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Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort

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BACKGROUND AND AIMS: Coronavirus disease 2019 (COVID-19) has been associated with acute liver injury (ALI) manifested by increased liver enzymes in reports worldwide. Prevalence of liver injury and associated clinical characteristics are not well defined. We aim to identify the prevalence of and risk factors for development of COVID-19-associated ALI in a large cohort in the United States.

APPROACH AND RESULTS: In this retrospective cohort study, all patients who underwent SARS-CoV-2 testing at three hospitals in the NewYork-Presbyterian network were assessed. Of 3,381 patients, 2,273 tested positive and had higher initial and peak alanine aminotransferase (ALT) than those who tested negative. ALI was categorized as mild if ALT was greater than the upper limit of normal (ULN) but <2 times ULN, moderate if ALT was between 2 and 5 times the ULN, and severe if ALT was >5 times the ULN. Among patients who tested positive, 45% had mild, 21% moderate, and 6.4% severe liver injury (SLI). In multivariable analysis, severe ALI was significantly associated with elevated inflammatory markers, including ferritin (odds ratio [OR], 2.40; $P < 0.001$) and interleukin-6 (OR, 1.45; $P = 0.009$). Patients with SLI had a more severe clinical course, including higher rates of intensive care unit admission (69%), intubation (65%), renal replacement therapy (RRT; 33%), and mortality (42%). In multivariable analysis, peak ALT was significantly associated with death or discharge to hospice (OR, 1.14; $P = 0.044$), controlling for age, body mass index, diabetes, hypertension, intubation, and RRT.

CONCLUSIONS: ALI is common in patients who test positive for SARS-CoV-2, but is most often mild. However, among the 6.4% of patients with SLI, a severe disease course should be anticipated. (Hepatology 2020;72:807-817).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic now includes >5 million confirmed cases worldwide, with an average mortality rate approaching 6.5%.[1] In the United States, New York City has >195,000 cases and >21,000 confirmed or suspected deaths.[1] COVID-19, the clinical syndrome caused by SARS-CoV-2, is primarily a respiratory disease leading in some to respiratory failure.[2] However, COVID-19 also has significant systemic manifestations, including acute kidney injury, myocarditis, thrombosis, and acute liver injury (ALI).[2-10]

Although the impact of COVID-19 on the liver remains poorly characterized, a significant proportion of patients with liver enzyme elevations have been reported. Elevations in transaminases are most often

Abbreviations: ALI, acute liver injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK, creatine kinase; COVID-19, coronavirus disease 19; CRP, C-reactive protein; ED, emergency department; HBV, hepatitis B virus; HCV, hepatitis C virus; HS troponin, high-sensitivity troponin; HTN, hypertension; ICU, intensive care unit; IL-6, interleukin-6; INR, international normalized ratio; IQR, interquartile range; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR , odds ratio; RRT, renal replacement therapy; SLI, severe liver injury; ULN, upper limit of normal.

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mild (1-2 times the upper limit of normal [ULN]), but severe liver injury (SLI) has been reported. In addition, patients with severe COVID-19 may be more likely to have liver injury than patients with less severe disease or asymptomatic carriers.[2,4,5,11] Although cholestasis and liver synthetic function abnormalities appear to be rare, hypoalbuminemia is emerging as a consistent risk factor for severe disease, even among patients without chronic illness.[5,10,11]

Emerging data suggest that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations are common among patients with COVID-19 in the United States as well, with AST and ALT elevations found in 38%-63% and 29%-39% of patients, respectively.[12,13] Interestingly, American patients may have higher admission transaminase elevations compared to previously published data, highlighting the potential geographic variability in COVID-19-related liver injury.[14]

The mechanism by which SARS-CoV-2 impacts the liver is not fully understood, but is thought to be a combination of direct virally mediated injury as well as the immune-mediated inflammatory response.[15] The SARS-CoV-2 cellular receptor, the angiotensin-converting enzyme 2 (ACE2) receptor, is present in biliary and hepatic endothelial cells, providing a plausible mechanistic explanation for the observed liver injury.[2,16,17] Among hospitalized patients, additional etiologies of liver injury must be considered, including drug-induced liver injury, sepsis, shock, congestion, and extrahepatic sources of AST.[15]

Several risk factors for severe COVID-19 have been identified, including advanced age, hypertension (HTN), diabetes, and obesity; however, little is known about risk factors and the clinical course for patients with significant liver injury attributed to COVID-19. Our aim is to describe the prevalence of and risk factors for development of ALI in patients with COVID-19, as well as investigate the impact of ALI on patient outcomes.

Participants and Methods

STUDY DESIGN AND PARTICIPANTS

Consecutive patients at the Columbia University Irving Medical Center, Morgan Stanley Children's Hospital, and Allen Hospital sites of NewYork-Presbyterian Hospital who had a test for SARS-CoV-2 infection between March 8 and April 14, 2020 were retrospectively enrolled. All outcomes were assessed on May 18, providing a minimum of 5 weeks of potential observation. Testing locations included outpatient clinics, the emergency department (ED), and inpatient locations at these institutions. This study was approved by the Columbia University Irving Medical Center Institutional Review Board with waiver of informed consent.

SARS-CoV-2 infection was defined by detection of the virus using reverse-transcriptase PCR by the Roche 6800 platform of nasopharyngeal swab specimens. For patients with multiple SARS-CoV-2 tests, if any test was positive the patient was included in the positive group, and the first positive test was used for the purposes of this analysis. Laboratory values, including liver enzymes from the time of the SARS-CoV-2 test until discharge or death, were obtained through automated data-extraction tools. Patients without any liver chemistry results were excluded.

These data were used to describe the initial and peak AST and ALT encountered in patients with positive

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and negative testing. Among patients who tested positive, liver injury was then categorized by degree of ALT elevation as none/mild (<2 times ULN), moderate (2-5 times ULN), and severe (>5 times ULN). ALT was selected to represent liver injury rather than AST because of the more predominant extrahepatic sources of AST rendering it less liver specific. Measures of synthetic dysfunction, including international normalized ratio (INR) and bilirubin, were not included in this definition given the multifactorial reasons for abnormal values in this clinical setting.

Clinical characteristics and comorbidities of patients with liver injury were examined. Presence of comorbidities, including presence and etiology of liver disease, were determined by extraction of International Classification of Diseases, Ninth Revision and International Classification of Diseases, Tenth Revision codes from the medical record. The association of category of liver injury with clinical outcomes was then assessed.

STATISTICAL ANALYSIS

Median values of ALT were compared between patients with positive versus negative SARS-CoV-2 testing using rank sum. The proportion of patients with ALT <2 times the ULN, 2-5 times the ULN, and >5 times the ULN were compared between those with positive versus negative SARS-CoV-2 testing using chi-square.

The ULN in our health care system is defined as 50 U/L for ALT and 37 U/L for AST.

The initial breakdown in proportions of patients with and without SARS-CoV-2 who had elevations in liver enzymes was then repeated using the more conservative cutoffs for ALT of 19 U/L for women and 30 U/L for men.[18]

Patients with a positive test for SARS-CoV-2 were evaluated in subsequent analyses and categorized into those with peak ALT consistent with no/mild liver injury (<2 times the ULN), moderate liver injury (2-5 times the ULN), and severe liver injury (>5 times the ULN). Continuous variables were compared across these categories with rank-sum and proportions with chi-square analysis. Multivariable logistic regression was used to identify predictors of SLI as well as the severe clinical outcomes of death or discharge to hospice. Continuous variables were log-transformed for logistic regression modeling. All covariates that were significant with $P < 0.05$ in univariable analysis were included in the final multivariable models. Given that body mass index (BMI) was not linear, it was dichotomized to above or below 35.

Results

IMPACT OF SARS-CoV-2 POSITIVITY ON LIVER ENZYMES

A total of 6,913 patients were tested for SARS-CoV-2 infection in the study period, 3,381 of whom had any ALT available and were included in this analysis. Of these 3,381 patients, 2,273 tested positive for SARS-CoV-2 and 1,108 tested negative. Overall median (interquartile range; IQR) observation time from testing until death, discharge, or last observation was 6 (3-13) days, and all patients were eligible for at least 5 weeks of follow-up from testing until final data collection.

Patients who tested positive for SARS-CoV-2 had higher median ALT values compared to patients who tested negative, including initial (28 vs. 21 U/L; $P < 0.001$) and peak (45 vs. 25 U/L; $P < 0.001$) values (Table 1). An ALT peak greater than the ULN (45% vs. 26%; $P < 0.001$) and >2 times the ULN (22% vs. 12%; $P < 0.001$) were also more common among patients with a positive test compared to negative. Peak ALT >5 times the ULN was not significantly different between groups (6.4% positive vs. 5.0% negative; $P = 0.12$).

When more conservative cutoffs for ALT of 19 U/L for women and 30 U/L for men are used, peak ALT greater than the ULN (76% vs. 52%; $P < 0.001$), greater than twice the ULN (45% vs. 26%; $P < 0.001$), and >5 times the ULN (16% vs. 9.5%; $P < 0.001$) were significantly more common among patients who tested positive compared to negative (Supporting Table S1).

CLINICAL CHARACTERISTICS OF PATIENTS WITH SARS-CoV-2 AND LIVER ENZYME ELEVATION

The clinical characteristics of the 2,273 patients who tested positive for SARS-CoV-2 are presented in Table 2. Overall median age at time of testing was 65, 57% were men, 50% were of Hispanic/Latino ethnicity, 23% were white, and 21% were black. Overall, patients with evidence of SLI were younger ($P < 0.001$) and more likely to be male ($P < 0.001$).

TABLE 1. Initial and Peak AST and ALT by SARS-CoV-2 Test Result

	SARS-CoV-2 Result			
	Overall (n = 3,381)	Positive (n = 2,273)	Negative (n = 1,108)	*P* Value
Initial ALT, median (IQR)	26 (17, 46)	28 (18, 49)	21 (14, 37)	<0.001
Initial ALT (%)				
>ULN	736 (22)	537 (24)	199 (18)	<0.001
>2× ULN	209 (6.2)	134 (5.9)	75 (6.8)	0.4
>5× ULN	58 (1.7)	29 (1.3)	29 (2.6)	0.007
Peak ALT, median (IQR)	37 (21, 76)	45 (25, 89)	25 (17, 52)	<0.001
Peak ALT (%)				
ALT peak >ULN	1,303 (39)	1,015 (45)	288 (26)	<0.001
ALT peak >2× ULN	624 (18)	489 (21)	135 (12)	<0.001
ALT peak >5× ULN	200 (5.9)	145 (6.4)	55 (5.0)	0.12
Initial AST, median (IQR)	37 (23, 62)	43 (28, 69)	26 (18, 47)	<0.001
Initial AST (%)				
>ULN	1,649 (49)	1,280 (56)	369 (33)	<0.001
>2× ULN	627 (19)	486 (21)	141 (13)	<0.001
>5× ULN	135 (4.0)	87 (3.8)	48 (4.3)	0.5
Peak AST, median (IQR)	52 (29, 100)	62 (36, 115)	33 (21, 62)	<0.001
Peak AST (%)				
>ULN	2,165 (64)	1,671 (74)	494 (45)	<0.001
>2× ULN	1,180 (35)	950 (42)	230 (21)	<0.001
>5× ULN	381 (11)	294 (13)	87 (7.9)	<0.001

Rates of medical comorbidities by the category of peak ALT elevation are displayed in Table 2. HTN and diabetes were the most common comorbidities, and both were inversely associated with a higher category of peak ALT elevation ($P < 0.001$). Chronic kidney disease was associated with a higher category of peak ALT elevation ($P < 0.001$).

Overall, 5.0% of patients had chronic liver disease, 1.4% with advanced fibrosis or cirrhosis. The most common etiologies of underlying liver disease included hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), hepatitis B virus (HBV), and alcohol-related liver disease. None of these baseline chronic liver diseases were significantly associated with category of liver injury.

CORRELATION BETWEEN LIVER ENZYMES AND LABORATORY MARKERS OF LIVER FUNCTION AND INFLAMMATION

Median peak AST and ALT among patients with SLI were 697 and 444 U/L, respectively (Table 3). Initial and nadir albumin levels were significantly lower in patients with SLI ($P = 0.009$ and $P < 0.001$, respectively). Although initial alkaline phosphatase levels were similar across all categories of ALT, median peak value was higher in patients with SLI ($P < 0.001$); however, it was only mildly elevated. Initial total bilirubin was higher in patients with SLI, although still in the normal range ($P < 0.001$); however, the median peak total bilirubin was modestly elevated up to 1.50 in the SLI group. Only 1.9% of patients in the entire cohort had total bilirubin >5 mg/dL. Similarly, median initial INR was in the normal range for all groups; however, there was a significant, but modest, elevation in peak INR among the SLI group at 1.5 ($P < 0.001$). SLI was also associated with a significantly higher white blood cell count and neutrophil-to-lymphocyte ratio (both $P < 0.001$).

Finally, SLI was associated with markers of end-organ dysfunction, including peak levels of high-sensitivity (HS) troponin, creatine kinase (CK), and serum creatinine, as well as inflammatory markers, including peak procalcitonin, C-reactive protein (CRP), D-Dimer, ferritin, and interleukin-6 (IL-6) levels (all $P < 0.001$).

TABLE 2. Patient Demographics and Comorbidities by Category of Peak ALT Elevation Among Patients With Positive Test for SARS-CoV-2

	Overall (n = 2,273)	ALT <2× ULN (n = 1,784)	ALT 2-5× ULN (n = 344)	ALT > 5× ULN (n = 145)	*P* Value
Age (years), median (IQR)	65 (52, 76)	66 (53, 78)	61 (50, 73)	63 (50, 71)	<0.001
Sex (%)					<0.001
Male	1,297 (57)	949 (53)	242 (70)	106 (73)	
Female	976 (43)	835 (47)	102 (30)	39 (27)	
BMI (kg/m^2), median (IQR)					
BMI >35 kg/m^2 (%)*	347 (17)	263 (17)	57 (18)	27 (20)	0.6
Hispanic/Latino ethnicity (%)	1,140 (50)	884 (50)	184 (53)	72 (50)	0.7
Race					
White	531 (23)	426 (24)	75 (22)	30 (21)	0.5
Black	478 (21)	387 (22)	66 (19)	25 (17)	0.3
Asian	20 (0.9)	15 (0.8)	2 (0.6)	3 (2.1)	0.2
Other/unknown	1,274 (56)	984 (55)	202 (59)	88 (61)	0.2
Comorbidities (%)					
HTN	1,375 (60)	1,130 (63)	166 (48)	79 (54)	<0.001
Diabetes	886 (39)	738 (41)	100 (29)	48 (33)	<0.001
Chronic kidney disease	470 (21)	346 (19)	69 (20)	55 (38)	<0.001
Asthma	308 (14)	259 (15)	34 (9.9)	15 (10)	0.036
COPD	185 (8.1)	163 (9.1)	15 (4.4)	7 (4.8)	0.004
Pulmonary fibrosis	17 (0.7)	15 (0.8)	1 (0.3)	1 (0.7)	0.6
Any pulmonary disease	430 (19)	364 (20)	45 (13)	21 (15)	0.002
Chronic liver disease (%)	114 (5.0)	91 (5.1)	15 (4.4)	8 (5.5)	0.8
Advanced fibrosis or cirrhosis	31 (1.4)	27 (1.5)	3 (0.9)	1 (0.7)	0.7
Alcohol-related liver disease	12 (0.5)	8 (0.4)	3 (0.9)	1 (0.7)	0.4
NAFLD or NASH	44 (1.9)	33 (1.8)	5 (1.5)	6 (4.1)	0.14
HBV	15 (0.7)	11 (0.6)	3 (0.9)	1 (0.7)	0.6
HCV	44 (1.9)	35 (2.0)	8 (2.3)	1 (0.7)	0.5
Autoimmune hepatitis	2 (<0.1)	1 (<0.1)	0 (0)	1 (0.7)	0.15
PBC	2 (<0.1)	2 (0.1)	0 (0)	0 (0)	>0.9
PSC	5 (0.2)	5 (0.3)	0 (0)	0 (0)	>0.9
Hemochromatosis	4 (0.2)	3 (0.2)	1 (0.3)	0 (0)	0.6

*N = 2,026.
Abbreviations: COPD, chronic obstructive pulmonary disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

PREDICTORS OF SLI

Uni- and multivariable logistic regression was performed to identify predictors of SLI with peak ALT >5 times the ULN (Table 4). In the final multivariable model, serological inflammatory markers, including peak ferritin (odds ratio [OR], 2.40; $P < 0.001$) and peak IL-6 (OR, 1.45; $P = 0.009$), were significantly associated with SLI, controlling for age, sex, and peak levels of D-dimer, CRP, procalcitonin, CK, and high sensitivity troponin.

CLINICAL OUTCOMES

Overall, the highest level of care required was outpatient only in 12 (0.5%), discharged from the ED in 92 (4.1%), inpatient admission in 1,640 (72%), and intensive care unit (ICU) care in 529 (23%; Table 5). Moderate and severe ALI was more common in patients who required ICU-level care ($P < 0.001$). Among the 92 patients discharged from the ED, 93% had an ALT <2 times the ULN. Among the 529 patients who required ICU-level care, 54% had an ALT <2 times the ULN, 27% had an ALT 2-5 times the ULN, and 19% had an ALT >5 times the ULN.

Severe clinical outcomes were also more common among patients with SLI. At the time of this analysis, with a minimum of 5 weeks of potential observation time, patients with SLI were significantly more likely to have been intubated compared to moderate or no/

TABLE 3. Laboratory Data by Category of Peak ALT Elevation Among Patients With Positive Test for SARS-CoV-2

	Overall (n = 2,273)	ALT <2× ULN (n = 1,784)	ALT 2-5× ULN (n = 344)	ALT >5× ULN (n = 145)	*P* Value
Liver enzymes and function					
ALT U/L[1]					
Initial	28 (18, 49)	25 (17, 39)	54 (31, 97)	63 (30, 177)	<0.001
Peak	45 (25, 89)	34 (22, 56)	140 (120, 180)	444 (294, 923)	<0.001
AST U/L[1]					
Initial	43 (28, 69)	37 (26, 58)	66 (45, 109)	91 (51, 199)	<0.001
Peak	62 (36, 115)	50 (32, 77)	160 (112, 227)	697 (256, 1,685)	<0.001
Total bilirubin, mg/dL[2]					
Initial	0.50 (0.30, 0.70)	0.40 (0.30, 0.60)	0.50 (0.40, 0.70)	0.60 (0.40, 0.90)	<0.001
Peak	0.60 (0.40, 1.00)	0.60 (0.40, 0.80)	0.90 (0.60, 1.60)	1.50 (0.90, 3.00)	<0.001
Alkaline phosphatase, U/L[2]					
Initial	78 (62, 104)	77 (62, 102)	78 (59, 107)	84 (59, 124)	0.2
Peak	95 (72, 142)	89 (70, 125)	126 (89, 219)	163 (108, 279)	<0.001
Albumin, g/dL[2]					
Initial	3.70 (3.40, 4.10)	3.80 (3.40, 4.10)	3.70 (3.40, 4.00)	3.60 (3.30, 4.00)	0.009
Nadir	3.10 (2.60, 3.60)	3.20 (2.80, 3.70)	2.70 (2.20, 3.20)	2.30 (1.80, 2.90)	<0.001
INR[3]					
Initial	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)	1.10 (1.00, 1.20)	1.20 (1.00, 1.30)	0.029
Peak	1.20 (1.10, 1.40)	1.20 (1.10, 1.30)	1.30 (1.20, 1.40)	1.50 (1.30, 2.20)	<0.001
Blood counts					
WBC ×1,000/μL[4]	8.0 (5.9, 11.0)	7.5 (5.6, 10.3)	9.4 (7.1, 12.4)	12.5 (8.5, 15.8)	<0.001
Hgb, g/dL[4]	12.09 (10.18, 13.50)	12.27 (10.43, 13.50)	11.73 (9.50, 13.57)	10.57 (8.95, 12.60)	0.001
Platelets ×1,000/μL[4]	231 (172, 302)	226 (170, 293)	270 (194, 323)	234 (166, 304)	<0.001
Neutrophil count/μL[5]	576 (398, 851)	535 (379, 800)	726 (487, 959)	872 (603, 1199)	<0.001
Lymphocyte count/μL[5]	111 (79, 148)	111 (80, 148)	110 (80, 151)	103 (75, 144)	0.7
Neutrophil-lymphocyte ratio[6]	5.6 (3.4, 9.3)	5.1 (3.2, 8.4)	6.8 (4.5, 11.4)	9.3 (5.8, 15.2)	<0.001
Additional markers of organ damage and inflammation					
Creatinine, mg/dL[7]					
Initial	1.07 (0.81, 1.62)	1.07 (0.80, 1.65)	1.03 (0.82, 1.52)	1.14 (0.80, 1.57)	0.6
Peak	1.31 (0.91, 2.65)	1.24 (0.88, 2.31)	1.42 (0.94, 3.29)	3.09 (1.26, 6.72)	<0.001
HS troponin, ng/L[8]					
Initial	17 (8, 44)	18 (8, 44)	14 (7, 36)	18 (9, 65)	0.011
Peak	25 (10, 79)	23 (9, 64)	29 (10, 108)	104 (24, 258)	<0.001
CK[9]					
Initial	162 (77, 360)	148 (73, 322)	194 (92, 492)	229 (118, 499)	<0.001
Peak	216 (93, 579)	184 (81, 432)	350 (137, 1,048)	502 (206, 2,151)	<0.001
Procalcitonin, ng/mL[10]					
Initial	0.23 (0.11, 0.60)	0.20 (0.10, 0.55)	0.30 (0.16, 0.75)	0.35 (0.16, 1.10)	<0.001
Peak	0 (0, 2)	0 (0, 1)	1 (0, 4)	3 (1, 18)	<0.001
CRP, mg/L[11]					
Initial	116 (57, 202)	107 (49, 188)	155 (84, 257)	146 (92, 225)	<0.001
Peak	166 (80, 277)	147 (65, 246)	246 (139, 300)	262 (180, 300)	<0.001
D-Dimer, ug/mL[12]					
Initial	1.5 (0.8, 3.2)	1.4 (0.8, 3.1)	1.7 (0.9, 3.6)	1.8 (0.9, 5.9)	0.002
Peak	2.5 (1.0, 10.8)	2.0 (1.0, 6.4)	5.3 (1.5, 20.0)	19.6 (3.9, 20.0)	<0.001
Ferritin, ng/mL[13]					
Initial	694 (347, 1,264)	614 (306, 1,091)	1048 (551, 1,982)	1,056 (541, 2,368)	<0.001
Peak	916 (435, 1,879)	760 (359, 1,402)	1621 (934, 2,872)	3,702 (1,552, 10,008)	<0.001

TABLE 3. *Continued*

	Overall (n = 2,273)	ALT <2× ULN (n = 1,784)	ALT 2-5× ULN (n = 344)	ALT >5× ULN (n = 145)	*P* Value
IL-6 level, pg/mL[14]					
Initial	21 (7, 51)	18 (6, 46)	27 (10, 59)	40 (16, 93)	<0.001
Peak	33 (10, 114)	25 (8, 73)	63 (19, 158)	158 (50, 158)	<0.001
LDH level, U/L[15]					
Initial	410 (299, 573)	379 (281, 525)	502 (379, 686)	576 (428, 892)	<0.001
Peak	472 (336, 688)	424 (313, 601)	617 (466, 842)	1,148 (640, 2,123)	<0.001

All continuous variables represented as median (IQR).
Superscripted numbers in left column represent: [1]N = 2,273, [2]N = 2,268, [3]N = 2,018, [4]N = 2,264, [5]N = 2,109, [6]N = 2,115, [7]N = 2,269, [8]N = 2,056, [9]N = 1,761, [10]N = 2,065, [11]N = 2,070, [12]N = 1,791, [13]N = 2,032, [14]N = 1,607, and [15]N = 2,052.
Abbreviations: Hgb, hemoglobin; LDH, lactate dehydrogenase; WBC, white blood cell count.

TABLE 4. Multivariable Predictors of Peak ALT >5× ULN Among Patients With Positive Test for SARS-CoV-2*

	Univariate Analysis			Multivariate Analysis		
Covariate	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	0.99	0.97, 1.00	0.015	0.98	0.97, 1.00	0.058
Female sex	0.48	0.30, 0.74	0.001	0.84	0.50, 1.40	0.5
BMI >35	0.75	0.47,1.23	0.2	0.71	0.40,1.28	0.2
Liver disease	1.33	0.54, 2.81	0.5			
Diabetes	0.87	0.58, 1.30	0.5			
HTN	0.95	0.64, 1.42	0.8			
Peak IL-6	2.16	1.77, 2.69	<0.001	1.45	1.10, 1.93	0.009
Peak ferritin	3.01	2.47, 3.72	<0.001	2.40	1.90, 3.08	<0.001
Peak D-Dimer	1.57	1.37, 1.82	<0.001	1.13	0.91, 1.39	0.3
Peak CRP	2.55	1.76, 3.94	<0.001	0.82	0.55, 1.33	0.4
Peak procalcitonin	1.48	1.35, 1.63	<0.001	0.99	0.84, 1.15	0.9
Peak CK	1.52	1.33, 1.73	<0.001	1.05	0.89, 1.24	0.5
Peak HS troponin	1.53	1.35, 1.75	<0.001	1.14	0.94, 1.37	0.2

*N = 1,176.
Abbreviation: CI, confidence interval.

mild liver injury (65% vs. 38% vs. 13%; $P < 0.001$), required renal replacement therapy (RRT; 33% vs. 15% vs. 7.5%; $P < 0.001$), and died in the hospital (42% vs. 23% vs. 21%; $P < 0.001$).

When looking specifically at the 145 patients with SLI, most had a severe COVID-19 course. Of these patients, 69% required ICU-level care, 65% were intubated, 70% required vasopressors, 12% inotropes, and 33% RRT during their hospitalization. Thirty-nine percent of patients were paralyzed, 10% proned, and 4 required extracorporeal membrane oxygenation. The most common COVID-19-targeted therapy given was hydroxychloroquine (76%), followed by corticosteroids (49%), tocilizumab (26%), sarilumab (6.2%), and remdesivir (4.8%). Of 7 patients who received remdesivir, 29% had peak ALT before medication, 29% had peak ALT within 7 days of medication, and 42% had peak ALT after 7 days from medication dose. Of 46 patients who received tocilizumab or sarilumab, 17% had peak ALT before medication, 44% had peak ALT within 7 days of medication, and 39% had peak ALT after 7 days from medication dose.

PREDICTORS OF DEATH OR DISCHARGE TO HOSPICE

Uni- and multivariable analysis was then performed to identify predictors of death or discharge to hospice

TABLE 5. Patient Outcomes by Category of Peak ALT Elevation Among Patients With Positive Test for SARS-CoV-2

	Overall (n = 2,273)	ALT <2× ULN (n = 1,784)	ALT 2-5× ULN (n = 344)	ALT >5× ULN (n = 145)	*P* Value
Highest level of care (%)					<0.001
Outpatient	12 (0.5)	11 (0.6)	1 (0.3)	0 (0)	
Discharged from ED	92 (4.1)	86 (4.8)	4 (1.2)	2 (1.4)	
Admitted	1,640 (72)	1,402 (79)	196 (57)	42 (29)	
ICU	529 (23)	285 (16)	143 (42)	101 (69)	
Intubated (%)	452 (20)	225 (13)	132 (38)	95 (65)	<0.001
Extubated (%)	99 (4.4)	58 (3.3)	25 (7.3)	16 (11)	<0.001
RRT (%)	231 (10)	133 (7.5)	50 (15)	48 (33)	<0.001
In-hospital mortality (%)	517 (23)	378 (21)	78 (23)	61 (42)	<0.001
Current disposition (%)					<0.001
Discharged	1,530 (67)	1,288 (72)	199 (58)	43 (30)	
Admitted (not intubated)	81 (3.6)	53 (3.0)	18 (5.2)	10 (6.9)	
Admitted (intubated)	130 (5.7)	51 (2.9)	48 (14)	31 (22)	
Deceased/discharged to hospice	532 (23)	392 (22)	79 (23)	61 (42)	

TABLE 6. Multivariable Predictors of Death or Discharge to Hospice Among Patients With Positive Test for SARS-CoV-2*

	Univariate Analysis			Multivariate Analysis		
Covariate	OR	95% CI	*P* value	OR	95% CI	*P* Value
Peak ALT	1.22	1.10, 1.35	<0.001	1.14	1.00, 1.30	0.044
Age	1.07	1.06, 1.08	<0.001	1.07	1.07, 1.10	<0.001
Female sex	0.83	0.67, 1.02	0.077			
BMI >35	1.57	1.17, 2.13	0.003	1.06	0.75, 1.52	0.7
Diabetes	1.65	1.34, 2.02	<0.001	1.30	1.01, 1.68	0.045
HTN	2.43	1.92, 3.10	<0.001	1.15	0.85, 1.56	0.4
Liver disease	0.66	0.39, 1.07	0.11			
Intubation	3.39	2.70, 4.26	<0.001	4.77	3.49, 6.55	<0.001
RRT	1.90	1.41, 2.54	<0.001	1.30	0.90, 1.88	0.2

*N = 2,026.
Abbreviation: CI, confidence interval.

(Table 6). In the final multivariable model, peak ALT was significantly associated with this severe outcome (OR, 1.14; $P = 0.044$), as were older age (OR, 1.07; $P < 0.001$), diabetes (OR, 1.30; $P = 0.045$), and intubation (OR, 4.77; $P < 0.001$), controlling for BMI, HTN, and the use of RRT.

Discussion

Liver injury, as manifested by ALT and AST elevation, is emerging as a clinically important consequence of COVID-19 and may predict a severe disease course. In this cohort with 2,273 cases and 1,108 controls, we demonstrate that initial and peak ALT are higher in those who test positive for SARS-CoV-2 compared to those who test negative with a similar clinical presentation. However, overall median initial and peak levels of liver enzymes were mildly elevated with <2 times the ULN in the majority of patients, even in this largely inpatient setting. Overall, moderate liver injury (peak ALT 2-5 times the ULN) was present in 22% and SLI (peak ALT >5 times the ULN) in 6.4% of the COVID-19 cohort. Severe elevation in peak ALT was not significantly more common in SARS-CoV-2-positive patients compared to SARS-CoV-2-negative patients when using our local ULN value, though was significantly elevated when using the more conservative ULN of 19 for women and 30 for men.

Prevalence of liver enzyme elevation observed here is similar to what has been reported in large cohorts in China, where prevalence has ranged from 3.75% to 53.1%, but most reporting a prevalence of ~20%-30%.[19] Whereas definitions of liver injury have been variable in the literature to date, here we used ALT cutoffs as defined by our local ULN, which are higher than the conservative cutoffs endorsed by the American Association for the Study of Liver Diseases.[18] While when looking at these more conservative cutoffs the prevalence of enzyme elevations was higher, our overall conclusions regarding the impact of COVID-19 on the prevalence of elevated liver enzymes did not significantly change.

As in other reports, we observed a largely hepatocellular pattern of liver injury with few patients with elevated bilirubin and/or elevated alkaline phosphatase, even in the SLI category. The mechanism of liver injury remains largely unknown and is thought to be a combination of both direct virally mediated effects as well as a result of the immune response.[15] Only limited cases of hepatic histology have been reported, though it is known that the ACE2 receptor is present on biliary epithelial cells,[16] so it is interesting that bilirubin was often normal even in extreme cases. Given the emerging impact of COVID-19 on coagulation, including clinical observations of thrombosis and disseminated intravascular coagulation, INR as a measure of synthetic function was not included in our definition of liver injury. Yet, only mild elevations in INR were noted even in the most severe cases. However, significant hypoalbuminemia was observed, particularly among patients with SLI.

Several clinical characteristics were significantly associated with SLI, including younger age and male sex. Interestingly, despite being associated with poor outcomes, SLI was inversely associated with the presence of HTN and diabetes. It is possible that younger patients mount a more robust immune and inflammatory response to infection, and that higher peak ALT is a manifestation of this response. This is supported by the fact that younger age, peak IL-6, and peak ferritin were the strongest predictors of SLI in multivariable modeling.

Overall, 5% of patients in our cohort had chronic liver disease, 1.4% with advanced fibrosis or cirrhosis. This is a higher rate than has been reported in recent data from other cohorts, and the clinical course of COVID-19 among patients with chronic liver disease or cirrhosis is not known. The presence of chronic liver disease, advanced fibrosis or cirrhosis, and type of liver disease (including NAFLD, HCV, and HBV) were not significantly associated with category of liver injury, which may be attributable, in part, to the overall low numbers of patients with these disease entities. Although the prevalence of NAFLD in this cohort may be under-reported because of the International Classification of Diseases–based diagnosis, it is notable that metabolic risk factors, including BMI >35, diabetes, and HTN, were not associated with SLI. Although it is clear that additional study is needed on the impact of underlying liver disease on clinical outcomes including death, it does not appear that patients with NAFLD or other metabolic risk factors are at increased risk of an acute rise in liver enzymes as part of their course.

It is possible that some patients with severe COVID-19 had additional liver insults, including ischemia, congestion, and drug-induced liver injury. In addition, extrahepatic sources of AST are likely common in this scenario, including from heart and skeletal muscle breakdown; thus, we focused on ALT in the majority of our analysis. However, it appears that ALT levels correlate well with markers of inflammation and are likely higher among patients with severe cytokine release syndromes.[4,7,10,11,13] This is supported by the significantly higher peak levels of all inflammatory markers among those with severe ALT elevation, including CRP, D-dimer, ferritin, and IL-6. IL-6 in particular has been described as a possible marker for severe COVID-19-related disease.[20] In addition, cytokine storm syndromes have been described in COVID-19 and are associated with severe elevations in liver enzymes.[21] It is possible that severe ALT elevations correlate with the inflammatory response to the virus.

Higher peak ALT values were also significantly associated with overall disease severity and measured clinical outcomes. Patients with SLI were significantly more likely to have respiratory failure requiring intubation as well as renal failure requiring RRT. Moreover, these patients were more likely to be admitted to the ICU and to have died in the hospital. When the 145 patients with SLI were evaluated in more detail, many required vasopressors and were treated with a broad range of COVID-19 treatment strategies, including agents such as tocilizumab, sarilumab, and remdesivir, that have been associated with liver enzyme elevation.

This highlights an important clinical challenge in these patients given that those with elevated ALT are often excluded from clinical trials of these agents.

Limitations of this analysis include that this represents an almost exclusively inpatient population and includes a period in our center when only the sickest patients were tested in general. Therefore, this information may not be applicable to outpatients or those with mild disease. In addition, it was not possible to characterize all the possible additional sources of liver injury, including the use of hepatotoxic medications, or to clearly attribute changes in parameters of liver synthetic function to liver injury alone. Finally, although all patients are eligible for a minimum of 5 weeks of follow-up, some patients in this cohort remain hospitalized (5.7% intubated, 3.6% not intubated), including several with SLI. Thus, the ultimate clinical outcomes are not yet known for the entire cohort, and many of these patients with prolonged intubated remain at risk of inpatient mortality. However, the final disposition is currently known in >90% of the cohort, and, given the overall large number of patients included, additional follow-up is unlikely to change the overall conclusions significantly.

In summary, in this cohort of 3,381 patients, ALI was more common among the 2,273 patients with confirmed SARS-CoV-2 than among those with a similar presentation who tested negative. However, SLI with ALT peak >5 times the ULN occurred in only 6.4% of patients. These liver enzyme elevations were rarely associated with cholestasis, but did correlate with other markers of end-organ injury as well as cytokines and markers of inflammation. Finally, SLI was associated with the most severe clinical outcomes, including death, and may be a useful prognostic marker for hospitalized patients.

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