Predictors and Outcomes of Hospitalized COVID-19 Patients with Liver Injury

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ABSTRACT

Objective. To determine incidence, predictors, and impact of liver injury among hospitalized COVID-19 patients

Methods. This is a retrospective cohort study of hospitalized COVID-19 patients at the University of the Philippines-Philippine General Hospital. Liver injury (LI) was defined as ALT elevation above institutional cut-off (>50 u/L) and was classified as mild (>1x to 3x ULN), moderate (>3x to 5x ULN), or severe (>5x ULN). Significant liver injury (SLI) was defined as moderate to severe LI. Univariate analysis of SLI predictors was performed. The impact of LI on clinical outcomes was determined and adjusted for known predictors -age, sex, and comorbidities.

Results. Of the 1,131 patients, 565 (50.04%) developed LI. SLI was associated with male sex, alcohol use, chronic liver disease, increasing COVID-19 severity, high bilirubin, AST, LDH, CRP, and low lymphocyte count and albumin. An increasing degree of LI correlated with ICU admission. Only severe LI was associated with the risk of invasive ventilation (OR: 3.54, p=0.01) and mortality (OR: 2.76, p=0.01). Severe LI, male sex, cardiovascular disease, and malignancy were associated with longer hospital stay among survivors.

Conclusion. The liver injury occurred commonly among COVID-19 patients and was associated with important clinico-demographic characteristics. Severe liver injury increases the risk of adverse outcomes among hospitalized patients.

Keywords: Liver injury; Coronavirus disease-19; Severe Acute Respiratory Syndrome Coronavirus-2; Clinical outcomes; Alanine aminotransferase elevation

INTRODUCTION

On March 12, 2020, COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic. Since the initial outbreak in Wuhan, China, last December 2019, confirmed cases have reached more than 170 million, with mortalities at approximately 3.5 million globally as of June 1, 2021. There are now roughly 1.2 million confirmed cases and 20,000 deaths in the Philippines as of the same date.[1]

SARS-CoV-2 is a novel enveloped RNA beta coronavirus that shares 82% genome sequence similarity to SARS-CoV and 50% genome sequence homology to Middle East respiratory syndrome coronavirus (MERS-CoV) — with all three coronaviruses known to cause severe respiratory symptoms. Interestingly, liver impairment was previously reported in up to 60% of patients with SARS-CoV in 2004.[2] MERS CoV, first isolated in Saudi Arabia in 2012, was also reported to cause liver test abnormalities such as elevated transaminases, bilirubin and hypoalbuminemia.[3,4]

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For COVID-19, the main symptoms include fever, cough, colds, and dyspnea. Some patients develop acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure. Liver involvement has been described mainly by abnormal aminotransferases. It has been described in 14-65% of COVID-19 patients.[5-10] Liver injury was observed more frequently among those with more severe COVID-19 than those with mild disease.[2,11] Elevated alanine aminotransferase (ALT) and bilirubin levels have been shown in pooled studies to be associated with poor survival and unfavorable clinical course.[12,13] In these previous studies, the authors stated that the reason they were related to poor outcomes was unclear. Still, they did highlight that recognizing an elevated ALT and bilirubin should alert physicians that these patients are likely to develop adverse outcomes and thus should prioritize early intervention.

There is no data on liver injury among COVID-19 patients in the Philippines, and there is limited data in Southeast Asia. This study aimed to determine the incidence, predictors, and impact of liver injury among patients with COVID-19 admitted to the hospital.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted at the University of the Philippines-Philippine General Hospital (UP-PGH), a tertiary and designated COVID-19 referral center. The study was approved by the Technical Review Board (TRB) of the Department of Internal Medicine and by the University of the Philippines Manila Research Ethics Board. Informed consent was waived due to its retrospective nature.

Study Population

All adult patients aged 19 years old and above with laboratory-confirmed COVID-19 disease (SARS-CoV-2 virus detected via RT-PCR on nasopharyngeal swab) and admitted to the UP-PGH from March 1, 2020, to September 15, 2020, were eligible for study inclusion. Patients who died or were discharged within 24 hours or transferred to another hospital, those with unavailable medical records, and those who remained admitted for a coexisting illness were excluded. Those who were asymptomatic (i.e., positive SARS-CoV-2 tests from contract tracing, surveillance, pre-employment evaluation, and admitted for reasons other than COVID-19 such as dialysis, surgery, and chemotherapy, pregnant on admission, and without ALT determination were also excluded from the study. (Figure 1)

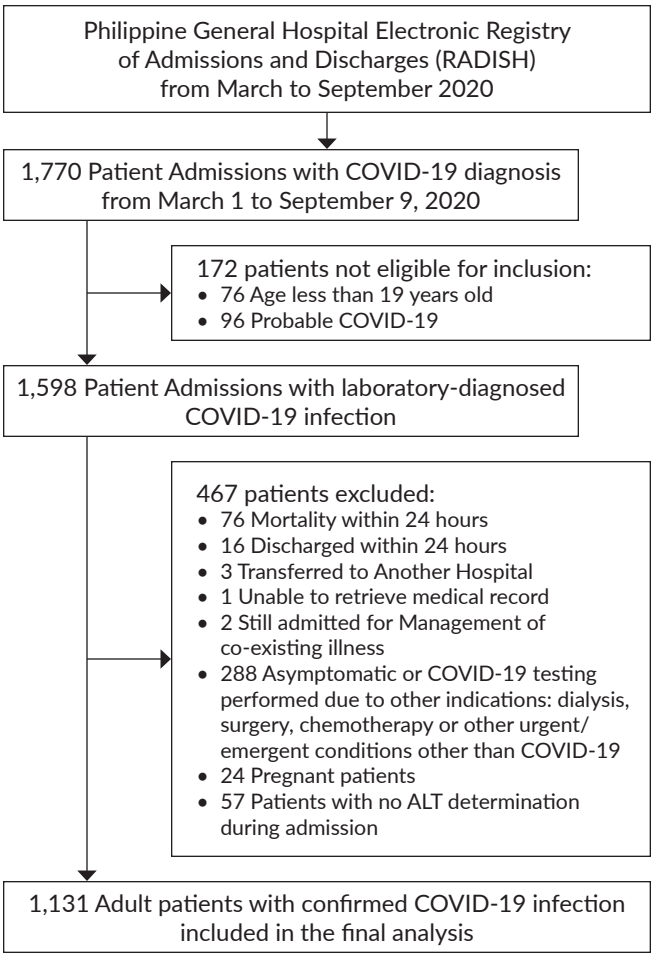

Figure 1. Flow diagram of the study.

Variables and Outcomes

Study variables included age, sex, comorbid illnesses, COVID-19 severity upon admission, baseline laboratory tests and peak ALT levels, use of COVID-19-specific medications, and length of hospital stay. The use of antibiotics was not included as part of the variables.

The severity of COVID-19 was classified according to the Interim Guidance on the Clinical Management of Adult Patients with Suspected or Confirmed COVID-19 Infection (Version 3.1).[14] COVID-19 was classified as mild - patients with symptoms of COVID-19 without pneumonia; moderate - patients with clinical and radiographic evidence of pneumonia but not requiring oxygen; severe - patients with clinical and radiographic evidence of pneumonia with oxygen saturation <92% on room air and requiring oxygen support; critical - patients with ARDS, septic shock, requiring mechanical ventilation and admission to the intensive care unit (ICU) or both.[14,15]

For this study, liver injury (LI) was defined as an elevation of ALT above the upper limit of normal (normal value was based on the institutional cut-off of 50 u/L) at any time during admission. ALT was chosen over AST because it is more specific to the liver. Other measures of liver function, including albumin, bilirubin, and international normalized ratio (INR), were not included in the definition, given the multifactorial causes for these abnormal values, especially in this clinical setting. The severity of LI was defined according to prior published studies.[16,17] and the Common Terminology

Criteria for Adverse Events (CTCAE) version 5.0.[18] Mild LI was an ALT level >1 to 3x ULN, moderate LI was an ALT level >3 to 5x ULN, and severe LI was an ALT >5x ULN. Significant liver injury (SLI) was defined as moderate to severe liver injury.

Clinical outcomes recorded included: ICU admission, intubation or invasive ventilation, renal replacement therapy (RRT), and in-hospital mortality. The patients were followed-up until discharge or death.

Data Collection and Statistical Analysis

The data were extracted by manual chart review and through established electronic databases [(e.g., RADISH - Computerized Registry of Admission and Discharges, PGH Medical Record System (OpenMRS)]. The principal investigator and designated encoders recorded the data using Microsoft Excel software.

Descriptive statistics were used, such as mean and standard deviation for age, while the median and interquartile range were used to present the laboratory values and length of stay. Frequency and percentage were used for the categorical data variables such as sex, presence of comorbid illnesses, and clinical outcomes.

One-way analysis of variance was used to analyze the association between age and liver injury. A series of chi-square and Kruskal-Wallis tests were used to analyze the association between remaining clinical and demographic variables and liver injury. Univariate logistic regression was performed to determine predictors of SLI. Only those variables with differences across the severity categories of LI with a p-value <0.05 were included. Given the limited number of patients with complete data points, multivariate logistic regression was not performed.

A series of univariate and multivariate logistic regression models were performed to determine the association between the severity of the liver injury and clinical outcomes. The adjustment was carried out for known adverse clinical outcomes risk factors such as age, sex, cardiovascular disease, diabetes, and malignancy.[19-23] cardiovascular disease was defined as the presence of either hypertension or heart disease, or both.

In addition, a pair of multiple linear regression models were used to determine the association between length of hospital stay and the selected covariates (i.e., the severity of LI, age, sex, comorbid conditions including cardiovascular disease, diabetes, and malignancy) in the logistic regression models – for the survivors and non-survivors in the study cohort.

The significance level for all analysis sets was set at a p-value <0.05 using two-tailed comparisons. The non-parametric methods did not provide a multiple comparisons procedure. Thus Wilcoxon rank-sum tests were used as post hoc methods. Data processing and analysis were then carried out using Stata 13 (College Station, Texas).

RESULTS

Association between clinical and demographic characteristics of patients admitted with COVID-19 and LI

Of the 1,770 patients admitted with a diagnosis of COVID-19 during the study period, 1,131 were included in the study cohort. Liver injury was seen in 565 (50%) patients, characterized as mild 374 (33.1%), moderate 110 (9.7%), and severe 81 (7.2%). The baseline clinical and demographic characteristics, COVID-19-specific medications, and length of stay of the entire cohort according to the severity of LI are summarized in Tables 1 and 2. The average age was 54.2 years, of whom 613 (54%) were males. Age was not associated with LI, but there were significantly more males with LI ($p < 0.01$). Hypertension (48%) and diabetes mellitus (26%) were the most common comorbidities. Chronic liver disease ($p < 0.01$) and chronic kidney disease ($p = 0.02$) were more common to patients with LI. There were 11 patients with chronic liver disease. The most common was Hepatitis B infection (6/11, 55%). Other causes of CLD included NAFLD (2/11, 18%), Hepatitis C infection (2/11, 18%), and hepatobiliary TB (1/11, 9%). Increasing severity of LI was demonstrated with increasing severity of COVID-19 ($p < 0.01$).

Liver injury was associated with lower hemoglobin ($p < 0.01$), higher hematocrit ($p < 0.01$), higher WBC ($p=0.01$), and lower lymphocyte count ($p < 0.01$). Increasing severity of liver injury was associated with higher AST ($p < 0.01$) and bilirubin levels ($p = 0.01$), and lower albumin levels ($p = 0.01$). Markers of inflammation were higher among patients with LI: lactate dehydrogenase (LDH), serum ferritin, procalcitonin, and C-reactive protein (CRP) (All $p < 0.01$).

A higher proportion of patients with LI received tocilizumab ($p < 0.01$) and remdesivir ($p < 0.01$). LI was associated with longer hospital stays ($p = 0.01$) which was only observed among survivors. No differences in the length of stay were seen among non-survivors ($p = 0.62$).

Predictors of Significant Liver Injury (SLI)

On univariate logistic regression, male sex ($p = 0.01$), alcohol use ($p < 0.01$), and the presence of chronic liver disease ($p = 0.01$) were significantly associated with SLI. Increasing severity of COVID-19 was associated with increasing risk of SLI. Among the laboratory values, SLI was associated with an increased level of total bilirubin ($p <0.01$), AST ($p = 0.01$) and inflammatory markers including LDH ($p < 0.01$), ferritin ($p = 0.01$) and CRP > 12 ($p < 0.01$). Conversely, a low lymphocyte count ($p < 0.01$) and albumin ($p = 0.01$) were both correlated with SLI. Tocilizumab use was associated with SLI ($p < 0.01$) while remdesivir was not. (Table 3)

Impact of LI on clinical outcomes

Two hundred twelve (18.7%) patients died during the study period. Of the 1131 patients, 443 (39.2%) required

Table 1. Baseline clinical and demographic characteristics of study cohort according to severity of liver injury (LI)

Characteristics	Overall n= 1131	Severity of Liver Injury				p-value
		No LI n= 566	Mild n= 374	Moderate n= 110	Severe n= 81	
Age in years *(mean ± SD)*	54.2 ± 16.5	53.9 ± 17.2	54.4 ± 15.9	54.1 ± 15.7	55.9 ± 15.3	0.79
Sex						
Female	518 (45.8%)	322 (56.9%)	130 (34.7%)	38 (34.6%)	28 (34.6%)	<0.01
Male	613 (54.2%)	244 (43.1%)	244 (65.2%)	72 (65.5%)	53 (65.4%)	
History of smoking	248 (21.9%)	108 (19%)	86 (22%)	27 (24.6%)	27 (33.3%)	0.01
History of alcohol drinking	270 (23.9%)	116 (20.5%)	95 (25.4)	33 (30%)	26 (32.1%)	0.01
Comorbid Conditions						
Diabetes mellitus	296 (26.2%)	159 (28.1%)	95 (25.4%)	25 (22.7%)	17 (21%)	0.39
Hypertension	552 (48.8%)	272 (48.1%)	191 (51%)	49 (44.6%)	40 (49.4%)	0.64
Heart Disease	158 (14%)	79 (13.96%)	53 (14.17%)	9 (8.18%)	17 (20.99%)	0.09
Chronic Liver Disease	11 (0.1%)	2 (0.4%)	2 (0.5%)	2 (1.8%)	5 (6.2%)	<0.01
Chronic Kidney Disease	102 (9.0%)	63 (11.1%)	24 (6.4%)	5 (4.6%)	10 (12.4%)	0.02
Chronic Obstructive Pulmonary Disease / Bronchial Asthma	112 (9.9%)	59 (10.4%)	38 (10.2%)	5 (4.6%)	10 (12.4%)	0.23
Malignancy	64 (5.7%)	38 (6.7%)	16 (4.3%)	7 (6.4%)	3 (3.7%)	0.36
Severity upon admission						
Mild	181 (16%)	129 (22.8%)	44 (11.8%)	5 (4.6%)	3 (3.7%)	<0.01
Moderate	450 (39.8%)	251 (44.4%)	142 (38%)	35 (31.8%)	22 (27.2%)	
Severe	169 (14.9%)	75 (13.3%)	61 (16.3%)	19 (17.3%)	14 (17.3%)	
Critical	331 (29.3%)	111 (19.6%)	127 (34%)	51 (46.4%)	42 (51.9%)	

Table 2. Baseline laboratory data, COVID-19 specific medication use, and length of stay of study cohort according to severity of liver injury (LI)

Characteristics	Overall n=1131	Severity of Liver Injury				p-value
		No LI n=566	Mild n=374	Moderate n=110	Severe n=81	
Clinical Parameters, *median (IQR)*						
Mean arterial pressure *(in mmHg)*	93 (16)	93 (16)	95 (16)	96 (14)	93 (16)	0.61
Hemoglobin *(g/L)*	132 (28)	130 (31)	134 (28)	136 (21)	130 (34)	<0.01
Hematocrit	40 (8)	39 (9)	41 (8)	41 (6)	40 (10)	<0.01
White blood count	7.7 (4.9)	7.4 (4.5)	7.7 (4.8)	9.0 (5.8)	8.5 (7.7)	0.01
Lymphocyte count *(%)*	18 (18)	22 (18)	17 (17)	12 (12)	14 (13)	<0.01
Platelet	270 (154)	275 (147)	264 (155)	286 (159)	254 (157)	0.38
AST *(U/L)*	48 (44)	33 (16)	60 (35)	107 (79)	118 (117)	<0.01
Albumin *(g/L)*	37 (9)	38 (10)	37 (8)	36 (6)	35 (10)	0.01
Total bilirubin *(µmol)*	12.0 (8.6)	10.3 (6.8)	12.0 (8.6)	17.1 (17.1)	13.7 (10.3)	0.01
LDH *(U/L)*	320 (242.5)	273 (163)	356 (258)	491 (340)	466 (328)	<0.01
Ferritin *(ng/mL)*	622 (1151)	342 (707)	891 (1247)	1300 (1510)	1320 (1570)	<0.01
Procalcitonin *(ng/mL)*	0.2 (0.6)	0.1 (0.5)	0.2 (0.5)	0.2 (0.7)	0.5 (2.6)	<0.01
C-reactive protein *(mg/L)* Category *n (%)*						
<6	306 (27.1%)	195 (34.5%)	83 (22.2%)	20 (18.2%)	8 (9.9%)	<0.01
6 to 12	81 (7.2%)	47 (8.3%)	27 (7.2%)	2 (1.8%)	5 (6.2%)	
>12	629 (55.6%)	262 (46.3%)	228 (61%)	79 (71.8%)	60 (74.1%)	
Medications *n (%)*						
Tocilizumab	170 (15.0%)	48 (8.5%)	73 (19.5%)	30 (27.3%)	19 (23.5%)	<0.01
Remdesivir	113 (10%)	34 (6.01%)	54 (14.4%)	16 (14.6%)	9 (11.1%)	<0.01
HCQ/Chloroquine	85 (7.5%)	39 (6.9%)	33 (8.8%)	6 (5.5%)	7 (8.6%)	0.56
Lopinavir/Ritonavir	31 (2.7%)	8 (1.4%)	16 (4.3%)	4 (3.6%)	3 (3.7%)	0.06
Length of Stay *(days), median (IQR)*						
Overall	13 (2-81)	12 (2-70)	13 (2-81)	14 (2-76)	16 (2-51)	0.01
Survivors (n= 919)	14 (2-81)	13 (2-70)	14 (2-81)	15 (5-53)	20 (5-51)	<0.01
Non-survivors (n= 212)	7 (2-76)	6 (2-53)	8 (2-53)	9 (2-76)	7 (2-45)	0.62

Table 3. Predictors of significant liver injury among COVID-19 patients

Predictors	Univariable Odds Ratio (95% CI)	p-value
Sex		
Female	1.00	
Male	1.75 (1.27-2.43)	0.01
Social History		
Smoking	0.98 (0.97-1.01)	0.06
Alcohol drinking	0.99 (0.98-0.99)	<0.01
Comorbid Conditions		
Chronic liver disease	8.90 (2.58-30.72)	0.01
Chronic kidney disease	0.84 (0.47-1.48)	0.54
Severity upon admission		
Mild	1.00	
Moderate	3.14 (1.46-6.72)	0.01
Severe	5.25 (2.35-11.73)	<0.01
Critical	8.45 (4.00-17.86)	<0.01
Clinical Parameters		
Hemoglobin	1.00 (0.97-1.01)	0.39
Hematocrit	1.02 (0.99-1.04)	0.09
White blood count	1.00 (0.99-1.01)	0.18
Lymphocyte count	0.95 (0.94-0.97)	<0.01
AST	1.01 (1.00-1.02)	0.01
Albumin	0.97 (0.94-0.99)	0.01
Total bilirubin	1.19 (1.09-1.30)	<0.01
LDH	1.02 (1.01-1.03)	<0.01
Ferritin	1.03 (1.02-1.04)	0.01
Procalcitonin	1.00 (0.98-1.01)	0.80
C-reactive protein Category		
<6	1.00	
6 to 12	0.94 (0.39-2.24)	0.89
>12	2.82 (1.83-4.34)	<0.01
Medications		
Tocilizumab	2.34 (1.60-3.40)	<0.01
Remdesivir	1.46 (0.91-2.34)	0.12

ICU admission, 235 (20.8%) required intubation and invasive ventilation, and 110 (9.7%) required renal replacement therapy. (Table 4)

Increasing severity of LI was associated with increasing risks of ICU admission [mild LI, OR 1.6 (1.2, 2.2), p = 0.01; moderate LI, OR 3.4 (2.2, 5.4), p < 0.01; and severe LI, OR 7.3 (4.2, 13.0), p < 0.01], intubation and invasive ventilation [severe LI, OR 3.5 (2.1, 6.0)] after adjusting for known risk factors such as age, sex and comorbidities. (Table 4) Increasing severity of LI was also associated with increased risks of RRT, although these estimates did not reach statistical significance after adjustment for known risk factors. Severe LI was associated with a nearly three-fold increased risk of death after adjustment for known risk factors (p = 0.01).

Association between the length of stay and severity of LI

The median length of stay for the study cohort was 13 days, 14 days among survivors, and seven days among non-survivors. On multivariate linear regression, the known risk factors for adverse clinical outcomes (i.e., the severity of LI, age, sex, comorbid conditions including cardiovascular disease, diabetes, and malignancy) did not predict the length of stay among non-survivors. (Table 5)

Among survivors, patients with severe LI were admitted six more days than those without LI. Other predictors of longer length of stay included sex, with male patients hospitalized for three days more than females. Those with cardiovascular disease and malignancy had 4 and 10 days longer admission, respectively, compared to those without cardiovascular disease and malignancy.

DISCUSSION

Our study is one of the largest cohorts in Southeast Asia, which evaluated the incidence of liver injury among hospitalized COVID-19 patients and its association with important clinical outcomes. Several key findings can be drawn from the analyses.

The incidence of LI among COVID-19 subjects in our cohort was 50%. This may be because we only included hospitalized patients and patients with a higher likelihood of severe disease, as our institution was designated as a tertiary COVID-19 referral center. Our findings are still consistent with published reports where the occurrence of elevated liver tests ranged from 14-65% among hospitalized patients.[2,10] The overall prevalence of chronic liver disease in our cohort was 0.1%, which is lower than other studies reporting 1.4-19.9% prevalence. [24,25] However, this may be an underestimation, as patients with chronic Hepatitis B and NAFLD are usually asymptomatic and may not have been tested all during this hospitalization.

Most liver injuries were mild, with only 7% of patients having SLI. The severity of LI directly correlated with increasing COVID-19 severity, as demonstrated by the finding that 28% of critical COVID-19 patients had SLI compared to only 4.4% with mild COVID-19. Previous studies have also shown similar results where abnormally elevated ALT levels were observed more in severe COVID-19.[5,24,25] Consistent with this association between SLI and COVID-19 severity is the finding that patients with SLI had lower lymphocyte count and albumin levels, which are both seen in patients with severe COVID-19.[26]

The mechanism of liver injury is not clearly understood but is thought to represent either direct cytopathic injury, immunologic injury from the profound inflammatory response, or drug-induced liver injury.[2] Liver biopsy specimens from COVID-19 patients have demonstrated a microvesicular, macrovesicular, and mixed type of steatosis and mild lobular and portal activity.[27,28]

Table 4. Predictors of clinical outcomes by severity of liver injury (LI)

Predictors	Unadjusted	p-value	Adjusted*	p-value
	Odds Ratio (95% CI)		Odds Ratio (95% CI)	
ICU Admission *(n=443)*				
No LI	1.00		1.00	
Mild	1.63 (1.24-2.14)	<0.01	1.62 (1.20-2.20)	0.01
Moderate	3.03 (1.99-4.61)	<0.01	3.43 (2.16-5.44)	<0.01
Severe	6.30 (3.74-10.61)	<0.01	7.36 (4.17-12.98)	<0.01
Intubation/Invasive ventilation *(n=235)*				
No LI	1.00		1.00	
Mild	0.99 (0.71-1.40)	0.99	0.93 (0.65-1.34)	0.71
Moderate	1.61 (1.00-2.59)	0.05	1.60 (0.96-2.67)	0.07
Severe	3.42 (2.10-5.58)	<0.01	3.54 (2.09-5.99)	0.01
Renal replacement therapy *(n=110)*				
No LI	1.00		1.00	
Mild	1.11 (0.71-1.76)	0.64	1.01 (0.63-1.63)	0.96
Moderate	1.57 (0.83-2.97)	0.16	1.57 (0.81-3.02)	0.18
Severe	2.06 (1.06-4.00)	0.03	1.93 (0.98-3.82)	0.06
Mortality *(n=212)*				
No LI	1.00		1.00	
Mild	0.84 (0.59-1.20)	0.33	0.77 (0.53-1.13)	0.18
Moderate	1.37 (0.84-2.25)	0.21	1.33 (0.78-2.27)	0.30
Severe	2.74 (1.66-4.52)	0.01	2.76 (1.61-4.73)	0.01

**Adjusted for age, sex, and comorbid conditions (cardiovascular disease, diabetes, malignancy)*

Table 5. Multivariate predictors of length of stay by severity of liver injury (LI) among survivors and non-survivors

Predictors	Non-Survivors	p-value	Survivors	p-value
	Beta (95% CI)		Beta (95% CI)	
ALT Category				
No LI	1.00		1.00	
Mild	1.53 (-2.33 to 5.39)	0.43	1.35 (-0.35 to 3.04)	0.12
Moderate	3.22 (-1.96 to 8.39)	0.22	2.23 (-0.46 to 4.92)	0.11
Severe	1.29 (-3.45 to 6.04)	0.59	5.75 (2.38 to 9.12)	0.01
Age	-0.09 (-0.21 to 0.02)	0.11	0.02 (-0.03 to 0.07)	0.44
Sex				
Female	1.00		1.00	
Male	-0.55 (-3.80 to 2.71)	0.74	2.72 (1.16 to 4.27)	0.01
Comorbid Conditions				
Cardiovascular disease	0.17 (-3.31 to 3.64)	0.92	3.48 (1.74 to 5.21)	<0.01
Diabetes mellitus	0.65 (-2.98 to 4.28)	0.72	1.35 (-0.50 to 3.19)	0.15
Malignancy	4.23 (-1.46 to 9.92)	0.14	9.79 (6.24 to 13.33)	<0.01

**Adjusted for age, sex, and comorbid conditions (cardiovascular disease, diabetes, malignancy)*

In our study cohort, SLI was associated with alcohol use and chronic liver disease, which may suggest that the ALT elevations in these patients reflect ongoing hepatic inflammation not directly related to COVID-19; however, abnormalities in liver biochemistries are reported in similar frequencies regardless of the presence of pre-existing liver disease.[10]

Similar to the findings of other studies, LI was also highly correlated with increasing levels of inflammatory markers, including LDH, ferritin, and CRP. This is again consistent with the association between the severity of LI and COVID-19 severity. The finding of higher tocilizumab use in patients with LI supports the notion that immunologic injury from the profound inflammatory response is an important cause of liver injury in COVID-19.

Liver injury manifested by elevated ALT has been directly correlated with disease severity and mortality among patients with COVID-19.[23,29-31] In this study, our analysis showed that LI predicted important clinical outcomes among hospitalized patients, including ICU admission, need for invasive ventilation, and mortality. Increasing severity

of LI was associated with a higher risk of these important clinical outcomes even after adjusting for known predictors of adverse effects such as age, sex, and comorbid illness. Because there are very few reports of frank liver failure in COVID-19 patients, the severity of LI in these patients may be a marker of a more robust inflammatory response that can potentially lead to adverse clinical outcomes, including mortality. LI in COVID-19 highlights a clinical challenge in patient management because several COVID-19-specific medications, such as remdesivir and tocilizumab, are contraindicated when the ALT levels are > 5x ULN. As shown in our results, these levels are more often seen in patients with severe COVID-19 for whom these medications are indicated. Studies on the efficacy and safety of these drugs in patients with severe LI are thus needed. Furthermore, severe LI was associated with longer hospitalization even after adjusting for age and comorbid illnesses. This may reflect that LI is a marker of severe disease associated with longer hospitalization. Because LI predicts both adverse clinical outcomes and length of stay, they can be used as markers during admission for prognostication. They may direct clinicians in prioritizing patients for intensive care, especially in resource-limited facilities.

The strength of this study is its large sample size, the enrollment of consecutive patients admitted to the hospital, and the extensive review of medical records and databases. However, the study has several limitations. The retrospective nature of the study design lends the study to recall and misclassification bias. Some potential causes of liver injury, including active viral hepatitis and the use of hepatotoxic medications or substances that may contribute to ALT elevations, may not have been accounted for. All retrieved data were from hospitalization, but the baseline laboratory tests before admission were not included or available. Essential information, including weight and body mass index, which are known to be associated with COVID-19 outcomes, were also not recorded.

The absence of data on several variables precluded the performance of the multivariate analysis of predictors of SLI. The study also included an entire inpatient population which may not be representative of all COVID-19 patients as those with less severe COVID-19 are likely managed as outpatients.

CONCLUSION

In summary, LI occurred commonly among patients admitted for COVID-19. SLI was associated with the severity of COVID-19 and with elevated markers of inflammation. The seriousness of LI measured by the degree of ALT elevation predicted adverse outcomes and length of hospital stay among survivors. Screening for LI and monitoring ALT, especially in patients with severe COVID-19 infection, may aid in anticipatory care, and determining the degree of LI can help in prognostication of patients.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

Author Disclosure

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