Cohort Study

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Liver injury at admission and outcomes in patients with COVID-19 disease: a prospective cohort study

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Background: The liver is one of the common extrapulmonary organs involved in the coronavirus disease 2019 (COVID-19) infection. We aimed to find the prevalence of liver injury at hospital admission and its effects on outcomes.

Methods: This is a single-center prospective observational study. All consecutive patients with COVID-19 admitted during the months of May to August 2021 were included in the study. Liver injury was defined as at least 2 times elevation of aspartate transaminase, alanine transaminase, alkaline phosphatase, and bilirubin above the upper limits on normal. The predictive efficacy of liver injury was measured as its effects on outcome variables, that is duration of hospital stay, requirement of ICU admission, mechanical ventilation, and mortality. Presence of liver injury compared with existing biomarkers markers of severe disease, that is lactate dehydrogenase, D-dimer, and C-reactive protein.

Results: A total of 245 consecutive adult patients with COVID-19 infection were included in the study. Liver injury was present in 102 (41.63%) of patients. There was a significant association between the presence of liver injury and duration of hospital stay (10.74 vs. 8.9 days; $P = 0.013$), the requirement of ICU admission (12.7 vs. 10.2%; $P = 0.018$), mechanical ventilation (10.6% vs. 6.5%; $P = 0.003$), and mortality (13.1% vs. 6.1%; $P < 0.001$). Liver injury was significantly associated ($P < 0.001$) with the corresponding elevation of serum biomarkers of severity.

Conclusion: The presence of liver injury in patients with COVID-19 infection at the time of hospital admission is the independent predictor of poor outcomes and can also be used as the marker of disease severity.

Keywords: biomarkers, COVID-19, disease severity, liver injury

Introduction

Coronavirus disease 2019 (COVID-19) pandemic which started in December 2019 in China and swept through the world, still poses a serious challenge to the healthcare system and economic sectors worldwide[1]. Though respiratory tract symptoms remain predominant in patients infected and hospitalized with COVID-19 infection, extrapulmonary manifestations remain common[2,3].

The liver is one of the most common organs to get involved in different diseases causing systemic involvement. The hepatic manifestations of COVID-19 have been found to be correlated with disease severity and mortality in different previous studies[4]. Though the mechanism of liver injury is not fully understood and can be multifactorial, like direct cytopathic effects of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), hyperinflammation, dysregulated immune responses, hypoxia, preexisting liver disease, and treatment related[5,6].

Many of the previous studies done from different parts of the world have shown heterogeneous results (14–76%) on the prevalence of liver injury and its effects on the outcome of the patient[7–10]. Many of the previous studies, which are usually done retrospectively, evaluated the liver biochemical parameters after hospital admission only. It can be possible that virus variants, clinical criteria used to define liver injury, and the geographical and demographic profiles of the patient can influence those results. The present study aimed to find the prevalence of liver injury in patients with COVID-19 infection at the time of hospitalization and its relationship with outcomes.

HIGHLIGHTS

- Concomitant liver injury with coronavirus disease 2019 (COVID-19) infection can be considered the hallmark of the severity.
- Liver injury in COVID-19 infection during hospital admission is an independent predictor of poor outcomes.
- Alternately, liver enzymes, particularly alanine aminotransferase, can be employed as indicators of severe illness.

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Methodology

Study design

This is a single-center prospective observational study. All consecutive patients with COVID-19 infection requiring hospitalization were included in the study between 23rd May to 30th August 2021, at a tertiary-level medical center. Data collection was started after approval from the institutional ethics committee.

Patients

All the adult patients of age 18 or more who gave written consent for enrollment were evaluated for their symptoms and signs as well as radiological and laboratory findings. Demographic, clinical, laboratory, treatment, and outcome data were collected using the proforma. All the clinical and investigational findings related to the liver injury were noted and followed up till the patients were admitted. The clinical course of patients and related morbidity and mortality data with liver injury were evaluated. Patients having preexisting chronic liver diseases (CLDs), including chronic viral hepatitis, were excluded from the study. Non-ICU patients who had rapid clinical deterioration and death with or without intubation and a short period of mechanical ventilation (< 6 h) were analyzed as non-ICU death.

Diagnosis, triage, and treatment of patients were done as per WHO guidelines[11]. Only positive reverse transcription polymerase chain reaction (RT-PCR) cases with the swabs taken from both nasopharyngeal and oropharyngeal regions were included. Patients with negative RT-PCR but positive COVID-19 antigen or antibody status with or without clinical and radiological evidence of COVID-19 infection were excluded from the study.

Significant liver injury

Defined as any of the following: Jaundice with total bilirubin level at least 2 mg/dl with at least 20% of total bilirubin being conjugated; alanine aminotransferase (ALT) aspartate and aminotransferase (AST), and alkaline phosphatase (ALP) at least 2 × upper limits of normal (ULN). ULN of ALT and AST were defined according to the criteria of The Asian Pacific Association for the Study of the Liver (40 U/l for both genders). ULN of ALP was defined according to the hospital laboratory range based on age and gender.

The primary endpoint was a composite of ICU admission, use of invasive mechanical ventilation and/or death. Serum C-reactive protein (CRP), D-dimer, and lactate dehydrogenase (LDH) levels as the marker of disease severity were compared in patients with and without significant liver injury. The ULN for serum LDH, D-dimer, and CRP was defined as levels more than 333 U/l, 0.5 mg/dl, and 10 g/dl, respectively.

Significant elevation of serum bilirubin level and ALP level was considered only after ruling out persisting liver disease with transabdominal ultrasonography (USG). Isolated elevation of unconjugated hyper bilirubin was not considered significant. Viral markers serology, mainly for HIV, hepatitis B virus, and hepatitis C levels, were sent (HIV, HBsAg, and anti-HCV, respectively) in all patients having a significant rise in transaminases levels and patients were included in the study only if reports came to negative. Patients having grade II/III fatty liver in ultrasound were excluded from the study.

Statistical analysis

Normally distributed continuous variables were expressed in mean ± SD, whereas other continuous variables were expressed in median (IQR). Categorical variables were expressed as percentages. The association between the presence of liver injury with demographic profiles was examined using Student's t test for continuous variables and Pearson's χ^2 test for categorical variables. All statistical tests were two-tailed and P value of less than 0.05 was considered statistically significant. Data were entered and analyzed with IBM SPSS Version 24 (IBM Corp, Armonk, New York, USA).

For data analysis, patients were divided into two groups, that is patients with significant liver injury and those without significant liver injury. Liver biochemistries were recorded only at the time of hospitalization to avoid drugs and other treatment-related factors. The work has been reported in line with the STROCSS (strengthening the reporting of cohort, cross-sectional and case–control studies in surgery) criteria[12].

Results

A total of 254 consecutive patients requiring hospital admission after informed written consent from patients and/or their relatives and who fulfilled the inclusion criteria were included in the study. Two patients with positive HBsAg, one patient with evidence of CLD on the USG abdomen, four patients with grade II/III fatty liver on USG abdomen, and two patients with dilated common bile duct on transabdominal USG were later excluded from the study. Hence, only 245 patients were evaluated (Fig. 1). Significant bilirubin and ALP level elevation were present only in a few patients (3.2%), while at least one of the markers was elevated significantly in 102 (41.63%) (Table 1).

There was no difference in the presence of liver injury with baseline clinical characteristics – age, sex, presence of comorbidities, or history of significant alcohol consumption or smoking habits. But the incidence of liver injury increased with age, that is liver injury was absent in patients with age less than 25 years

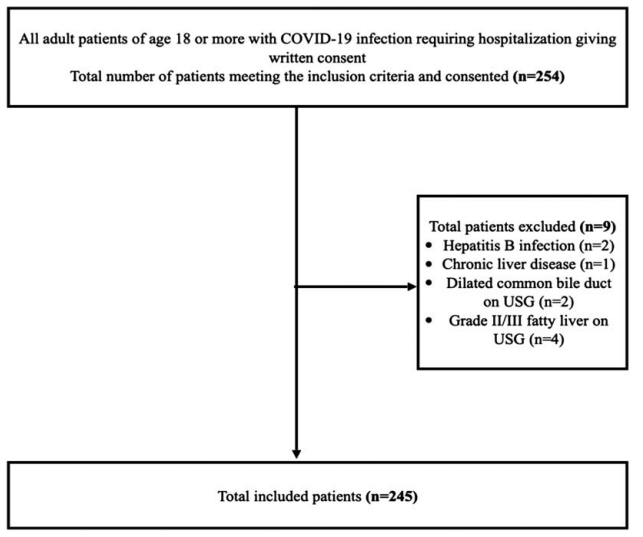

Figure 1. Flow diagram of patient selection. COVID-19, coronavirus disease 2019; USG, ultrasonography.

Table 1

Liver biochemistries as marker of liver injury.

	At significance level		Below significance level	
Parameters	Total cases, *N* (%)	Average value	Total cases *N* (%)	Average value
Bilirubin	5 (2.04)	2.6 ± 1.04	240 (97.96)	0.8 ± 1.9
AST	70 (28.57)	101.5 ± 70.33	175 (71.43)	40 ± 12.4
ALT	81 (33.06)	116 ± 74.26	164 (66.94)	35 ± 17.35
ALP	17 (6.94)	602 ± 339.09	228 (93.06)	189.5 ± 88.78
AST or ALT	94 (38.37)		151 (61.63)	
ALT and AST	56 (22.86)		189 (77.14)	
At least one biomarker	102 (41.63)		143 (58.37)	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate and aminotransferase.

while it was 51.51% in patients who were more than 75. While there was no significant difference in the blood level of hemoglobin, urea, or creatinine in the presence or absence of liver injury, white blood cell (WBC) counts were significantly higher ($P = 0.029$) in patients having significant liver injury (Table 2).

A total of 56 (22.86%) had the requirement of ICU admission, with 42 (17.1%) requiring mechanical ventilation. Mortality was present in 47 (19.1%) patients, with 12 (4.9%) of them being non-ICU death. There was a significant association between the presence of liver injury and outcomes of the patient in terms of duration of hospital stay (10.74 vs. 8.9 days; $P = 0.013$), the requirement of ICU admission (31 vs. 25; $P = 0.018$), the requirement of mechanical ventilation ($P = 0.03$), and death (32 vs. 15; $P < 0.001$) (Table 3).

Most commonly used biomarkers, that is serum CRP, D-dimer level, and serum LDH level, were found to be independently and significantly associated ($P < 0.001$) with the presence of significant liver injury (Table 4).

On using serum ALT level as the only marker of liver injury, we found a similar result as of combined use of all liver biochemical tests. Duration of hospital stay ($P = 0.031$), the requirement of ICU admission ($P = 0.002$), the requirement of mechanical ventilation ($P = 0.003$), and mortality ($P < 0.001$) were all significantly associated with significant rise in serum ALT level. Furthermore, there was also a significant association ($P < 0.001$) between elevated serum biomarkers and elevation of ALT level (Table 5).

Table 2

Demographic and baseline parameters.

Variables	Liver injury ($n = 102$)	No liver injury ($n = 143$)	*P*
Age (years)	57.04 ± 15.752	54.18 ± 17.251	0.187
< 25	4 (100%)	0	0.092
25–50	36 (40%)	54 (60%)	0.397
50–75	49 (41.52%)	69 (58.47%)	0.715
> 75	17 (51.51%)	16 (48.48%)	
Sex			0.354
Male	61 (44.2%)	77 (55.8%)	
Female	41 (38.3%)	66 (61.7%)	
Alcohol	8 (3.3%)	13 (5.3%)	0.731
Smoking	7 (2.9%)	11 (4.5%)	0.806
Comorbidities			
Diabetes	16 (6.5%)	34 (13.9%)	0.121
Hypertension	30 (12.2%)	39 (15.9%)	0.714
Hemoglobin (g/dl)	12.978 ± 1.941	12.905 ± 2.396	0.798
WBC (/mm^3)	8709.31 ± 4863.45	7434.48 ± 4189.915	0.029
Serum urea (mg/dl)	41.5 ± 24.93	39.5 ± 36.34	0.639
Serum creatinine (mg/dl)	1.138 ± 1.26	1.046 ± 1.53	0.623

WBC, white blood cell.

Table 3

Liver injury and outcome variables.

Variables	Liver injury ($n = 102$)	No liver injury ($n = 143$)	*P*
Duration of hospital stay	10.74 ± 5.3	8.9 ± 5.948	0.013
ICU requirement	31 (12.7%)	25 (10.2%)	0.018
Mechanical ventilation	26 (10.6%)	16 (6.5%)	0.03
Death	32 (13.1%)	15 (6.1%)	< 0.001

Discussion

Advanced age and preexisting clinical comorbidities, including organ failure, immunosuppressed state, and severe disease, are well-established predictors of poor outcomes in COVID-19 patients[13]. Furthermore, preexisting CLDs are associated with increased disease severity and poor outcome[14–16]. The presence of liver injury and its role in outcomes in patients without preexisting liver disease is highly variable among different studies[8].

In this prospective observational study done in patients without previous known liver or biliary diseases and using four liver biochemical tests, that is AST, ALT, ALP, and bilirubin as the markers of liver injury, 102(41.63%) out of 245 were found to have a liver injury. It is comparable to most of the previous studies[17,18]. As AST and ALT are raised during the process of hepatocellular injury, using only these two markers without bilirubin or ALP, liver injury was present in 94 (38.37%).

Using the significant elevation of either of the four markers as the presence of liver injury, there was no significant association with the baseline parameters except for the WBC level, which was significantly increased in patients with liver injury. Liver injury was significantly associated with all four outcome variables. Drugs such as antivirals and/or antibiotics can affect the liver enzyme profile and could be a major confounding factor when addressing the prognostic value of these tests and raise questions about whether these abnormalities of liver parameters are due to the severity of the infection or the drugs administered, or even both. To address this, we included those patients who were not previously treated and LFT (liver function tests) at the time of hospital admission only was considered for liver injury. Here, we have not included the patient having sudden deterioration and death and general or high care bed in ICU or ventilator requiring group. Hence, the mortality rate was more than that of the rate of ventilator requirement and ICU admission. The overall mortality

Table 4

Liver injury and biomarkers of severity.

Variables	Liver injury ($n = 102$)	No liver injury ($n = 143$)	*P*
Serum CRP	92.2 ± 65.08	56.82 ± 65.79	< 0.001
D-dimer	0.93 ± 1.45	0.43 ± 0.33	< 0.001
Serum LDH level	661.05 ± 279.76	384.22 ± 209.48	< 0.001

CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 5

Outcomes and biomarkers with alt as only marker for liver injury.

Variables	Liver injury ($n=81$)	No liver injury ($n=164$)	P
Duration of hospital stay	10.79 ± 5.3	9.1 ± 5.89	0.031
ICU requirement	28 (11.4%)	28 (11.4%)	0.002
Mechanical ventilation	22 (9.0%)	20 (8.2%)	0.003
Death	29 (11.8%)	18 (7.3%)	< 0.001
Serum CRP	100.3 ± 65.31	57.36 ± 64.39	< 0.001
D-dimer	1.082 ± 1.59	0.42 ± 0.32	< 0.001
Serum LDH	704 ± 264.42	398.40 ± 222.06	< 0.001

ALT, alanine aminotransferase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

rate was 19.8%, with 13.1% being the patient with a significant level of liver injury.

A similar result was found when ALT as a liver-specific marker was used for determining the presence of liver injury. Elevation in serum level of biomarkers was more significant in parallel with the ALT elevation.

Different inflammatory markers like interleukin (IL)-6, ferritin, LDH, CRP, cardiac troponin – I and D-dimer have been used in different studies as the biomarker of the severity[19–21]. Here we used serum levels of CRP, D-dimer, and LDH measured on the first day of admission as the biomarkers of severity and poor outcomes in patients with COVID-19 infections. A meta-analysis done 10 491 patients from 32 different studies using different biomarkers, including an elevated level of CRP, D-dimer, and LDH, showed that all these three markers were independently associated ($P < 0.001$) with poor outcomes[22]. Similar to the previous studies, liver biochemical test elevation was associated with a corresponding significant level elevation of biomarkers ($P \leq 0.001$). Hence, these liver enzymes can alternatively be used as the biomarkers of severe disease.

This study gives new insight into the possible relationship between liver injury at admission and outcomes in COVID-19 disease. Overall hospital requirements between the two groups (with or without liver injury at admission) were analyzed irrespective of the requirement of ICU, ventilator, and other treatment. There are limitations to this study due to a single-center design and a limited sample size. This study was not designed for long-term follow-up of patients after hospital admission. As the use of cross-sectional imaging like MRI was not feasible and cost-effective during the COVID-19 wave, we did not include it for evaluation.

Conclusion

The presence of significant liver injury in patients with COVID-19 infection at the time of hospitalization should be considered the hallmark of the severe disease. Liver biochemical tests, especially ALT can not only be used to determine the worse outcome in hospitalized patients but also as a biomarker of severe disease.

Ethical approval

It was obtained from the institutional ethics committee of Kathmandu Medical College Teaching Hospital (Ref: 2005202103).

Patient consent

Written informed consent was obtained from the patients for the publication of this manuscript.

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All the financial burden was carried out by the government, and no extra expenses were done by the patient or government side. No extra financial support was sought from any agencies during the study procedure.

Author contribution

S.P., S.C.P., and M.B.: concept and design; A.M. and A.B.: acquisition of data; S.P., S.C.P., and A.A.: interpretation of data; S.P. and A.M.: statistical analysis; S.P., S.C.P., A.M., A.A., and A.K.: drafting and critical revision of the manuscript.

Conflicts of interest disclosure

None of the authors have any conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Research registration unique identifying number (UIN)

1. Name of the registry: not applicable.
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Provenance and peer review

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