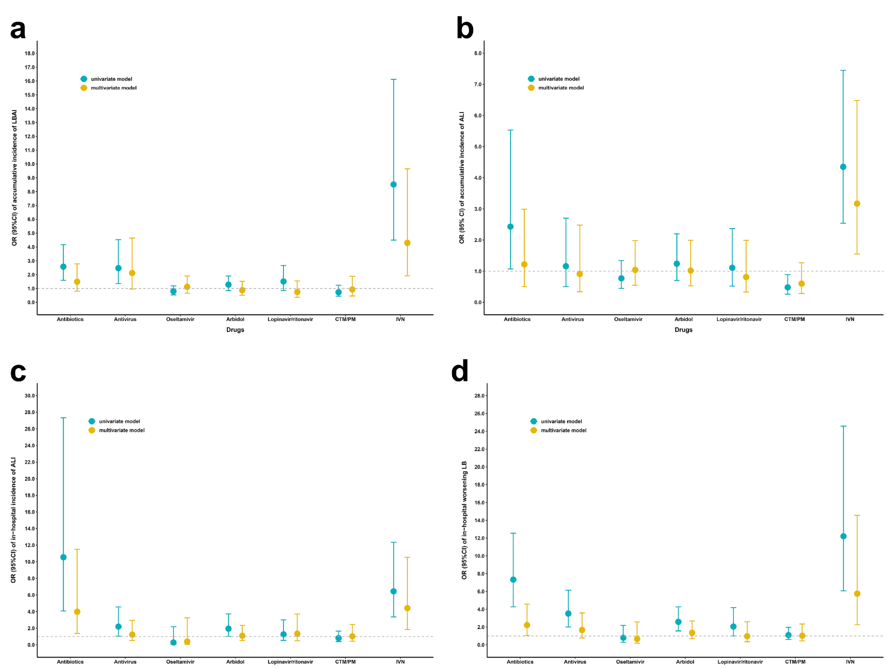
Data are presented as n (%).

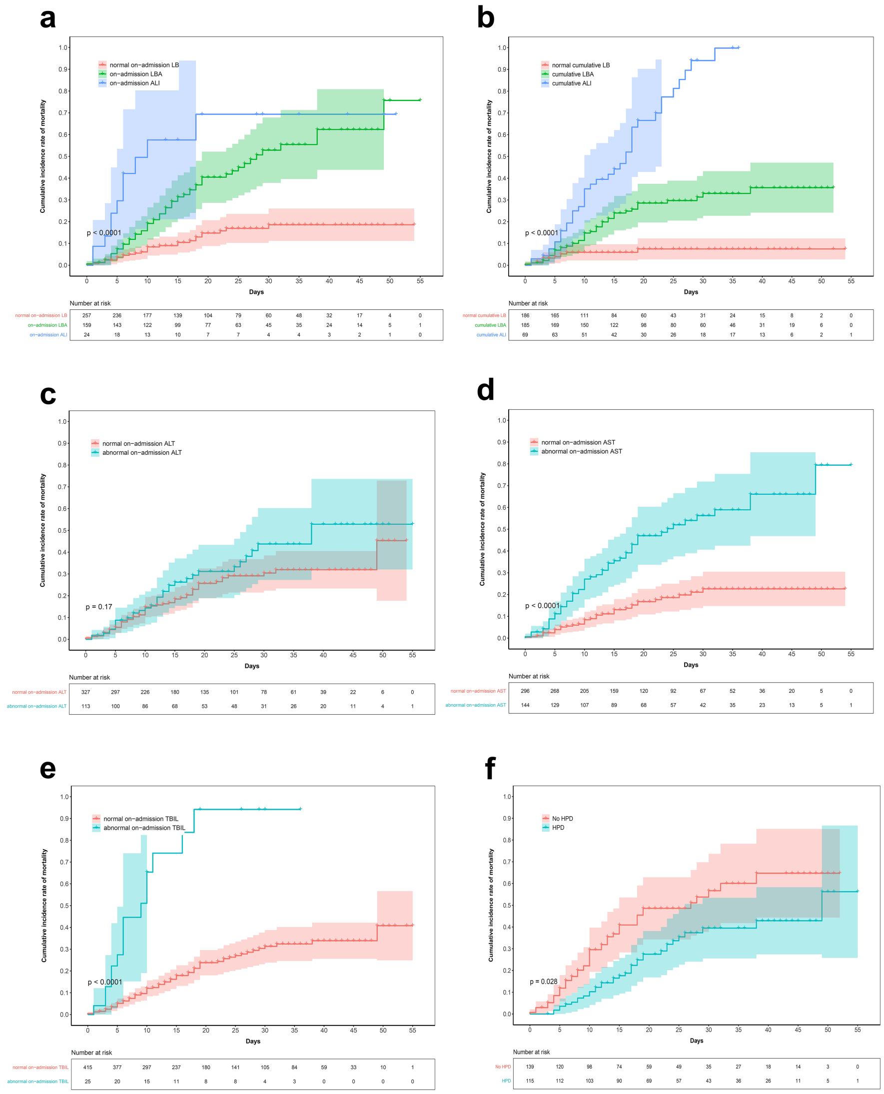
* Comparison of the characteristics between normal cumulative LB and cumulative LBAI were calculated by Pearson's chi-square test for outcomes and a nonparametric Mann-Whitney U test was used for time.

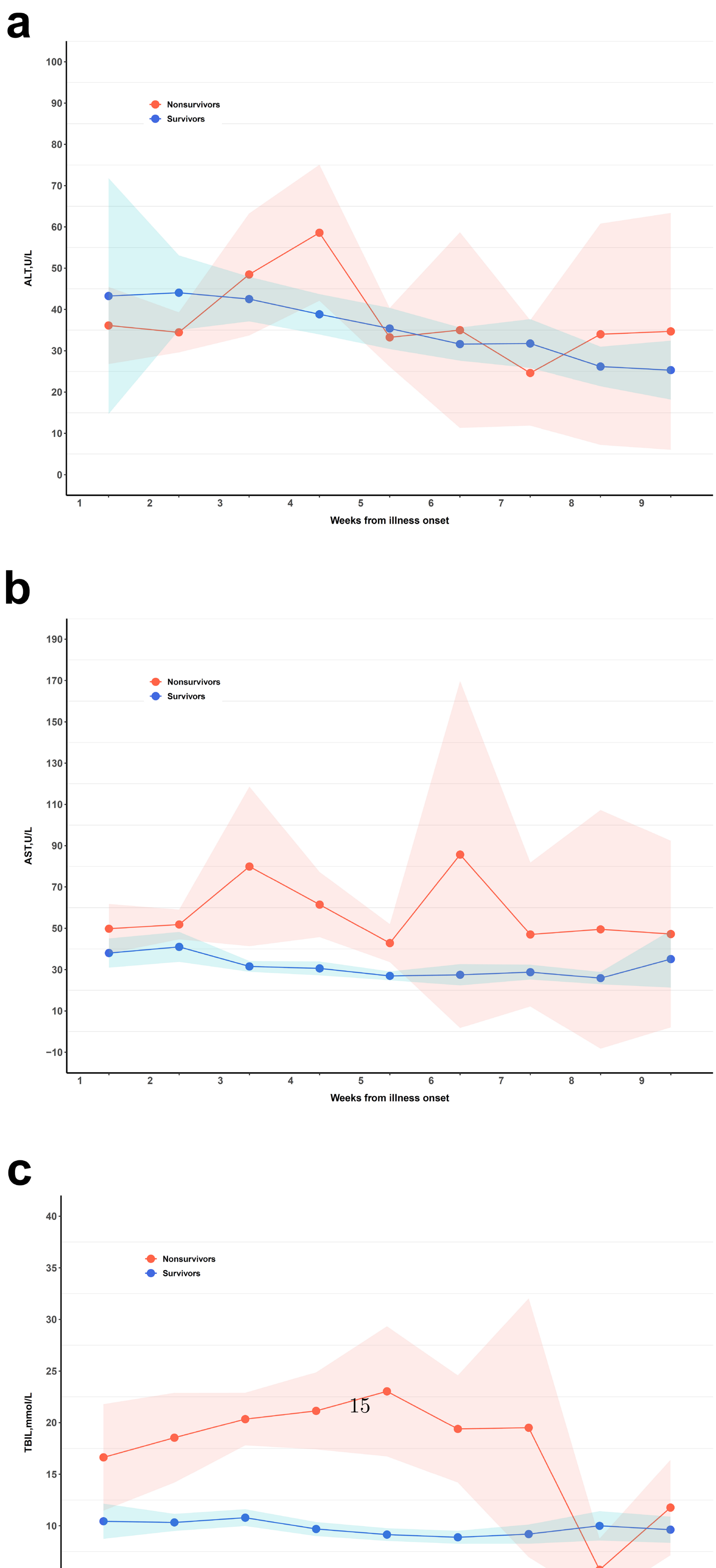
§ Comparison of the distribution of disease outcomes (discharge, death, and still in hospital) between normal cumulative LB and cumulative LBAI.

COVID-19, coronavirus disease 2019; LB, liver biochemistry; LBA, liver biochemical abnormality; LBAI, liver biochemical abnormality or injury; ALI, acute liver injury; ICU, intensive care unit; IQR, interquartile






a
normal on−admission LB
on−admission LBA
on−admission ALI
p < 0.0001
b
normal cumulative LB
cumulative LBA
cumulative ALI
p < 0.0001
c
normal on−admission ALT
abnormal on−admission ALT
p = 0.17
d
normal on−admission AST
abnormal on−admission AST
p < 0.0001
e
normal on−admission TBIL
abnormal on−admission TBIL
p < 0.0001
f
No HPD
HPD
p = 0.028
Cumulative incidence rate of mortality
Days
Number at risk


a
Nonsurvivors
Survivors
ALT,U/L
0
10
20
30
40
50
60
70
80
90
100
1
2
3
4
5
6
7
8
9
Weeks from illness onset
b
Nonsurvivors
Survivors
AST,U/L
−10
10
30
50
70
90
110
130
150
170
190
1
2
3
4
5
6
7
8
9
Weeks from illness onset
c
Nonsurvivors
Survivors
TBIL,mmol/L
10
15
20
25
30
35
40