The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities

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Background Coronavirus disease 2019 (COVID-19) has caused a global pandemic unprecedented in over a century, with ≈35 million cases, and more than 1 million deaths globally. Though predominantly a lower respiratory illness, other organ injuries are well-recognized. Among these, liver injury is of major interest.
Objective To define prevalence, pattern, predictors, and impact of liver injury among patients hospitalized with COVID-19.
Methods Demographic, clinical, and biochemical data were collected retrospectively among patients admitted to St. Luke's University Hospital with COVID-19 between 1 March and 18 April 2020. Association of liver tests (LTs) with mortality and need for mechanical ventilation, adjusted for demographic, clinical and biochemical predictors, was examined.
Results Data were available on 551 patients. Prevalence of any or ≥3 × upper limit of normal transaminase elevation on was 61.2 and 9.4% on admission, and 72.1 and 22.4% at peak. Bilirubin and alkaline phosphatase elevations were less common on admission (11.4 and 12.6%, respectively), and at peak (17.7 and 22%, respectively). All liver test (LT) elevations were consistently predicted by inflammatory markers. Hyperbilirubinemia predicted mortality on admission and at peak. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had opposite impact on mortality with AST positively, and ALT negatively associated with mortality. Hence, besides hyperbilirubinemia, AST:ALT ratio emerged as the best marker for mortality among the LTs.
Conclusion LT elevations among patients presenting with COVID-19 are very common, though majority are mild. Admission and peak bilirubin ≥1 mg/dl, as well as admission and peak AST:ALT ratio were significant predictors of mortality, along with age, myocardial injury, and chronic medical illness. Eur J Gastroenterol Hepatol 33: e274–e281

Introduction

Coronavirus disease 2019 (COVID-2019), caused by the beta-coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused a global pandemic unprecedented in over a century. At the time of writing, there have been almost 35 million cases and over a million deaths due to COVID-19 globally [1]. Though two major epidemics of lower respiratory tract illness have been caused by beta-coronaviruses, the SARS-CoV epidemic of 2002 and the Middle East respiratory syndrome epidemic of 2012, rapid spread and global scope of COVID-19 certainly set it apart. Given the relative novelty and scope of COVID-19, several aspects of pathophysiology, clinical features, and outcomes remain under avid investigation. In this regard, the angiotensin-converting enzyme 2 (ACE2) receptor, firmly established as the cellular receptor for SARS-CoV-2 [2,3], is widely expressed by alveolar type 2 cells in the lungs. Given obvious direct environmental exposure of pulmonary alveoli, lungs are a major portal of entry for SARS-CoV-2, and respiratory symptoms predominate among those infected. However, there is significant incidence of extra-pulmonary organ involvement, including myocardial injury, acute kidney injury (AKI), and hepatic injury [4–6]. Parsing out the relative significance of these is essential to refine risk-stratification of patients at admission as well as during the course of illness.

Among the myriad manifestations and complications of COVID-19, liver injury has garnered some attention. Several series have reported a high prevalence of liver test (LT) elevation at presentation, as well as during hospitalization, as discussed subsequently. However, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have wide tissue distributions. AST is found in liver, heart, skeletal muscle, kidney, brain, pancreas, and leucocytes among other tissues and isolated AST elevations usually indicate skeletal muscle/myocardial injury. Though more specific, ALT is also found in skeletal muscle, myocardium, lungs, and kidneys. Hence, minor AST/ALT elevations remain nonspecific, especially in severe illness with multi-organ injury, as in severe COVID-19. Unsurprisingly, there is heterogeneity in the reported literature regarding incidence and impact of liver injury in COVID-19.

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To add to extant information, we attempted to define prevalence, patterns and predictors of LT abnormalities in a large cohort of hospitalized COVID-19 patients.

Methods

Population and data collection

Baseline (on admission) clinical and biochemical data of patients admitted to St Luke's University Hospital (Bethlehem, Pennsylvania, USA), were collected retrospectively among adult patients admitted with a primary diagnosis of COVID-19 between 1 March and 18 April 2020. Detailed data collection methodology has been described [4]. Briefly, baseline demographic variables including age, sex, race, along with medical co-morbidities were collected from electronic health records, the last using pre-specified ICD-10 codes. Inflammatory markers, cardiac troponin (cTn), metabolic markers, and LTs, including AST, ALT, total bilirubin, and alkaline phosphatase (ALP) on admission and at peak were also collected. All data were collected in a spreadsheet for analysis. The study protocol was approved by the St Luke's Hospital Institutional Review Board.

Data synthesis and outcome definition

Baseline (at the time of admission) and peak (highest during entire hospitalization) plasma biochemical, metabolic, and inflammatory markers levels were transformed into categories defined by the respective reference range. Specifically, for LTs, cutoffs of ≥45 U/L, ≥40 U/L, and ≥116 U/L, and ≥1 mg/dl were used for AST, ALT, ALP, and total bilirubin, respectively. For parsimony, major medical comorbidities, including hypertension, diabetes mellitus, chronic kidney disease (CKD) stage 3 or higher, heart failure, autoimmune disease, chronic pulmonary disease, malignancy, or chronic liver disease, were transformed into a single variable-chronic medical illness. For some analyses, specifically for predictors of LT abnormalities, we tested chronic medical illness without liver disease and chronic liver disease as distinct variables. AKI on admission was defined as creatinine ≥1.5 mg/dl in those with no history of CKD. AKI during hospitalization was defined as (1) increase in creatinine by ≥0.3 mg/dl from admission levels, or (2) increase in creatinine to ≥1.5 times admission creatinine in patients with no AKI on admission. Myocardial injury on admission and at peak was defined as elevated cTn to ≥0.05 ng/ml at the respective time-points. LT elevations, both at baseline and at peak were categorized by any elevation, and elevation to ≥3 times over normal reference range [3 × upper limit of normal (ULN)]. Primary outcomes of interest were death and mechanical ventilation.

Statistical analysis

Clinical variables, biochemical and inflammatory markers, and LTs were compared across groups defined by primary outcomes. Continuous variables were compared using Student's *t*-test when normally distributed and Mann–Whitney *U* test when not. Categorical variables were compared using χ^2-test or Fisher's exact test, as appropriate. Multivariate analyses using backward logistic regression were performed to find independent predictors of each LT abnormality, including age, sex, chronic medical illness, chronic liver disease, myocardial injury, AKI, other LTs, and the inflammatory markers, ferritin, procalcitonin and d-dimer. Univariate logistic regression was performed to identify individual LTs associated with death or mechanical ventilation. LTs found significant on univariate analysis (at $P < 0.05$) were included in the multivariate model along with age, medical comorbidities, myocardial injury, AKI, and inflammatory markers. All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, New York, USA).

Results

Population characteristics

Baseline demographic characteristics, metabolic, and inflammatory markers of the entire cohort have been previously reported [4]. Demographic/clinical features, inflammatory markers, and outcomes stratified by baseline and peak AST/ALT elevation are summarized in Table 1. Importantly, patients with elevated AST/ALT at baseline and peak were younger, more often males, and less often suffered chronic medical illnesses, the latter likely due to being younger. Interestingly, the inverse relation between age and AST/ALT elevation was driven largely by ALT [median age 68 (27) years versus 60 (20) years, $P < 0.001$ by baseline AST/ALT elevation and 68 (27) years versus 61 (19) years, $P < 0.001$ by peak elevation], with no age difference noted by AST elevation either on admission [median age 64 (19) years versus 63 (21) years, P = NS] or peak [median age 63 (25) years versus 63 (21) years, P = NS]. On the other hand, most inflammatory markers (except d-dimer) were higher in those with elevated baseline/peak transaminases, as was incidence of AKI and mechanical ventilation. Mortality was similar regardless of peak/admission AST/ALT.

Prevalence and patterns of liver function test abnormalities

Prevalence of LT abnormalities on admission, at peak, and occurring de-novo after admission, stratified by mortality and mechanical ventilation are summarized in Table 2. On admission, 364/551 (66.1%) patients had at least one LT elevated. Among these, 244 (67%) had isolated AST/ALT elevation, 25 (6.9%) had isolated ALP or bilirubin elevation, and the rest (95/364, 26.1%) had a mixed pattern. Among patients with elevated AST or ALT, 67 (19.9% of those with elevated AST/ALT) had isolated AST, 219 (64.9%) had both transaminases, while 51 (15.1%) had isolated ALT elevations. Vast majority of transaminase elevations were mild, with only 52 patients (15.4% of AST/ALT ≥ ULN) having elevations ≥3 × ULN. Finally, bilirubin ≥2 mg/dl occurred in <2%.

At peak, 417 (75.5% of total) had any LT elevation. Transaminitis remained the predominant pattern, with 237 (56.8%) having isolated AST/ALT, 18 (4.3%) having isolated ALP or bilirubin, and 162 (38.8%), having mixed elevation. Among patients with AST/ALT elevation at peak 48 (12.1%) had isolated ALT, 305 (77%) had both transaminases, and 43 (10.9%) had isolated AST elevation. Again, majority of transaminase elevations were mild, with 123 patients (32.8% of those with elevated AST/ALT, 22.4% of total) having AST/ALT elevated to ≥3 × ULN, with no difference by mortality or mechanical

Table 1. Baseline demographic, and baseline and peak inflammatory and select outcome measures stratified by LT abnormalities

	Admission AST and ALT		Peak AST and ALT	
Variable	ALT/AST < ULN	ALT/AST ≥ ULN	ALT/AST < ULN	ALT/AST ≥ ULN
Age	67 (27)	62 (20)[a]	68 (27)	62 (20)[a]
Males	99/212 (46.7)	200/339 (64.9)[a]	71/153 (46.4)	249/399 (62.4)[b]
Race				
Caucasian	101/212 (47.6)	132/339 (38.9)[c]	75/153 (49)	159/399 (39.8)
Hispanic	54/212 (25.5)	124/339 (36.6)[b]	38/153 (24.8)	140/399 (35.1)[c]
African American	37/212 (17.5)	62/339 (18.3)	27/153 (17.6)	72/399 (18)
Asian	4/212 (1.9)	10/339 (2.9)	2/153 (1.3)	12/399 (3)
Other/unknown	16/212 (7.1)	11/339 (3.2)[c]	11/153 (6.5)	16/399 (4)
BMI	29.75 (11.2)	30.80 (8.50)	29.7 (11.40)	30.8 (9.02)
Morbid obesity	51/210 (24.3)	67/334 (20.1)	35/151 (23.2)	83/394 (21.1)
DM	82/212 (38.7)	112/339 (33)	60/153 (39.2)	134/399 (33.6)
HTN	125/212 (59)	151/339 (44.5)[b]	96/153 (62.7)	181/399 (45.4)[a]
CHF	31/261 (11.9)	22/290 (7.6)[b]	23/153 (15)	31/399 (7.8)[c]
CKD ≥ stage 3	55/212 (25.9)	57/339 (16.8)[c]	42/153 (27.5)	70/399 (17.5)[c]
Vascular disease	23/212 (10.8)	11/339 (3.2)[a]	19/153 (12.4)	16/399 (4)[a]
Malignancy	6/212 (2.8)	8/339 (2.4)	5/153 (3.3)	9/399 (2.3)
Pulmonary disease	29/212 (13.7)	17/339 (5)[a]	22/153 (14.4)	24/399 (6)[b]
Chronic liver disease	8/212 (3.8)	18/339 (5.3)	5/153 (3.3)	21/399 (5.3)
Inflammatory markers				
WCC ≥ 10	28/212 (13.2)	65/339 (19.2)	48/153 (31.4)	251/399 (62.9)[a]
CRP ≥ 10	149/160 (93.1)	278/283 (98.2)[b]	94/102 (92.2)	339/342 (99.1)[a]
d-dimer ≥ 1.0	76/140 (54.3)	174/277 (62.8)	45/86 (52.3)	236/331 (71.3)[b]
Ferritin ≥ 500	60/161 (37.3)	214/292 (73.3)[a]	39/103 (37.9)	264/351 (75.2)[a]
Procalcitonin ≥ 0.5	26/195 (13.3)	68/328 (20.7)[c]	20/136 (14.7)	140/388 (36.1)[a]
Outcomes				
Myocardial injury	39/179 (21.8))	57/300 (19)	27/127 (21.3)	84/351 (23.9)
AKI	11/212 (5.2)	37/339 (10.9)[c]	24/153 (15.7))	93/399 (23.3)[c]
Respiratory failure (mechanical ventilation)	29/211 (13.7)	83/333 (24.9)[b]	8/153 (5.2)	104/392 (26.5)[a]
LoS	6 (6)	7 (7) [c]	5 (5)	7 (8)[a]
Mortality	30/211 (14.2)	48/337 (14.2)	20/153 (13.1)	59/396 (14.9)

Inflammatory markers, myocardial injury, and AKI are reported as for respective timing of assays. Hence, baseline (on admission) values/prevalence of these variables are reported stratified by baseline liver tests (LTs), and peak values/prevalence at peak in the case of peak LT groups.
[a]$P < 0.001$.
[b]$P < 0.01$.
[c]$P < 0.05$.
AKI, acute kidney injury; CHF, chronic heart failure; CKD, chronic kidney disease; CRP, c-reactive protein; DM, diabetes mellitus; HTN, hypertension; LoS, length of stay; LT, liver test; ULN, upper limit of normal; WCC, white cell count.

ventilation. Prevalence of hyperbilirubinemia to ≥2 mg/dl was rare (<3%) and no different by either outcome.

Finally, among patients with normal LTs on admission (n = 186), 28.5% (n = 53) developed any new LT abnormality. Among these, 40 (75.5%) had isolated transaminase elevation without bilirubin/ALP abnormalities, one patient had isolated bilirubin elevation, and the remaining 12 (22.6%) had a mixed pattern. Only five patients had new-onset transaminase elevations to ≥3 × ULN.

Predictors of liver test abnormalities

Significant predictors of individual admission and peak LT abnormalities adjusted for age, sex, chronic medical illnesses, chronic liver disease, AKI, myocardial injury, other LTs, and inflammatory markers are depicted in Tables 3 and 4, respectively. Unsurprisingly, each LT was consistently associated with other LT abnormalities. Simultaneously, each LT had distinct demographic/clinical predictors. Most notably, besides LTs, inflammatory markers were consistently associated with admission and peak LT abnormalities, plasma Ferritin being most prominent. To further validate 'non-LT' markers, we repeated the analysis without LTs (Table S1, Supplemental digital content 1, *http://links.lww.com/EJGH/A643*). Though there was some decrease in areas under the curve (AUC), overall odds ratios (ORs) remained stable for most predictors, validating significant associations.

Impact of liver test abnormalities on outcomes

Univariate association between LT abnormalities and mortality or mechanical ventilation are summarized in Table S2 (Supplemental digital content 1, *http://links.lww.com/EJGH/A643*). Multivariate analysis including age, chronic medical illness, myocardial injury, renal injury, inflammatory markers, and LTs found significant on univariate analysis for the two outcomes of mortality and mechanical ventilation is summarized in Table 5. Given the apparently opposing impact of peak ALT and peak AST on mortality, we repeated the multivariate analysis replacing ALT and AST elevation with the AST:ALT ratios (Table 6). Indeed, admission as well as peak AST:ALT ratios were significant independent predictors of mortality. When using AST:ALT ratio, procalcitonin was no longer significant on admission. It is important to note that both admission AST and ALT had a significant correlation with admission procalcitonin (Spearman's $\rho = 0.322$, $P < 0.001$ and $\rho = 0.152$, $P < 0.001$, respectively).

Discussion

We present perhaps the most in-depth analysis to date of prevalence, pattern, predictors, and impact of LT abnormalities among hospitalized COVID-19 patients. As reported previously, mild LT abnormalities were common, both on admission and at peak; about two-thirds and

Table 2. Prevalence and patterns of liver test abnormalities on admission, at peak, and in those with normal admission tests

Liver test	Overall	Survivors	Non-survivors	*P* value	Non-intubated	Intubated	*P* value
On admission							
AST (U/L)	46 (40)	45.5 (39)	49 (42.3)	0.208	44 (37.8)	57.5 (41.8)	0.014
ALT (U/L)	39 (40)	40 (41.3)	33.5 (29.5)	0.001	39 (40.8)	40.5 (38)	0.337
ALP (U/L)	74 (38)	74 (37)	75.5 (44)	0.861	75.5 (36)	68.5 (38.8)	0.139
T. bilirubin	0.50 (0.32)	0.51 (0.30)	0.50 (0.40)	0.182	0.51 (0.30)	0.53 (.39)	0.763
AST ≥ ULN	286/552 (50.8)	240/470 (51.1)	44/79 (55.7)	0.446	210/433 (48.5)	70/112 (62.5)	0.008
ALT ≥ ULN	270/551(49)	243/470 (51.7)	27/78 (34.6)	0.005	207/432 (47.9)	60/112 (53.6)	0.286
AST or ALT ≥ ULN	337/551 (61.2)	289/470 (61.5)	48/78 (61.5)	1.000	250/432 (57.9)	83/112 (74.1)	0.002
ALP ≥ ULN	71/552 (12.6)	60/470 (12.8)	11/79 (13.9)	0.777	52/433 (12)	18/112 (16.1)	0.252
T. bilirubin ≥1 mg/dl	64/552 (11.4)	48/470 (10.2)	16/79 (20.3)	0.010	46/433 (10.6)	17/112 (15.2)	0.179
T. bilirubin ≥2 mg/dl	10/549 (1.8)	8/470 (1.7)	2/79 (2.5)	0.610	8/433 (1.8)	2/112 (1.8)	0.965
AST ≥3 × ULN	35/552 (6.2)	31/470 (6.6)	4/79 (5.1)	0.606	24/433 (5.5)	11/112 (9.8)	0.100
ALT ≥3 × ULN	45/551 (8.2)	45/470 (9.6)	0/78 (0)	0.004	36/432 (8.3)	9/112 (8)	0.919
AST or ALT ≥3 × ULN	52/551 (9.4)	48/470 (10.2)	4/78 (5.1)	0.156	38/432 (8.8)	14/112 (12.5)	0.235
ALP ≥3 × ULN	4/ 552 (0.7)	4/470 (0.9)	0 (0)	0.411	3/433 (0.7)	1/112 (0.9)	0.825
Peak LT during entire hospital course (including admission)							
AST (U/L)	59 (52)	57 (51)	69 (74)	0.024	51 (55.5)	76.5 (55.5)	<0.001
ALT (U/L)	54 (69)	54 (74)	47 (54)	0.008	49 (62.8)	76 (91.8)	<0.001
ALP (U/L)	82 (43)	80 (41)	87 (59)	0.075	79 (39.8)	102 (61.8)	<0.001
T. bilirubin	0.60 (0.40)	0.60 (0.40)	0.70 (0.61)	0.005	0.59 (0.40)	0.74 (0.51)	<0.001
AST ≥ ULN	348/560 (62.1)	290/479 (60.5)	58/81 (71.6)	0.058	243/444 (54.7)	101/112 (90.2)	<0.001
ALT ≥ ULN	353/549 (64.3)	311/470 (66.2)	42/79 (53.2)	0.026	260/433 (60)	90/112 (80.4)	<0.001
AST or ALT ≥ ULN	396/549 (72.1)	337/470 (71.6)	59/79 (74.7)	0.584	288/433 (66.5)	104/112 (92.9)	<0.001
ALP ≥ ULN	121/549 (22)	95/470 (20.2)	26/79 (32.9)	0.012	76/433 (17.6)	44/112 (39.3)	<0.001
T. bilirubin ≥1 mg/dl	97/549 (17.7)	72/470 (15.3)	25/79 (31.6)	<0.001	56/433 (12.9)	39/112 (34.8)	<0.001
T. bilirubin ≥2 mg/dl	16/549 (2.9)	13/470 (2.8)	3/79 (3.8)	0.614	12/433 (2.8)	4/112 (3.6)	0.655
AST ≥3 × ULN	67/549 (12.2)	56/470 (11.9)	11/79 (13.9)	0.614	45/433 (10.4)	22/112 (19.6)	0.008
ALT ≥3 × ULN	110/549 (20)	103/470 (21.9)	7/79 (8.9)	0.007	77/433 (17.8)	32/112 (28.6)	0.011
AST or ALT ≥3 × ULN	123/549(22.4)	110/470 (23.4)	13/79 (16.5)	0.171	86/433 (19.9)	36/112 (32.1)	0.235
ALP ≥3 × ULN	6/549 (1.1)	5/470 (1.1)	1/79 (1.3)	0.873	3/430 (0.7)	3/112 (2.7)	0.073
New LT elevation during hospitalization among those with normal admission LFTs (normal AST, ALT, ALP, and total bilirubin)							
AST ≥ ULN	33/186 (17.7)	25/163 (15.3)	8/23 (34.8)	0.022	17/163 (10.4)	16/23 (69.6)	<0.001
AST ≥3 × ULN	2/186 (1.1)	2/163 (1.2)	0/23 (0)	1.000	1/163 (0.6)	1/23 (4.3)	0.232
ALT ≥ ULN	44//186 (23.7)	40/163 (24.5)	4/23 (17.4)	0.603	30/163 (18.4)	14/23 (60.9)	<0.001
ALT ≥3 × ULN	5/186 (2.7)	5/163 (3.1)	0/23 (0)	1.000	3/163 (1.8)	2/23 (8.7)	0.116
AST or ALT ≥ ULN	51/186 (27.4)	43/163 (26.4)	8/23 (34.8)	0.398	34/163 (20.9)	17/23 (73.9)	<0.001
AST or ALT ≥3 × ULN	5/186 (2.7)	5/163 (3.1)	0/23 (0)	1.000	3/163 (1.8)	2/23 (8.7)	0.116
ALP ≥ ULN	8/186 (4.3)	5/163 (3.1)	3/23 (13)	0.061	2/163 (1.2)	6/23 (26.1)	<0.001
ALP ≥3 × ULN	0/186	-	-	-	-	-	-
T. bilirubin ≥1 mg/dl	7/186 (3.8)	6/163 (3.7)	1/23 (4.3)	1.000	4/163 (2.5)	3/23 (13)	0.042

Values are reported as median (IQR) for continuous variables and incidence (%) for categorical variables.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; ULN, upper limit of normal.

three-fourths, respectively. Though this is much higher than the reported 20–40% earlier during the pandemic, most early studies and meta-analyses were from China, and included significantly younger cohorts [7–11]. More recent reports from the USA have reported prevalence similar to ours [12,13]. Combined with our findings, these latter reports suggest Americans hospitalized with COVID-19 may be at higher risk of liver injury. Besides age, the higher risk is likely multifactorial, including perhaps a higher prevalence of obesity and nonalcoholic steatohepatitis, chronic hepatitis C, alcohol use, and more widespread chronic medication use (e.g. statins). Whether this higher risk should factor into selective use and monitoring of hepatotoxic medications (antibiotics, anti-virals, statins, etc.) is worth further investigation. Also similar to previous reports, the predominant pattern of LT abnormalities in our cohort was hepatocellular, that is, transaminase elevation without ALP or bilirubin elevation. Notably, about one-fifth of patients during the course of their illness developed AST or ALT ≥3 × ULN, a rate that is fairly consistent among the few reports that have examined degrees of transaminase elevations [12–14]. However, almost all these cases occurred in patients who had some admission AST/ALT elevation, indicating liver involvement begins early, and there is a continuum of liver injury as some of these patients develop severe hepatic injury during the course of disease. Put another way, majority of LT elevations were present on admission, before healthcare and hence hepatotoxic medication exposure. Second, inflammatory markers-most importantly ferritin-emerged as the most consistent 'non-LT' predictors of LT elevations. To our knowledge, the only other cohort reporting inflammatory markers, Phipps *et al.* [13] found ferritin to be the only inflammatory marker associated with ALT >5 × ULN.

Intriguingly, age in our cohort was inversely associated with either AST or ALT elevation, when the latter two are considered a single variable. However, this relationship was driven largely by the impact of age on ALT, but not AST. Consistent with our findings, Hundt *et al.* [12], among 1827 hospitalized COVID-19 patients, found that patients with any admission ALT elevation or ALT ≥5 × ULN at peak were significantly younger than those without. Similarly, Phipps *et al.* [13], among 3381 patients (inpatient and outpatient) found that patients with ALT <2 × ULN were significantly older than those with ALT 2–5 × ULN or ALT >5 × ULN. Although age in their cohort was negatively predictive of ALT >5 × ULN on univariate analysis (OR

Table 3. Predictors of admission LT during hospitalization, adjusted for age, sex, chronic medical illness (hypertension, heart failure, chronic renal disease stage 3 or higher, vascular disease, malignancy, autoimmune disease, or pulmonary disease), chronic liver disease, myocardial injury, renal injury, other LT, procalcitonin, ferritin, and d-dimer

		Admission		
LT abnormality	Predictor	OR (95% CI)	*P* value	Model AUC
AST ≥ ULN	AKI on admission	3.074 (1.055–8.959)	0.040	0.839 (0.800–0.878)
	Ferritin ≥ 500	2.092 (1.204–3.634)	0.009	
	D-dimer >1.0	1.785 (1.035–3.079)	0.037	
	ALT elevated	9.834 (5.748–16.824)	<0.001	
	ALP elevated	2.435 (1.020–5.814)	0.045	
	T. bilirubin ≥ 1 mg/dl	2.948 (1.157–7.510)	0.023	
ALT ≥ ULN	Age	0.971 (0.953–0.988)	0.001	0.858 (0.821–0.895)
	Tn ≥ 0.05 ng/ml	0.412 (0.211–0.805)	0.010	
	Ferritin ≥ 500	2.576 (1.463–4.536)	0.035	
	AST elevated	11.753 (6.792–20.337)	<0.001	
ALP ≥ ULN	Ferritin ≥ 500	0.423 (0.211–0.846)	0.015	0.693 (0.622–0.765)
	AST elevated	3.042 (1.413–6.550)	0.0048	
	T. bilirubin ≥ 1 mg/dl	2.428 (1.112–5.303)	0.026	
T. bilirubin ≥ 1.0	Male sex	6.961 (2.393–20.247)	<0.001	0.775 (0.714–0.835)
	AST elevated	2.999 (1.322–6.803)	0.009	
	ALP elevated	2.479 (1.090–5.638)	0.030	
AST or ALT ≥ ULN	Age	0.982 (0.967–0.998)	0.025	0.761 (0.715–0.807)
	AKI on admission	3.995 (1.362–11.720)	0.012	
	Elevated ALP	5.704 (2.161–15.054)	<0.001	
	T. bilirubin ≥ 1 mg/dl	2.727 (1.051–7.076)	0.039	
	Ferritin ≥ 500	5.303 (3.214–8.750)	<0.001	
AST or ALT ≥ 3 × ULN	Elevated ALP	6.234 (2.583–15.045)	<0.001	0.749 (0.681–0.817)
	T. bilirubin ≥ 1 mg/dl	3.783 (1.615–8.860)	0.002	
	Ferritin ≥ 500	11.741 (2.626–52.483)	0.001	

AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; IQR, interquartile range; LT, liver test; OR, odds ratio; ULN, upper limit of normal.

0.99, 0.97–1.0, $P = 0.015$), it was borderline significant on multivariate analysis (OR 0.98, 0.97–1.00, $P = 0.058$). As background, it has been amply demonstrated in large population studies that ALT declines significantly with age, likely due to decreasing adiposity, muscle mass, vitamin B6 deficiency (required for ALT biosynthesis), declining liver mass/function, and lower prevalence of alcohol use with advancing age [15–17]. On the other hand, most early cohorts from China have not found any age difference between those with or without elevated transaminases, perhaps partly because most used the composite end-point of elevated AST or ALT, in addition to being much younger [7,14,18,19]. Under normal circumstances, plasma AST and ALT levels reflect an equilibrium between enzyme leak resulting from normal hepatocyte turnover and clearance from plasma. Since ALT is far more liver-specific than AST, it stands to reason that a declining hepatocellular mass- as can be expected with aging- should express itself as a declining plasma ALT activity more so than the less specific AST. In general, AST levels have been found to be higher than ALT levels among COVID-19 patients, especially in studies from outside China [20,21].

We found only peak AST was associated with both severe disease and mortality. On the other hand, we found an inverse relationship between peak ALT and mortality, which was independent of age. Put another way, a failure or inability to raise ALT as the disease progressed portended a worse outcome. Importantly, low ALT levels have been well-established as markers of frailty, especially in the elderly, and have been significantly associated with long-term mortality as well as worse short-term outcomes among a wide range of hospitalized patients [22–26]. Ours is the first cohort to suggest that this adverse prognostic value of low ALT may extend to hospitalized COVID-19 patients. Intriguingly, Hundt *et al.* [12] found a negative independent association between elevated peak ALT and death (OR 0.88), albeit not reaching statistical significance. Moreover, our findings suggest that combining the two variables (AST or ALT) into one, as has often been done in published reports, is likely not sound practice. Indeed, when we combined the two as one variable, that is, defined liver injury as either AST or ALT elevation, it ceased to have a significant association with mortality. Hence, defining liver injury as either AST or ALT elevation is likely to confound any analysis of outcomes among COVID-19 patients. On the other hand, the AST/ALT ratio, by incorporating both risk factors, that is, elevated AST and low ALT, intuitively emerges as an attractive predictor to examine. Indeed, we found the AST:ALT ratio on admission as well as peak independently predicting mortality, arguably even proving superior to inflammatory markers. Famously known as the De Ritis Ratio, the AST:ALT ratio has been known for over half a century to have utility as an indicator of the etiology of liver injury, usually <1.0 in viral hepatitis and >1.5–2.0 in alcoholic hepatitis [27]. Though usually <1.0 in acute viral hepatitis, an inverted ratio (where AST is much higher than ALT) has been noted to be a marker of fulminant hepatitis and a poor prognosis [27]. Moreover, a high AST:ALT ratio has also been noted to be a marker of underlying fibrosis/cirrhosis among patients with chronic liver disease of diverse etiologies [28–30]. Several mechanisms have been proposed to explain the prognostic utility of the AST:ALT ratio, depending on the underlying insult [27].

Interestingly, and certainly a novel finding, we found elevated admission and peak total bilirubin to be a significant predictor of mortality. Though by no means a novel finding, ours is the first cohort to demonstrate it is an independent marker of mortality when adjusted for age, medical co-morbidities, other major organ injuries,

Table 4. Predictors of peak LT during hospitalization, adjusted for age, sex, chronic medical illness (hypertension, heart failure, chronic renal disease stage 3 or higher, vascular disease, malignancy, autoimmune disease, or pulmonary disease), chronic liver disease, myocardial injury, renal injury, other LT, procalcitonin, ferritin, and d-dimer

	Peak LTs during hospitalization			
LT abnormality	Predictor	OR (95% CI)	*P* value	Model AUC
AST ≥ ULN	Elevated peak ALT	25.127 (12.214–51.691)	<0.001	0.882 (0.844–0.919)
	Peak T. bilirubin ≥ 1.0 mg/dl	4.236 (1.172–15.313)	0.028	
	Peak procalcitonin ≥ 0.5	4.586 (1.947–10.800)	<0.001	
	Peak ferritin ≥ 500	2.457 (1.292–4.672)	0.006	
	Peak d-dimer ≥ 1.0	2.115 (1.093–4.092)	0.026	
ALT ≥ ULN	Male sex	2.310 (1.234–4.325)	0.009	0.875 (0.839–0.911)
	Tn ≥ 0.05 ng/ml	0.411 (0.187–0.903)	0.027	
	Elevated peak AST	28.859 (13.928–59.795)	<0.001	
	Elevated peal ALP	2.545 (1.029–6.299)	0.043	
ALP ≥ ULN	Male sex	0.506 (0.279–0.919)	0.025	0.727 (0.672–0.783)
	Elevated peak ALT	3.462 (1.581–7.584)	0.002	
	Peak T. bilirubin ≥ 1.0 mg/dl	2.749 (1.474–5.128)	0.001	
	Peak Tn ≥ 0.05 ng/ml	1.885 (1.040–3.418)	0.037	
	Peak procalcitonin ≥ 0.5	1.983 (1.129–3.483)	0.017	
T. bilirubin ≥ 1.0 mg/dl	Male sex	5.998 (2.703–13.309)	<0.001	0.809 (0.763–0.854)
	Elevated peak AST	6.323 (1.864–21.446)	0.003	
	Elevated peak ALP	2.824 (1.429–5.580)	0.003	
	AKI	2.162 (1.013–4.615)	0.046	
	Peak Procalcitonin ≥ 0.5	1.914 (1.025–3.573)	0.042	
AST ≥ 3 × ULN	Peak ALT ≥ 3 × ULN	26.321 (11.096–62.434)	<0.001	0.922 (0.891–0.952)
	Elevated peak ALP	3.153 (1.424–6.986)	0.005	
	Peak T bilirubin ≥ 1.0 mg/dl	3.298 (1.477–7.368)	0.004	
	Peak d-dimer ≥ 1.0	2.889 (1.043–8.001)	0.041	
ALT ≥ 3 × ULN	Peak AST ≥ 3 × ULN	22.867 (9.556–54.716)	<0.001	0.841 (0.798–0.884)
	Elevated peak ALP	2.099 (1.040–4.236)	0.038	
	Peak Ferritin ≥ 500	5.252 (1.932–14.278)	0.001	
AST or ALT ≥ ULN	Age	0.971 (0.952–0.990)	0.003	0.815 (0.766–0.863)
	Elevated peak ALP	5.398 (1.784–16.331)	0.003	
	Peak T. bilirubin ≥ 1.0 mg/dl	4.194 (1.214–14.491)	0.023	
	Peak ferritin ≥ 500	3.558 (1.993–6.350)	<0.001	
	Peak procalcitonin ≥ 0.5	2.187 (1.001–4.779)	0.050	
AST or ALT ≥ 3 × ULN	Elevated peak ALP	3.775 (2.068–6.892)	<0.001	0.790 (0.746–0.834)
	Peak T. bilirubin ≥ 1.0 mg/dl	2.478 (1.353–4.542)	0.003	
	Peak ferritin ≥ 500	5.743 (2.426–13.594)	<0.001	

AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; LT, liver test; OR, odds ratio; ULN, upper limit of normal.

Table 5. Impact of LT abnormalities on mortality and risk of mechanical ventilation

	Mortality			Mechanical ventilation	
Predictor	OR (95% CI)	*P* value	Predictor	OR (95% CI)	*P* value
Admission variables					
Age	1.076 (1.046–1.107)	<0.001	D-dimer ≥ 1.0	2.486 (1.441–4.288)	0.001
Ch. medical illness	3.563 (1.438–8.832)	0.006	Ferritin ≥ 500	2.322 (1.335–4.039)	0.003
Tn ≥ 0.05 ng/ml	3.347 (1.664–6.733)	0.001	Procalcitonin ≥ 0.5	1.788 (1.011–3.160)	0.046
Bilirubin ≥ 1.0 mg/dl	3.553 (1.524–8.281)	0.003			
Procalcitonin ≥ 0.5	2.256 (1.069–4.761)	0.033			
Peak variables					
Age	1.082 (1.049–1.115)	<0.001	AKI	2.844 (1.572–5.144)	0.001
Chronic medical illness	2.508 (0.964–6.522)	0.059	Elevated peak AST	2.798 (1.304–6.001)	0.008
Elevated peak ALT	0.118 (0.038–0.362)	<0.001	Peak D-dimer ≥ 1.0	3.738 (1.706–8.190)	0.001
Elevated peak AST	9.770 (2.496–38.247)	0.001	Peak procalcitonin ≥ 0.5	3.017 (1.710–5.323)	<0.001
Peak bilirubin ≥ 1.0 mg/dl	4.099 (1.752–9.587)	0.001			
Peak Tn ≥ 0.05 ng/ml	3.146 (1.507–6.568)	0.002			
Peak procalcitonin ≥ 0.5	2.296 (1.012–5.209)	0.047			

Admission markers and mortality: $R^2 = 0.344$; AUC = 0.848 (0.796–0.900, $P < 0.001$).
Admission markers and mechanical ventilation: $R^2 = 0.119$; AUC = 0.694 (0.637–0.752, $P < 0.001$).
Peak markers and mortality: $R^2 = 0.454$; AUC = 0.865 (0.819–0.911, $P < 0.001$).
Peak markers and mechanical ventilation: $R^2 = 0.355$; AUC = 0.825 (0.781–0.870, $P < 0.001$).
AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; LT, liver test; OR, odds ratio; ULN, upper limit of normal.

as well as other LT abnormalities. Hundt *et al.* [12] found elevated bilirubin to be the only LT on admission predictive of death, when adjusted for age, diabetes, sex, BMI, other LTs, and select medications. Furthermore, hyperbilirubinemia is common in acute illness, due to a combination of cholestasis, inflammation, hemolysis, medications, etc., and is incorporated into multiple prediction and organ assessment scores [31]. In the current

Table 6. Multivariate predictors of mortality at admission, and at peak, adjusted for age, chronic medical illness (hypertension, diabetes, heart failure, chronic kidney disease, malignancy, chronic pulmonary disease, and chronic liver disease), aspartate aminotransferase:alanine aminotransferase ratio, total bilirubin, and the inflammatory marker ferritin, d-dimer and procalcitonin

Predictor	Mortality, OR (95% CI)	*P* value	Model AUC/R^2
Admission variables			
Age	1.071 (1.042–1.101)	<0.001	R^2 = 0.366
Chronic medical illness	3.872 (1.536–9.763)	0.004	AUC = 0.848 (0.794-0.902, P < 0.001)
Tn ≥ 0.05 ng/ml	3.011 (1.477–6.139)	0.002	
Bilirubin ≥ 1.0 mg/dl	3.656 (1.553–8.603)	0.003	
Admission AST:ALT ratio	2.049 (1.273–3.300)	0.003	
Peak variables			
Age	1.071 (1.041–1.102)	<0.001	R^2 = 0.455
Chronic medical illness	2.601 (1.021–6.628)	0.045	AUC = 0.867 (0.820-0.915, P < 0.001
Peak Tn ≥ 0.05 ng/ml	2.563 (1.217–5.398)	0.013	
Peak bilirubin ≥ 1.0 mg/dl	3.842 (1.697–8.697)	0.001	
Peak procalcitonin ≥ 0.5	2.931 (1.314–6.535)	0.009	
Peak AST:ALT ratio	2.755 (1.630–4.658)	<0.001	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; CI, confidence interval; OR, odds ratio.

context, disease severity scores such as the Sequential Organ Failure Assessment score which incorporate elevated bilirubin have consistently been found to predict mortality among hospitalized COVID-19 patients [8,32,33]. Interestingly, of the 64 patients in our cohort with elevated bilirubin, 12 occurred in patients with no transaminase or ALP elevation, and 37 occurred in those with elevated transaminases but normal ALP, indicating that about 20% of patients likely had hyperbilirubinemia of non-hepatic origin, and cholestasis was not the underlying mechanism in majority of patients. Moreover, that bilirubinemia ≥2 mg/dl was extremely rare on admission and at peak argues against cholestasis as a significant mechanism. In this regard, we found AKI to be an independent predictor of elevated peak bilirubin, suggesting a putative mechanism for bilirubin elevation independent of the liver. Additionally, some degree of hemolysis that usually occurs during any severe illness could be contributing. Hence, we performed a purely exploratory analysis in a subset of patients with plasma lactate dehydrogenase (LDH) levels assayed (Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A643*). In fact, there was a significant, though admittedly not very strong linear association between bilirubin and LDH levels, both on admission (R = 0.244, R^2 = 0.06, P < 0.001) and at peak (R = 0.30, R^2 = 0.091, P < 0.001, Supplementary Appendix, Supplemental digital content 1, *http://links.lww.com/EJGH/A643*). However, the nonspecificity of LDH in general, and expected elevation in patients with liver and myocardial injuries make it difficult to categorically make such an assertion from our data.

Liver injury in COVID-19 is likely multifactorial, as in most severe infections, including hypoxia, inflammation, hemodynamic stress due to septic shock, as well as drug-induced liver injury from antibiotics/anti-viral commonly administered to these patients. It remains unclear whether there is direct cytopathic effect of SARS-CoV-2 on hepatocytes. Several findings argue against direct hepatic cytopathy. First, the ACE2 receptor, now firmly established as the cellular receptor for SARS-CoV-2, is relatively scantily expressed in the liver, and that too mostly in cholangiocytes [34–37]. Intuitively, if direct cytopathy were a significant contributor to hepatic injury, bilirubinemia should be significantly more common, and indeed more severe, than has been observed in our cohort and by others. Second, vast majority of LT elevations among COVID-19 patients are mild (<3 × ULN). Lastly, autopsy series among COVID-19 patients have shown generally nonspecific liver findings, with between patient differences explained largely by underlying infection severity. A 12-patient autopsy series from Washington state revealed predominantly chronic changes, variable congestion, and centrilobular necrosis seen in shock liver, with scant inflammation, as would be expected with direct cytopathy.38 Moreover, weak hepatic SARS-CoV-2 staining was indistinguishable from background. Similar findings have been reported in multiple autopsy series [38–41]. Contrariwise, viral RNA has been isolated from the liver in several series. Interestingly, Wichmann *et al.* [40], in an autopsy series of 12 patients with COVID-19 found SARS-CoV-2 RNA in the lungs of all 12 patients regardless of presence of viremia. On the other hand, viral RNA was only detected in the liver among viremic patients, suggesting that the presence of viral RNA in liver is a natural consequence of the viremia, rather than evidence of direct hepatocellular involvement.

To conclude, the strong association between systemic inflammation and LT abnormalities, a predominance of LT elevation in what would be considered mild range, a lack of association between the more specific transaminase (ALT) and mortality-indeed the reverse- as demonstrated in our cohort, and a lack of histopathological evidence of direct hepatocellular cytopathy, all argue that the role of liver in COVID-19 is that of an 'innocent bystander'. Regardless, by being a surrogate for the degree of inflammation, and hypoxic/ischemic burden in severely sick patients, it remains a significant predictor of mortality, specifically hyperbilirubinemia. The most novel findings in our cohort was a divergent association between ALT/AST and mortality. Hence, AST:ALT ratio may be a better prognostic marker than either transaminase alone.

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Data supporting the findings in this study are available from the corresponding author upon reasonable request.

Conflicts of interest

There are no conflicts of interest.

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