



Original Article

Coronavirus Disease 2019 and Liver Injury: A Retrospective Analysis of Hospitalized Patients in New York City

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Abstract

Background and Aims: Coronavirus disease 2019 (COVID-19) is a global threat, affecting more than 100 million people and causing over 2 million deaths. Liver laboratory test abnormalities are an extrapulmonary manifestation of COVID-19, yet characterization of hepatic injury is incomplete. Our objective was to further characterize and identify causes of liver injury in patients with COVID-19. **Methods:** We conducted a retrospective cohort study of 551 patients hospitalized with COVID-19 at NewYork-Presbyterian Hospital/Columbia University Irving Medical Center between March 1, 2020 and May 31, 2020. We analyzed patient demographics, liver laboratory test results, vital signs, other relevant test results, and clinical outcomes (mortality and intensive care unit admission). **Results:** Abnormal liver laboratory tests were common on hospital admission for COVID-19 and the incidence increased during hospitalization. Of those with elevated serum alanine aminotransferase and/or alkaline phosphatase activities on admission, 58.2% had a cholestatic injury pattern, 35.2% mixed, and 6.6% hepatocellular. Comorbid liver disease was not associated with outcome; however, abnormal direct bilirubin or albumin on admission were associated with intensive care unit stay and mortality. On average, patients who died had greater magnitudes of abnormalities in all liver laboratory tests than those who survived. Ischemic hepatitis was a mechanism of severe hepatocellular injury in some patients. **Conclusions:** Liver laboratory test abnormalities are common in hospitalized patients with COVID-19, and some are associated with increased odds of intensive care unit stay or death. Severe hepatocellular injury is likely attributable to secondary effects such as systemic inflammatory response syndrome, sepsis, and ischemic hepatitis.

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Abbreviations: ACE2, angiotensin-converting enzyme 2; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease 2019; CUIMC, Columbia University Irving Medical Center; DBIL, direct bilirubin; ICD, International Classification of Diseases; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; ULN, upper limit of normal.

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Introduction

In December 2019, the first cases of coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were identified in Wuhan, China.^{1–3} SARS-CoV-2 has since spread rapidly, infecting more than 100 million people and causing over 2 million deaths worldwide (as of February 3, 2021).⁴ Common symptoms of COVID-19 include fever, cough, dyspnea, and fatigue; multiorgan dysfunction and death can occur in severe cases.⁵ Although several studies have examined hepatic abnormalities in patients with COVID-19, the types and causes of liver injury and the influence of pre-existing liver disease on outcome remain poorly characterized.^{6–10} There are also reported differences in the prevalence of liver laboratory test abnormalities in patients with COVID-19 from different parts of the world.⁶

SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor to enter target cells, where it replicates and infects nearby cells.^{1,11–13} Preliminary reports suggest that ACE2 receptor is expressed in cholangiocytes at a level comparable to alveolar type 2 cells, but is only minimally expressed in hepatocytes, revealing a potential mechanism for direct infection and damage of bile ductules by SARS-CoV-2.¹⁴ While SARS-CoV-2 has been detected in post-mortem liver samples from patients with COVID-19, histopathologic features do not show significant hepatocyte or cholangiocyte damage but rather nonspecific hepatitis and macrovesicular steatosis.^{15–17} This suggests that COVID-19-related liver injury may result from secondary causes.

Previous data from a New York City cohort shows that elevated serum alanine aminotransferase (ALT) activity is common in patients who test positive for SARS-CoV-2.¹⁸ The injury is most often considered mild, although patients with serum ALT more than 5 times the upper limit of normal (ULN) have worse outcomes. In the current study, we characterize abnormalities in ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, and albumin in hospitalized patients with COVID-19. We correlate abnormalities in these parameters at admission and subsequently during hospitalization with clinical outcomes. Finally, we establish a likely etiology of severe hepatocellular injury observed in a subset of patients hospitalized with COVID-19.

Methods

Inclusion criteria and data collection

Study participants were admitted to NewYork-Presbyterian Hospital/Columbia University Irving Medical Center (referred to as CUIMC) between March 1 and May 31, 2020 with an encounter diagnosis of COVID-19 (International Classification of Diseases, Tenth Revision [ICD-10] code U07.1 documented in the problem list), resulting in the inclusion of 551 patients. ICD-10 code U07.1 is only used for a confirmed diagnosis of COVID-19 as documented by the provider. We used this criterium, rather than including all patients with a positive SARS-CoV-2 test result, to exclude patients who may have tested positive while admitted for other reasons but did not experience symptoms of COVID-19. All subjects had a positive reverse transcription-PCR nasal swab for SARS-CoV-2 RNA.

The Columbia University Institutional Review Board approved the protocol with a waiver of informed consent. Patient demographics, laboratory values, vital signs, clinical outcomes, and medical histories were obtained by query of the Epic Systems electronic health record. Outcomes were assessed at the time of data collection on July 21, 2020. Race and ethnicity data were self-reported in prespecified categories. Liver laboratory test abnormalities were defined as: AST >37 U/L, ALT >50 U/L, ALP >129 U/L, direct bilirubin (DBIL) > 0.3 mg/dL, total bilirubin (TBIL) >1.3 mg/dL, and serum albumin <3.9 g/dL, per CUIMC laboratory reference ranges.

Admission laboratory values were defined as results documented closest to and within 60 hours of admission. Admission ALT, AST, ALP, TBIL, and albumin were available for 533 (96.7%) patients, whereas admission DBIL was available for 531 (96.4%). Peak laboratory values were defined as the highest ALT, AST, ALP, DBIL, and TBIL, and the lowest albumin recorded during hospitalization. Peak values for each liver laboratory test were available for 539 (97.8%) patients.

Characterization of liver injury

Liver injury for patients with abnormal ALT and/or ALP was characterized as cholestatic, mixed, or hepatocellular at the time of admission by calculating the R factor, computed as serum ALT/ULN divided by serum ALP/ULN. $R \geq 5$ is considered hepatocellular liver injury, $R \leq 2$ cholestatic, and $2 < R < 5$ is interpreted as a mixed type of liver injury.^{19,20}

Statistical analyses

All analyses were performed using MATLAB R2020a (version 9.8.0.1396136; The MathWorks, Inc., Natick, MA, USA). A p -value ≤ 0.05 was considered statistically significant. Comorbidities and laboratory test results were correlated with mortality and intensive care unit (ICU) admission (primary and secondary outcomes, respectively) using Fisher's exact test for nonrandom association between two categorical variables. Laboratory test result trends were stratified by outcome and plotted against time as the mean of each patient's individual change from their admission level, with error bars representing the 95% confidence interval of each point estimate. Outliers were defined as elements more than three standard deviations from the mean and were removed from these point estimates to prevent large fluctuations caused by a few extreme values.

Table 1. Characteristics of patients hospitalized with COVID-19

| Characteristic | No. (%) |
|--------------------------------------|------------|
| Total no. | 551 |
| Deaths | 115 (20.9) |
| Age in years | |
| <25 | 31 (5.6) |
| 25–49 | 86 (15.6) |
| 50–64 | 149 (27) |
| 65–79 | 194 (35.2) |
| >80 | 91 (14.5) |
| Sex | |
| Female | 235 (42.6) |
| Male | 316 (57.4) |
| Race | |
| Asian | 9 (1.6) |
| African American | 102 (18.5) |
| White | 136 (24.7) |
| Other/Multiracial | 199 (36.1) |
| Declined | 113 (20.5) |
| Ethnicity | |
| Hispanic or Latino | 284 (51.5) |
| Not Hispanic or Latino | 159 (28.9) |
| Declined | 108 (19.6) |
| Body Mass Index in kg/m ² | |
| Underweight, <18.5 | 20 (3.6) |
| Normal, 18.5–24.9 | 127 (23.0) |
| Overweight, 25.0–29.9 | 153 (27.8) |
| Obese, 30.0–39.9 | 150 (27.2) |
| Extremely obese, >40 | 40 (7.3) |
| Unknown | 61 (11.1) |
| Comorbidities | |
| Liver disease | 32 (5.8) |
| Kidney disease | 96 (17.4) |
| Cardiovascular disease | 307 (55.1) |
| Diabetes | 177 (32.1) |

Results

Study cohort characteristics

Clinical characteristics and demographics of the patient cohort are summarized in Table 1. A total of 551 patients met inclusion criteria, of which 170 (30.9%) were admitted to the ICU and 115 (20.9%) died during hospitalization. Mean age was 63 years (range: 1–102 years), 57.4% were male, and 34.5% were obese with a body mass index (BMI) ≥ 30.0 . Only 5.8% of patients suffered from comorbid liver disease.

Mean and median length of hospital stay were 16 days

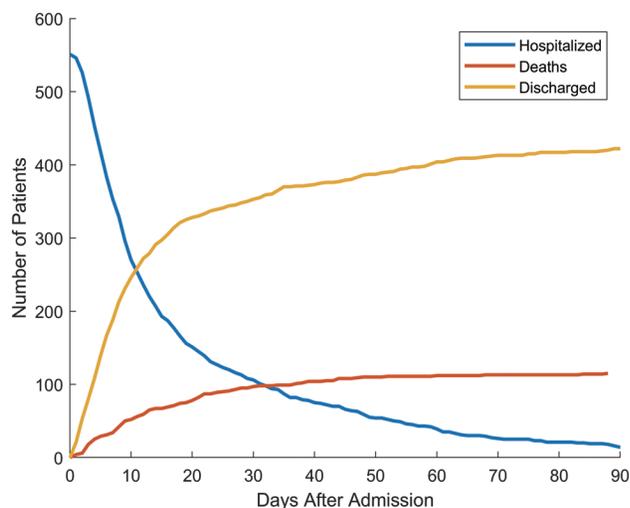


Fig. 1. Hospital course of the patient cohort. A total of 551 patients were studied. At the time of data collection, 115 patients had died, 424 patients had been discharged, and 12 patients remained hospitalized. The mean and median length of hospital stay was 16 days and 9 days, respectively, with a range of 0–104 days.

and 9 days, respectively, with a range of 0–104 days. Over half the patients were discharged or died after 10 days (Fig. 1). At the time of data collection, 12 patients remained hospitalized.

Liver laboratory test abnormalities

Abnormal admission liver laboratory tests were common in patients with COVID-19 (Fig. 2A–F). ALT was abnormally elevated in 28.1%, AST in 61.0%, ALP in 19.1%, DBIL in 18.5%, and TBIL in 7.9%; albumin was below normal in 65.9%. Peak ALT was abnormal in 55.7% of patients, AST in 79.2%, ALP in 39.7%, DBIL in 44.3%, and TBIL in 21.5%; albumin was below normal in 93.0% of patients during their illness (Fig. 2G–L).

For patients with abnormal ALT, ALP, or both at time of admission, we calculated each patient's R factor to determine if the pattern of liver injury was mostly likely cholestatic, hepatocellular, or mixed. The pattern of laboratory test abnormalities suggested that liver injury was most often cholestatic. In 213 patients, 58.2% had a cholestatic injury pattern, 35.2% mixed, and 6.6% hepatocellular (Fig. 3). Given that the rate of abnormal AST elevation (61.0%) was notably higher than the rate of abnormal ALT (28.1%) elevation in our cohort, we computed the R factor for each patient using the admission AST value rather than ALT. In this instance, we found that in the 352 patients with an abnormal AST and/or ALP on admission, 36.1% had a cholestatic injury pattern, 45.4% mixed, and 18.5% hepatocellular.

Association of liver abnormalities with patient outcomes

Certain admission laboratory test abnormalities were associated with ICU admission or death; however, pre-existing liver disease was not (Table 2). Pre-existing cardiovascular disease was associated with increased odds of death. While there was not a significantly increased mortality rate in patients that presented with a history of pre-existing liver dis-

ease, they presented with a significantly higher prevalence of abnormalities in ALP (34.4% vs. 19.1%, $p=0.035$) and TBIL (21.9% vs. 7.9%, $p=0.0086$), but not aminotransferases, DBIL, or albumin. There were no significant differences in the prevalence of abnormal peak liver tests; however, the mean peak DBIL (2.97 vs. 0.77, $p=1.61e-6$) and TBIL (3.74 vs. 1.18, $p=4.29e-7$) were significantly higher in the subcohort of patients with pre-existing liver disease than those with no history of liver disease. Abnormal admission DBIL and albumin were associated with ICU admission and mortality, elevated AST was associated with ICU admission but not mortality, and elevated TBIL was associated with death but not ICU admission. Elevated admission ALT and ALP were not associated with mortality or ICU admission. Mortality risk was increased in patients who presented with normal liver laboratory tests (ALT, AST, ALP, DBIL, TBIL, and albumin) on admission but subsequently had an abnormal ALP, DBIL, or TBIL. A subsequent abnormal ALT, AST, or albumin was not associated with mortality in these patients. The risk of ICU admission was increased in patients who presented with normal liver laboratory tests on admission but had an abnormal ALP or DBIL later during their hospital course. Subsequently abnormal ALT, AST, TBIL, or albumin were not associated with ICU admission in these patients.

Laboratory test result trends showed a rise in mean ALT, AST, ALP, TBIL, and DBIL, and a decrease in mean albumin during the first 14 days of hospitalization (Fig. 4). In patients who died, a spike in mean serum aminotransferase activities occurred around day 8 (Fig. 4A, B), followed by a corresponding increase in ALP (Fig. 4C), DBIL (Fig. 4D), and TBIL (Fig. 4E) about 2 days later. Of patients who survived, a gradual increase in mean ALT, ALP, and DBIL occurred with a corresponding decrease in average serum albumin concentration (Fig. 4F). On average, patients who died had greater magnitude abnormalities in all liver laboratory tests during hospitalization than those who survived.

Patients with COVID-19 and severe hepatocellular injury

During hospitalization, 21 of 551 (3.81%) patients suffered severe hepatocellular injury, defined as an ALT greater than 10 times the ULN. Of these patients, 19 were admitted to the ICU, 17 were intubated, and 9 died. At the time of peak serum ALT activity, 19 had a hepatocellular pattern of injury (R factor ≥ 5), 2 a mixed pattern ($2 < \text{R factor} < 5$), and none had a cholestatic injury pattern (R factor ≤ 2). The mean \pm standard deviation R factor in this subcohort at the time of peak ALT activity was 35.3 ± 37.9 ; the median was 21.1, and range was 3.18–173.

To investigate the etiology of severe hepatocellular liver injury in this subcohort, we plotted the trend of ALT activities along with systemic markers of pathology: mean arterial pressure, body temperature, oxygen saturation, white blood cell count, platelet count, and serum creatinine concentration (Supplementary Fig. 1). One-third of these patients were hypoxic (oxygen saturation $< 90\%$), and 38% showed signs of sepsis indicated by fever (temperature $> 100.4^\circ\text{F}$), and an elevated white blood cell count ($> 8.44 \times 10^3/\mu\text{L}$).

Data from three representative patients that had consistent documentation of laboratory test results and vital signs revealed a pattern consistent with ischemic hepatitis likely secondary to septic shock (Fig. 5). In these cases, mean arterial pressure dropped prior to a spike in serum aminotransferase activities, with subsequent increases in the serum TBIL concentration in two of the three. Associated

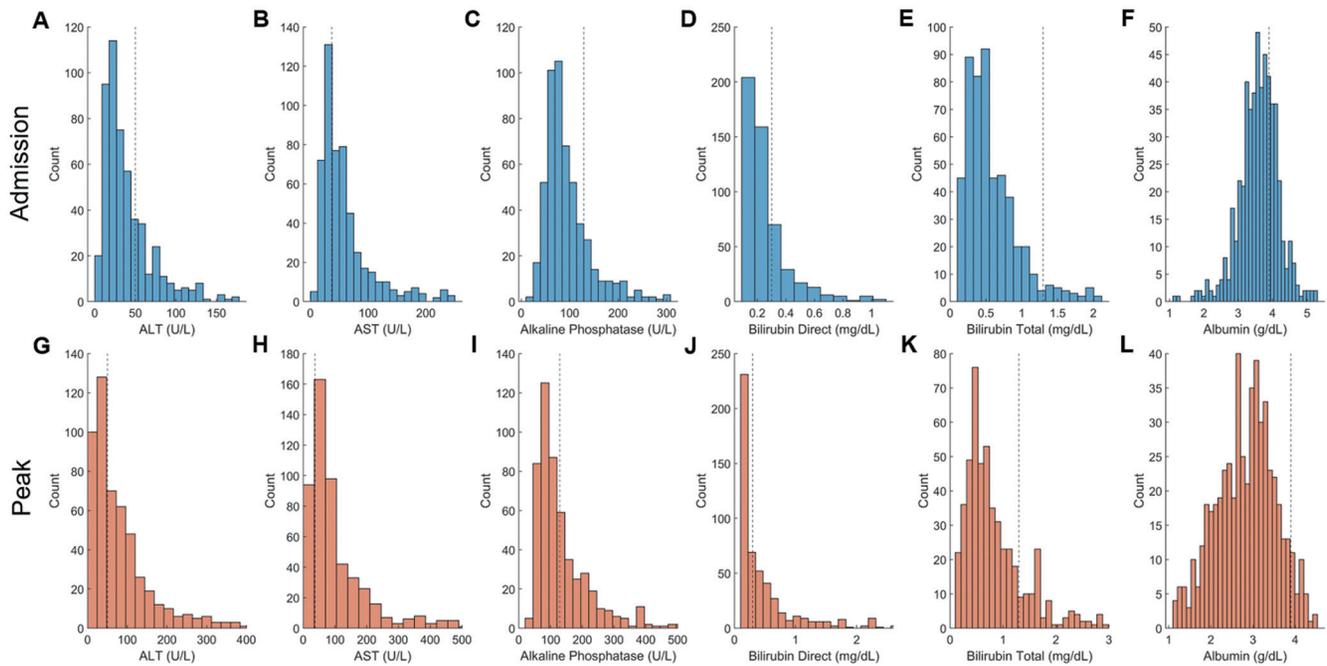


Fig. 2. Histograms of admission and peak liver laboratory test results. ALT (A) was abnormally elevated on admission in 28.1%, AST (B) in 61.0%, ALP (C) in 19.1%, DBIL (D) in 18.5%, and TBIL (E) in 7.9%; serum albumin concentration (F) was below normal on admission in 65.9%. Peak ALT (G) was abnormal in 55.7% of patients, AST (H) in 79.2%, ALP (I) in 39.7%, DBIL (J) in 44.3%, TBIL (K) in 21.5%; serum albumin concentration (L) was below normal in 93.0% of patients. Dashed lines represent the ULN for ALT, AST, ALP, DBIL, and TBIL, and the lower limit of normal for serum albumin. Histograms are scaled to show the bulk of the data; therefore, some outliers are not shown.

increases in the serum creatinine concentrations indicated concurrent kidney dysfunction. Elevated white blood cell counts in all three, and fever in two out of three suggested concurrent infection; decreasing platelet counts suggested possible disseminated intravascular coagulation (Supplementary Fig. 2).

Discussion

Our results show that liver laboratory test abnormalities are common in hospitalized patients with COVID-19. The numbers of patients with abnormalities in these laboratory tests increase during hospitalization. For serum aminotransferase activities, a higher prevalence of elevations in AST compared to ALT may be attributable to non-hepatic sources, as AST is expressed to a great degree in heart, skeletal muscle, and erythrocytes.²¹ Among hospitalized patients with

COVID-19, a subset of about 4% develop severe hepatocellular injury often associated with hypoxia, signs of sepsis, and systemic hypotension.

Our cohort was restricted to patients admitted to a tertiary care academic medical center and, as such, was likely significantly sicker than most patients with COVID-19. We included only patients with an encounter diagnosis of COVID-19, which eliminated subjects who may have been hospitalized for other reasons and subsequently tested positive for SARS-CoV-2. Almost a third of our patients were transferred to the ICU during the course of hospitalization and 20.9% died, resulting in a case fatality rate higher than generally reported previously in most studies.²²⁻²⁵ However, our cohort's case fatality rate was similar to that reported in 5,700 patients hospitalized with COVID-19 in the New York City area.²⁶ Similar to our study, 39.0% and 58.4% of subjects in that cohort had elevated ALT and AST, respectively; however, data on ALP, DBIL and TBIL were not provided.

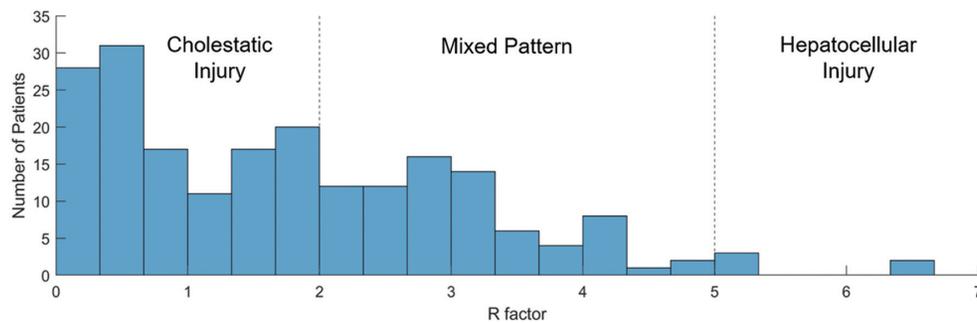


Fig. 3. Liver injury at time of admission in patients with abnormal ALT or ALP results characterized by R factor. In 213 patients with abnormal ALT and/or ALP activities on admission, 58.2% had a cholestatic injury pattern, 35.2% mixed, and 6.6% hepatocellular. Dashed lines at R=2 and R=5 represent the borders between cholestatic, mixed, and hepatocellular liver injury. The plot is scaled to show the bulk of the data; therefore, some outliers are not shown.

Table 2. Correlation of comorbidities and liver-related laboratory tests with outcome

| Comorbidity | Odds of death | | | Odds of ICU admission | | |
|------------------------|---------------|----------------|----------|-----------------------|----------------|----------|
| | OR* | 95% CI** | <i>p</i> | OR | 95% CI | <i>p</i> |
| Liver disease | 0.689 | (0.259, 1.829) | 0.6534 | 0.617 | (0.262, 1.456) | 0.326 |
| Kidney disease | 1.333 | (0.795, 2.233) | 0.2716 | 0.623 | (0.372, 1.042) | 0.877 |
| Cardiovascular disease | 1.649 | (1.075, 2.528) | 0.0264 | 0.866 | (0.602, 1.246) | 0.458 |
| Diabetes | 1.346 | (0.876, 2.067) | 0.1794 | 1.069 | (0.727, 1.573) | 0.767 |
| Obesity: BMI ≥30 | 0.904 | (0.577, 1.416) | 0.733 | 1.072 | (0.730, 1.575) | 0.768 |

| Patients with abnormal liver laboratory tests on admission | | | | | | |
|--|---------------|----------------|----------|-----------------------|----------------|----------|
| Laboratory test | Odds of death | | | Odds of ICU admission | | |
| | OR | 95% CI | <i>p</i> | OR | 95% CI | <i>p</i> |
| ALT | 0.817 | (0.507, 0.316) | 0.478 | 1.460 | (0.981, 2.173) | 0.077 |
| AST | 1.458 | (0.938, 2.268) | 0.1025 | 1.778 | (1.203, 2.627) | 0.0041 |
| ALP | 1.372 | (0.829, 2.272) | 0.225 | 1.183 | (0.749, 1.869) | 0.4780 |
| DBIL | 2.275 | (1.017, 3.953) | 0.0014 | 2.077 | (1.325, 3.257) | 0.0017 |
| TBIL | 2.005 | (1.017, 3.953) | 0.0488 | 1.239 | (0.641, 2.396) | 0.6033 |
| Albumin | 1.947 | (1.204, 3.151) | 0.0069 | 1.926 | (1.278, 2.903) | 0.0016 |

| Patients with normal admission liver laboratory tests but abnormal peak values | | | | | | |
|--|---------------|----------------|----------|-----------------------|-----------------|----------|
| Laboratory test | Odds of death | | | Odds of ICU admission | | |
| | OR | 95% CI | <i>p</i> | OR | 95% CI | <i>p</i> |
| ALT | 1.041 | (0.348, 3.119) | 1.00 | 1.923 | (0.633, 5.846) | 0.290 |
| AST | 1.719 | (0.429, 6.898) | 0.533 | 2.439 | (0.267, 22.291) | 0.657 |
| ALP | 8.017 | (1.235, 12.17) | 0.022 | 15.30 | (4.19, 55.86) | 7.326e-6 |
| DBIL | 2.941 | (2.249, 28.58) | 0.001 | 8.123 | (2.467, 26.748) | 0.0004 |
| TBIL | 6.58 | (1.731, 25.01) | 0.007 | 3.429 | (1.04, 11.302) | 0.0571 |
| Albumin | Inf*** | (Inf, Inf) | 0.181 | Inf | (Inf, Inf) | 0.173 |

*OR, odds ratio; **CI, confidence interval; ***Inf, infinity. *P*-values were calculated using Fisher's exact test for nonrandom association between two categorical variables.

We found no significant association between pre-existing liver disease and clinical outcome, consistent with the findings in a small cohort of 60 patients studied at Massachusetts General Hospital, another academic tertiary care center.²⁷ In contrast, in a study of 363 patients in a single healthcare system in Massachusetts with two tertiary care centers and seven community hospitals, 69 patients with chronic liver disease had worse outcomes, and cirrhosis was an independent predictor of mortality.²⁸ In a USA multi-center study of 2,798 patients, there was also an increased relative risk of mortality in a subset of 250 with pre-existing liver disease.²⁹ The overall severity of illness, high mortality rate, and small number of patients with cirrhosis in our cohort may explain the difference. Similar factors may explain why we did not find a correlation between diabetes mellitus or obesity with poor outcomes.

Certain liver laboratory test results increased the odds of a poor clinical outcome. Evidence of liver dysfunction rather than simply injury, as manifested by an abnormally elevated DBIL either at the time of admission or during hospitalization in patients who initially had normal liver laboratory tests, correlated with an increased risk of both ICU admission and death. At the time of admission, an elevated serum AST, but not ALT, correlated with ICU admission, while

neither correlated with mortality, consistent with a study of patients in the Yale New Haven Health System.³⁰ Elevated AST, more so than elevated ALT, may reflect extrahepatic organ involvement, such as COVID-19-related myocarditis or other myocardial injury.³¹

Elevations in serum liver enzyme activities and bilirubin concentration can occur secondary to systemic infection, systemic inflammatory response syndrome, or sepsis.^{32,33} These are likely causes of serum liver laboratory test abnormalities in our cohort. This is supported by the fact that the serum albumin was below normal in 65.9% of patients on admission and in 93.0% sometime during hospitalization. The half-life of albumin in adult plasma is approximately 3 weeks.³⁴ Therefore, in acute inflammatory states, the decreasing serum albumin concentration is not due to defective hepatic synthesis or secretion, but rather capillary leak, possible kidney dysfunction, or other systemic factors. While some patients in our cohort may have had pre-existing chronically low serum albumin, hypoalbuminemia is strongly associated with systemic inflammatory response syndrome and sepsis.^{35,36} The finding that an abnormal ALP and or DBIL during hospitalization increased the risk of death in patients who had normal liver laboratory test results on admission could also reflect the development of

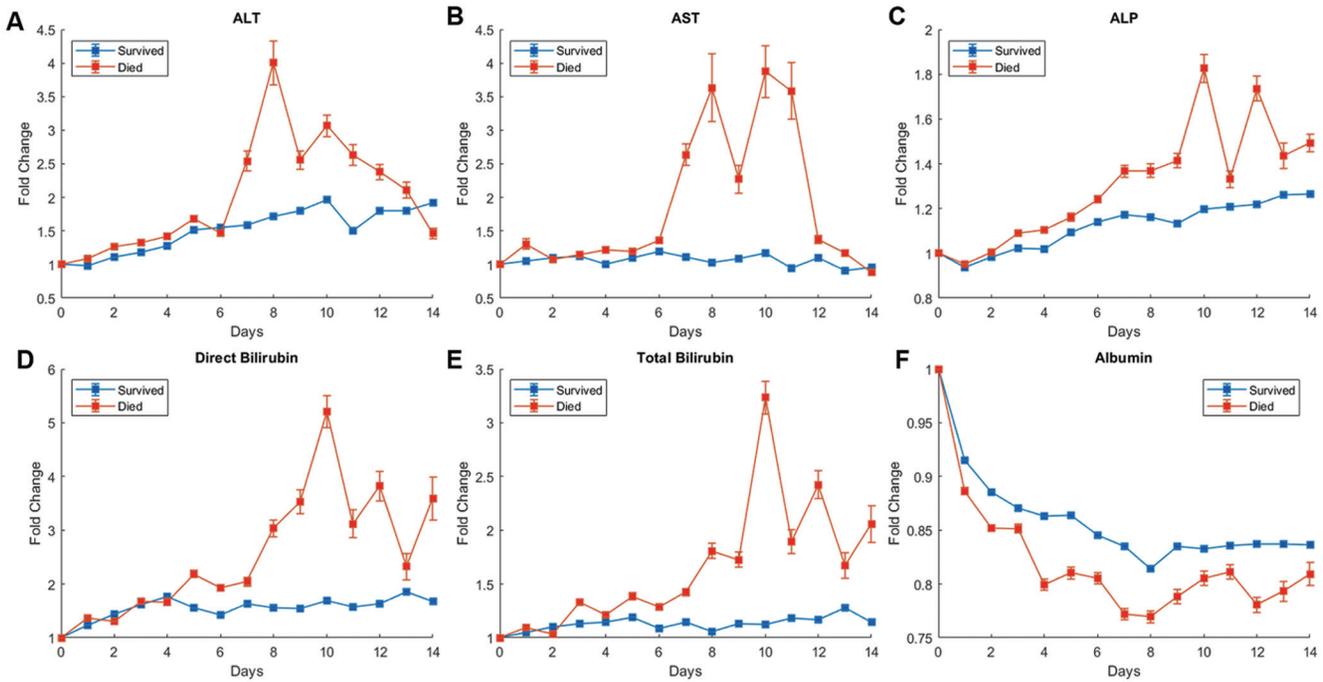


Fig. 4. Trends for ALT (A), AST (B), ALP (C), DBIL (D), TBIL (E) and albumin (F) stratified by outcome and plotted against time. Values are the mean of every patient’s individual change from their admission value, with error bars representing the 95% confidence interval of each point estimate. Outliers were defined as elements more than three standard deviations from the mean and were removed from these point estimates in order to prevent large fluctuations caused by a few extreme values.

sepsis, given its association with cholestasis.³² The most common pattern of ALT and ALP elevations on hospital admission suggested cholestatic or mixed liver injury. Only 6.6% of patients had a pattern suggestive of purely hepatocellular injury on admission. We characterized the injury pattern using the R factor, a metric originally developed for drug-induced liver injury and not widely validated in other situations. However, an American College of Gastroenterology Clinical Guideline has recommended that it be used more broadly to characterize abnormal liver chemistries.³⁷ When computing the R factor with AST instead of ALT, we found that in 352 patients with an abnormal AST and/or ALP on admission, 36.1% had a cholestatic injury pattern, 45.4% mixed, and 18.5% hepatocellular. However, the R factor has only been validated for use with ALT and would thus require further study to validate its use with AST in place of ALT. AST is also more likely than ALT to arise from non-hepatic sources such as striated muscle. Cholestatic or mixed injury raises the suspicion that SARS-CoV-2 could infect cholangiocytes, as suggested in preliminary studies,¹⁴ and supported by data from the mouse Gene Expression Database³⁸ showing that *Ace2* is expressed in the biliary system. Nonetheless, this theoretical mechanism of cholestatic liver injury in COVID-19 remains unproven. Another potential cause of cholestatic and hepatocellular injury in hospitalized patients is drug toxicity. However, we were unable to establish associations of liver laboratory test abnormalities to specific drugs given the myriad agents administered at different times. In contrast to our findings of primarily cholestatic liver injury, a study from Italy reported that the predominant liver injury in patients with COVID-19 is hepatocellular, using vague criterion of “predominantly raised” ALT and AST.³⁹ We identified a subset of 21 patients with COVID-19 who developed severe hepatocellular injury, defined as an ALT >10 times the ULN. We realize that this cutoff is subjective and selected it in order to isolate and study the patients suf-

fering from a severe acute liver injury, indicated by massive amounts of hepatocyte death, as measured by a highly elevated serum ALT. Other authors have also suggested ALT >10 times the ULN as “severe” or “marked.”^{40,41} Of the patients that suffered severe hepatocellular injury, 81% were intubated and 43% died. In a few of these cases, we identified hypotension along with evidence of sepsis and acute renal failure, suggesting ischemic hepatitis secondary to shock as the etiology of liver injury. However, hypotension is documented in only approximately half of patients with ischemic hepatitis, with cardiac failure, sepsis, and respiratory failure accounting for most cases.⁴⁰⁻⁴² Indeed, the term hypoxic hepatitis is often used alternatively to emphasize that the liver injury may be due to decreased oxygen delivery to hepatocytes rather than solely low blood perfusion.^{9,42-44} There has been considerable heterogeneity in geographic location, sample sizes, and patient populations among previous studies of the liver in patients infected with SARS-CoV-2 (Supplementary Table 1). Some included only hospitalized patients, while others also included outpatients and those discharged from emergency rooms. Our results on the prevalence of liver laboratory abnormalities with COVID-19 are similar to a study of 1,827 patients in the Yale New Haven Health System,³⁰ and another study of 2,780 patients across 34 health care organizations in the United States.²⁹ They surprisingly differ, however, from those reported in another study of inpatients and outpatients in New York City, which did not find TBIL or ALP elevations to be common and did not observe any clinically significant acute liver injury.⁴⁵ This may be because approximately 27% of the patients in that study were not hospitalized. In a cohort of 60 patients in Boston, ALP and TBIL elevations were also reported to be rare; however, 17% of patients developed serum aminotransferase activities more than 5 times the ULN.²⁷ A meta-analysis of international data showed that the pooled prevalence of elevated serum aminotransferase

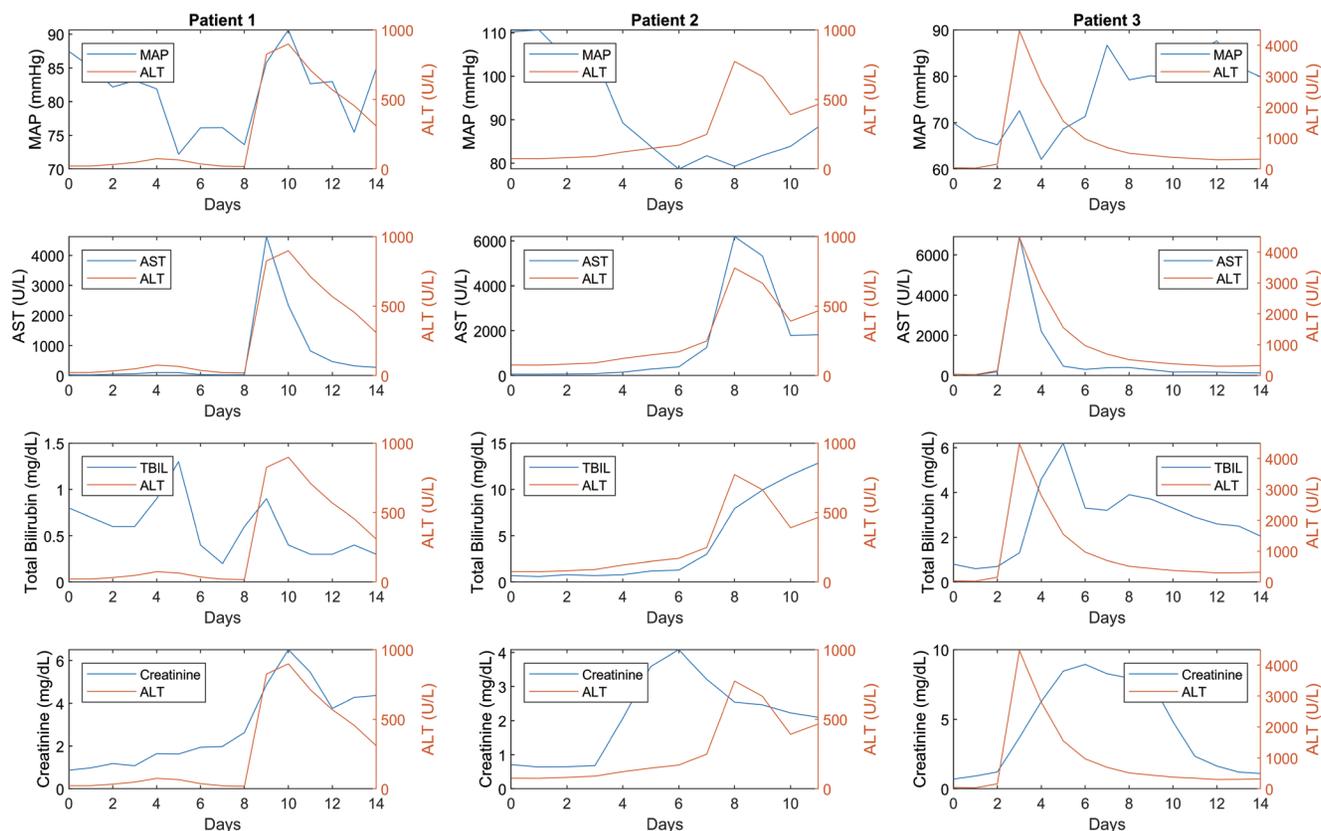


Fig. 5. Trends of mean arterial pressure, aminotransferase activities, TBIL, and serum creatinine over the first 14 days of hospitalization in three representative patients that suffered severe hepatocellular injury. Severe hepatocellular injury was defined as an ALT activity greater than 10 times the upper limit of normal. Day 0 represents the date of admission, and each value was computed as the mean of all laboratory test results documented on that day of hospitalization.

activities in patients with COVID-19 was approximately 15.0%, with higher percentages reported from countries outside of China.⁶ In one cohort of 115 hospitalized patients with COVID-19 in Wuhan, China, only 9.57% had an abnormally elevated ALT, 14.8% an elevated AST, and 5.2% an elevated ALP on admission; however, closer to our findings, 9.69% had an elevated TBIL and 54.8% a low albumin.⁴⁶ In 329 patients hospitalized with COVID-19 in Italy, 58% had abnormalities in liver function tests and this correlated with a higher risk transfer to an ICU or death.³⁹

Our study, as others like it, had limitations. We used a retrospective observational cohort design with inclusion restricted to patients hospitalized at a single medical center with an encounter diagnosis of COVID-19. This excluded some patients that may have tested positive for SARS-CoV-2 but did not have any symptoms of COVID-19. Further study of liver injury in a broader group of all patients that test positive for SARS-CoV-2 is warranted. Our study also included only a small number of patients with pre-existing liver disease. Daily laboratory tests were not obtained in many patients, hindering our ability to trend results in some over their entire hospital course. We had minimal past medical history for many patients who accessed our healthcare system for the first time. Finally, although we restricted our inclusion criteria to patients with an encounter diagnosis of COVID-19, factors such as comorbidities, simultaneous illnesses, and medications could have contributed to laboratory test results and outcomes.

Our results confirm that liver laboratory test abnormalities are common in hospitalized patients with COVID-19, some of which are associated with ICU stay or mortality.

While our data cannot exclude direct SARS-CoV-2 infection of the liver as a cause of injury, they are consistent with secondary hepatic involvement from systemic inflammatory response syndrome, sepsis, or ischemic hepatitis. The mechanisms of liver injury in patients with COVID-19 are therefore most likely similar to what occurs in many other critically-ill patients.^{32,33,47,48}

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (JMB, HJW), acquisition of data (JMB), analysis and interpretation of data (JMB, HJW), statistical analysis (JMB), writing of the manuscript (JMB, HJW), and obtaining of funding (JMB).

Data sharing statement

All data are available upon request.

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