

PREDICTION OF MORTALITY AND TRANSFER TO ICU BASED ON ABNORMAL LIVER FUNCTION TESTS IN PATIENTS HOSPITALIZED WITH COVID-19 IN A TERTIARY CARE CENTRE (SOUTH- INDIA)**C.G. Sridhar¹, Anabhra Sharma¹, Soundappan Somasundaram², Shikha Sharma⁴, Mohd. Juned Khan¹, Raghunath D.³, Dhivahar G.³ and Aravinth S.⁵**¹Department of Medical Gastroenterology.²Department of Surgical Gastroenterology.³Department of Emergency and Critical Care Medicine.⁴Department of Preventive and Social Medicine; Kota Medical College; Rajasthan.⁵Department of Pathology; Gem Hospital and Research Center, Coimbatore; Tamilnadu.***Corresponding Author: C.G. Sridhar**
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ABSTRACT

Background: The pandemic of coronavirus (COVID-19) has rapidly emerged as a relevant threat for humans worldwide. The main clinical feature is pneumonia characterized by a high mortality rate, however, increasing data suggest that COVID-19 is a systemic disease affecting other organs/systems including liver, kidney and coagulation system and heart.^[2-5] An increase in liver function tests (LFTs) (14%-75% of hospitalized patients in the world) has been found in patients with COVID-19.^[2,3,6-11] **Aim** of this study was to assess the prevalence and the clinical impact of abnormal LFTs in hospitalized COVID-19 patients to predict mortality. **Methodology:** Patients hospitalized between 1/5/21 to 25/5/21 in COVID-Unit of GEM Hospital and research centre were retrospectively identified. **Inclusion criteria** were as follows: (a) patients hospitalized with a SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction method; (b) age >12 years old. **Exclusion criterion** involve patients admitted to ICU within 6 hours of admission as they were likely to be critically ill at admission with other unknown comorbidities and we wanted to target patients managed in regular wards so that a prediction model can be studied for future admissions. Verbal or written informed consent was taken and study approval permission given by local Ethics Committee. The study was performed according to the Institutional ethical guidelines and according to the principles of Declaration of Helsinki (Seventh edition). **Results:** Median age was 52 years with more prevalence in men (58.5%). All patients reported flu-like symptoms: fever (137 [77.8%]), cough (116 [65.9%]), fatigue (55 [31.3%]) and muscle pain (15 [8.5%]); gastrointestinal symptoms were observed in 39 patients (22.2%). Dyspnoea was present in 73 (41.5%) patients. At least one comorbidity was recognised in about 43% of positive patients. Among the total admitted patients, 44 (25%) patients were shifted to ICU in need for either ventilatory support or hemodynamic instability and this was significantly associated with patients having SIRS, high CRP & D-Dimer values (p-value =0.001). The final outcome in any form was seen to be significantly associated with COVID profile of the patient (raised CRP with p-value =0.002) and no significant association was seen between in hospital mortality and LFT derangement of a patient. **Conclusion:** LFT abnormalities are common at admission in patients with COVID-19, but it cannot be used as an independent predictor of transfer to ICU or death unlike other markers of systemic inflammation and multi-organ dysfunction. **Lay summary:** Liver test abnormalities (in particular elevations in the levels of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and total bilirubin [T-Bil]) were observed commonly after symptom onset in patients who were admitted with coronavirus disease 2019 (COVID-19). Abnormal levels of these liver function tests cannot be used as an independent predictors of COVID-19 related mortality and morbidity.

KEYWORDS: Liver injury, SARS-CoV-2, sepsis, ICU mortality.

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; ALI, acute liver injury; ARDS, acute respiratory distress syndrome; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST,

aspartate aminotransferase; Hb, Haemoglobin; TLC, Total leucocyte count; WBC, White blood cells; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-Reactive protein; HR, heart rate; LFTs,

liver function tests; LDH, lactate dehydrogenase; ICU, intensive care unit; IL, Interleukin; T-Bil, Total bilirubin; RR, respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV-2, severe acute respiratory syndrome Coronavirus 2; SIRS, systemic inflammatory response syndrome; ULN, upper limit of normal.

INTRODUCTION

The pandemic of coronavirus (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has rapidly emerged as a relevant threat for humans worldwide after first case reported on December 31, 2019 in Wuhan, China.^[1] The main clinical feature of COVID-19 is pneumonia, which is characterized by a high mortality rate, however, increasing data suggest that COVID-19 is a systemic disease affecting other organs/systems including liver, kidney and coagulation system including heart.^[2-5] An increase in liver function tests (LFTs) (14%-75% of hospitalized patients in the world) has been found in patients with COVID-19.^[2,3,6-11] During the past SARS outbreak, hepatic impairment was described in up to 60% of patients^[15], and was associated with elevation of

serum transaminases, hypoproteinaemia and prolongation of prothrombin time.

Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus, an un-controlled immune reaction, sepsis or drug-induced liver injury. Given the higher expression of ACE2 receptors in cholangiocytes, the liver is a potential target for SARS-CoV-2. Overall, there is a paucity of studies assessing the prevalence, the pattern (hepatocellular, cholestatic, mixed) and the clinical impact of LFTs, in particular in Indian patients. **Aim** of this study was to assess the prevalence and the clinical impact of abnormal LFTs in hospitalized COVID-19 patients to predict mortality.

METHODS

Study design and study Participants

Patients hospitalized in COVID-Unit in GEM Hospital and research centre were retrospectively identified between 1/5/21 to 25/5/21. During the study period 190 patients who tested positive for SARS-CoV-2 infection were admitted in the covid ward of our hospital and included in the following analysis.

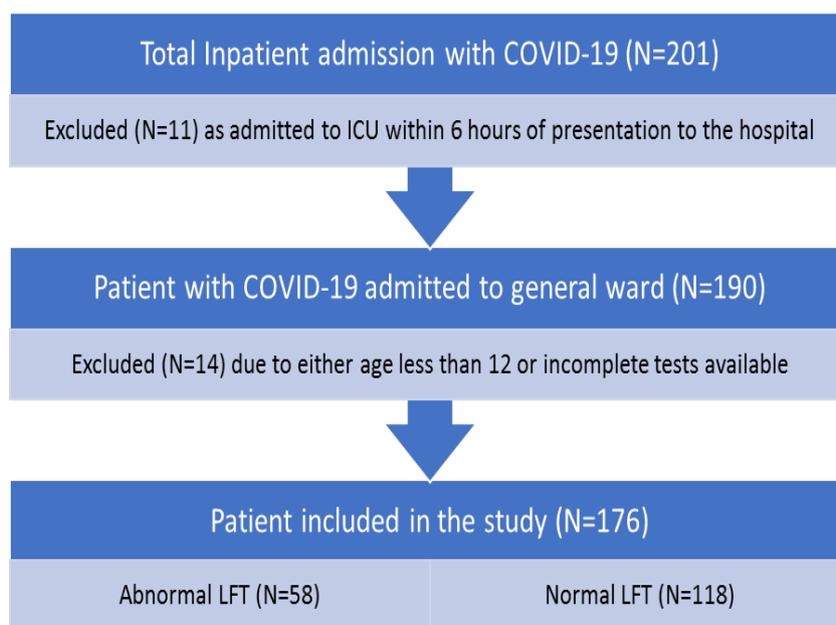


Figure 1: Flow chart of the study.

Abbreviations: COVID-19, coronavirus disease 19; LFT, Liver function tests.

Inclusion criteria were as follows: (a) patients hospitalized with a SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction method; (b) age >12 years old.

Exclusion criterion involve patients admitted to ICU within 6 hours of admission as they were likely to be critically ill at admission with other unknown comorbidities and we wanted to target patients managed in regular ward so that a prediction model can be studied for future admissions.

To investigate the prevalence of liver damage in our cohort of patients, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin and albumin were collected at baseline admission. At the same timepoints C-reactive protein (CRP), ferritin, D-dimer as inflammatory markers and platelets (PLTS), white blood cells (WBC), neutrophils and lymphocytes counts were also recorded. History of liver disease and other comorbidities were also assessed.

Verbal or written informed consent was taken and study approval permission given by local Ethics Committee. The study was performed according to the Institutional ethical guidelines and according to the principles of Declaration of Helsinki (Seventh edition).

Data collection

Patients' characteristics with medical history (comorbidities, symptoms of infection and laboratory examinations) were reported as median and interquartile range (continuous variables) or as frequencies and percentages (categorical variables).

Baseline serum levels of LFT (i.e. AST, ALT, ALP) were stratified according to three cut-offs ($>ULN$; $>ULN$ but up to $3 \times ULN$ and last cohort of $>3 \times ULN$) for a better definition of possible alterations. Missing data for each variable in the database accounted for $<5\%$. Scores

of severities of the disease such as systemic inflammatory response syndrome (SIRS) was calculated at admission and patients were sub grouped into three subcategories (a) need for hospitalisation (b) severity of disease (c) admission to ICU.^[17] Statistical averages like mean and standard deviation test were used to measure associations. The strength of association between liver function test & covid profile with admission to ICU (severity) and final outcome (death) was done by Multiple logistic regression test.

The other events occurred during the hospitalization were also collected: mechanical ventilation, non-invasive ventilation, acute kidney injury, renal replacement therapy, treatment with vasopressors, occurrence of multiorgan failure, acute liver failure (jaundice, coagulopathy and encephalopathy) and death.

Terminology	Definitions
Liver abnormalities	Liver abnormalities were defined as serum level of AST, ALT, ALP or T-Bil exceeding the ULN
Liver injury	Liver injury was considered in patients with an increase in ALT or AST of at least $3 \times ULN$, or an increase in ALP, T-Bil or D-Bil of at least $2 \times ULN$ as defined by clinical guidelines of ACG ^[18,19]
Types of liver abnormalities	Hepatocellular type: if the hepatocellular-related indices including ALT or AST levels were above ULN and ALP level was in the normal range; Cholestatic type: if ALP levels were increased but with normal AST and ALT levels; Mixed type: in the presence of elevation of both ALP and ALT/AST levels; Others: if patterns of liver abnormalities were not matched with types of liver abnormalities mentioned above such as isolated elevation of GGT or bilirubin.
Acute liver injury	Acute liver injury was considered if patients with liver injury and showing disorder of coagulation (INR >-1.5) and jaundice (T-Bil level of > 3 mg/ dl) within 26 weeks of the onset of illness
Acute liver failure	Acute liver injury was measured in patients without chronic liver diseases. Acute liver failure was diagnosed in patients with acute liver injury and manifestations of hepatic encephalopathy (grade >-2 , according to the West Haven criteria). ^[20]

Data Analysis

Data collection and statistical analysis was performed using SPSS statistical package version 20. P-value of <0.005 was taken as the level of significance.

RESULTS

Table 1: Frequency distribution of demographic, clinical symptoms and outcome of study participants.

Demographic factors		Frequency	Percent
1	Age		
	15-29 years	14	8.0
	30-44 years	40	22.7
	45-59 years	58	33.0
	60-74 years	48	27.3
	>75 years	16	9.1
	Total	176	100.0
2	Gender		
	Male	103	58.5
	Female	73	41.5
	Total	176	100.0
CLINICAL FEATURES			
1	Fever		
	Yes	137	77.8
	No	39	22.2

	Total	176	100.0
2	Dyspnoea		
	Yes	73	41.5
	No	103	58.5
	Total	176	100.0
3	Cough		
	Yes	116	65.9
	No	60	34.1
	Total	176	100.0
4	Fatigue		
	Yes	55	31.3
	No	121	68.8
	Total	176	100.0
5	Myalgia		
	Yes	15	8.5
	No	161	91.5
	Total	176	100.0
6	Nausea and vomiting		
	Yes	14	8.0
	No	162	92.0
	Total	176	100.0
7	Diarrhoea		
	Yes	22	12.5
	No	154	87.5
	Total	176	100.0
8	Headache		
	Yes	10	5.7
	No	166	94.3
	Total	176	100.0
9	Altered sensorium		
	Yes	11	6.3
	No	165	93.8
	Total	176	100.0
SHIFTED TO ICU			
1	Yes	44	25.0
2	No (managed in ward)	132	75.0
3	Total	176	100.0
FINAL OUTCOME			
1	Discharged in stable condition	138	78.4
2	Death of the patient	22	12.5
3	Ongoing treatment	13	7.4
4	Discharged against medical advice	3	1.7
5	Total	176	100.0

Table 1: Median age was 52 years with more prevalence in men (58.5%). All patients reported flu-like symptoms: fever (137 [77.8%]), cough (116 [65.9%]), fatigue (55 [31.3%]) and muscle pain (15 [8.5%]); gastrointestinal symptoms were observed in 39 patients (22.2%) and included diarrhoea (22), vomiting (14), abdominal pain (3). Dyspnoea was present in 73 (41.5%) patients. In 153 patients (86.9%) radiological signs of pneumonia were observed at the first clinical evaluation in emergency room.

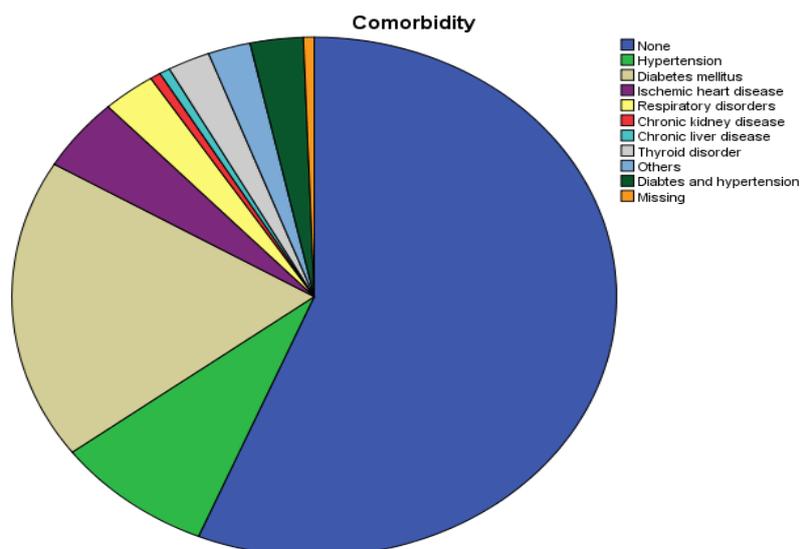


Figure 2: Pie Chart Showing Distribution of Co-Morbidity Among Study Participants.

Figure 2: At least one co-morbidity was recognised in about 43% of SARS-CoV-2-positive patients and 2.9% of them presented with more than one pre-existing pathologic condition. The most commonly associated ones were: hypertension (15 [8.6%]), cardiovascular disease (8 [4.6%]), diabetes mellitus (33 [18.9%]),

respiratory disorders including chronic obstructive pulmonary disease (5 [2.9%]), chronic renal disease (1 [0.6%]). Previously known chronic liver disease without clinical and blood chemistry signs of decompensated cirrhosis were observed in 1 (0.6%) patient.

Table 2: Comparison of patients shifted to ICU with their covid profile and LFT profile.

COVID PROFILE		Mean	Std. Dev	P value
CRP	Patient managed in ICU	78.97	68.708	0.001
	Patient managed in ward	38.95	70.26	
D-Dimer	Patient managed in ICU	2257.53	3135.26	0.001
	Patient managed in ward	672.73	1626.07	
CT severity score on admission	Patient managed in ICU	8.45	4.184	0.01
	Patient managed in ward	6.53	4.683	
SIRS	Patient managed in ICU	1.36	.487	0.001
	Patient managed in ward	1.64	.483	
LFT PROFILE				
AST	Patient managed in ICU	54.05	47.23	0.05
	Patient managed in ward	42.32	30.43	
ALT	Patient managed in ICU	38.05	27.05	0.43
	Patient managed in ward	34.05	30.36	
ALP	Patient managed in ICU	77.64	26.99	0.85
	Patient managed in ward	78.88	40.68	
Total Bilirubin	Patient managed in ICU	.54	.22	0.39
	Patient managed in ward	.61	.55	

Table 2: Among the total admitted patients, 44 (25%) patients were shifted to ICU. Overall, 76 (43%) patients had one or the other signs of systemic inflammatory response syndrome (SIRS) who needed shifting in ICU (p-value = 0.001). Indirect markers of systemic inflammation such as CRP (p-value = 0.001) and D-dimer (p-value = 0.001) were increased in all patients at baseline and were higher in patients requiring hospitalisation with SIRS or admitted to ICU. Among the entire patients, liver test abnormalities were found in 58 (33%) patients that included all hepatocellular,

cholestatic and mixed pattern of injury. Increase in AST, ALT and ALP above ULN was found in 25.6%, 17.3% and 11.8%, respectively; these alterations were mostly mild/moderate (lower than $3 \times$ ULN), and in only 3% of cases a more severe increase ($>3 \times$ ULN) was observed. Relevant alteration of serum bilirubin was seen only in a minority of patients. AST or ALT elevation was more frequent than ALP elevation in both categories of patient presented with SIRS and patient transferred to ICU during in hospital treatment.

Table 3: Comparison of patients' final outcome with their covid profile and LFT profile.

LFT PROFILE		Mean	Std. Dev	P value
AST	Discharged in stable condition	41.61	29.699	0.05
	Death of the patient	65.50	56.630	
	Ongoing treatment	51.46	42.655	
	Discharged against medical advice	36.67	8.505	
ALT	Discharged in stable condition	34.32	30.82	0.72
	Death of the patient	41.45	29.69	
	Ongoing treatment	33.62	15.56	
	Discharged against medical advice	27.67	5.85	
ALP	Discharged in stable condition	80.10	40.68	0.76
	Death of the patient	74.23	27.22	
	Ongoing treatment	70.31	18.88	
	Discharged against medical advice	77.00	1.000	
Total Bilirubin	Discharged in stable condition	.602	.54	0.96
	Death of the patient	.57	.22	
	Ongoing treatment	.62	.26	
	Discharged against medical advice	.46	.11	
COVID PROFILE				
CRP	Discharged in stable condition	38.22	62.29	0.001
	Death of the patient	90.44	70.47	
	Ongoing treatment	106.85	121.37	
	Discharged against medical advice	10.433	5.607	
D-Dimer	Discharged in stable condition	908.45	2052.94	0.03
	Death of the patient	2399.42	3310.708	
	Ongoing treatment	780.45	491.85	
	Discharged against medical advice	208.42	96.604	
CT severity score	Discharged in stable condition	6.83	4.685	0.09
	Death of the patient	8.95	4.337	
	Ongoing treatment	5.23	4.126	
	Discharged against medical advice	8.67	1.528	
SIRS	Discharged in stable condition	1.60	.491	0.05
	Death of the patient	1.32	.477	
	Ongoing treatment	1.69	.480	
	Discharged against medical advice	1.33	.577	

Table 3: After a median follow-up of 15 (10-25) days, 22 (12.5%) patients died, 138 (78.4%) were discharged in a stable condition, 3 (1.7%) were discharged against medical advice and 13 (7.4%) were still admitted either in wards or ICU of our hospital. The final outcome in

any form was seen to be significantly associated with COVID profile of the patient (raised CRP, p-value =0.001) and no significant association was seen with patient outcome and LFT profile of a patient.

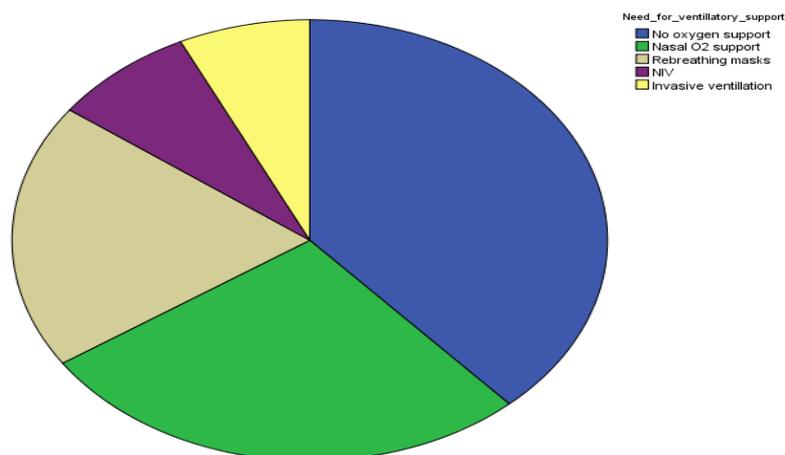


Figure 3: Oxygen requirement among all the patients admitted in both ward and ICU.

Figure 3: Among the patients managed in our hospital most were managed with only medications and lung exercises not requiring any oxygen support(59%). Among all the patients shifted to ICU during the time of treatment, 22 patients were placed on Non-invasive ventilator and 22 patients could only be managed on mechanical ventilator. Out of the all 44 patients who were once in the ICU, 19 (10.8%) patients had no organ

failure, 9(5.1%) had liver failure and 16 (9.1%) had multi-organ failure. Out of the all 44(25%) patients, 16 patients were transferred back to the wards and finally discharged in the stable condition. The need for inotropes was felt in 31 (17.6%) patients. 22(12.5%) patients were declared dead to the relatives while being treated in the ICU but 2 patients went discharge against medical advice due to personal reasons.

Table 4: Multiple linear regression analysis between LFT & Covid parameters with Shifting in ICU and final outcome in terms of mortality.

	category	B	Std. Error	Beta Coefficient	t	Sig.
Shift to ICU (dependent variable)	Constant	2.118	.153		13.852	.000
	Abnormal LFT	-.072	.078	-.079	-.932	.353
	CRP	-.002	.000	-.264	-3.389	.001
	D-Dimer	-4.849	.000	-.265	-3.388	.001
Final outcome (dependent variable)	Constant	.826	.269		3.070	.003
	Abnormal LFT	.163	.137	.110	1.190	.236
	CRP	.003	.001	.272	3.173	.002
	D-Dimer	5.787	.000	.002	.023	.982

Table 4: The prevalence of liver test alteration in patients with SIRS was [16.5%] and in those requiring admission to ICU were [10.2%]. Liver test alterations at baseline were not associated with higher risk of ICU admission (p value-0.35) and also in hospital mortality (p-0.24). The cumulative incidence of discharge was similar between patients with or without liver test abnormalities at baseline. Instead, markers of inflammation such as serum ferritin, serum albumin and serum creatinine were associated with an increased risk of mortality in our multiple linear regression model.

DISCUSSION

This study demonstrates that in patients without severe chronic liver disease, liver involvement during SARS-CoV-2 infection is usually mild, is not associated with both increased risk of ICU admission and mortality which even tends to resolve over time of hospital admission. Our study found a 33% prevalence of liver test abnormalities in patients admitted with SARS-CoV-2 infection, which was slightly lower than reported in previous Western^[21-22] and Chinese studies.^[9] Pure cholestatic alterations characterized by increase in ALP were extremely rare (5.6%). Noteworthy, all the alterations recorded were mild and did not require any liver specific interventions. Most of the studies^[9,21] including our study addressed liver test abnormalities at the time of admission but newer studies are also focussing on longer follow-up on liver involvement upto 1-2 months after getting viral infection exert a direct damage to the liver. Viral cytopathic effect is exerted on both liver cells and cholangiocytes; indeed, SARS-CoV-2 binds the angiotensin-converting enzyme 2 (ACE2) receptor to enter the cells,²⁴ which is mainly expressed on cholangiocytes, vascular endothelium and smooth muscle cells.^[25,26] Therefore, both vascular and cholangiocellular damage may represent the reasons for

the increase in transaminases and cholestasis parameters in infected patient. however, liver test tends to normalise in due course if viral replication is controlled which suggests that liver injury due to direct viral cytopathic effect is usually of mild entity, and is involved in the development of liver tests abnormalities mostly in the early phases of the infection. Liver damage can also be consequence to inflammation associated with cytokine storm during viral infection. In our population of patients, abnormal liver tests not correlated with ICU admission in contrast with other studies previously reported.^[9] We also demonstrated that other factors to predict mortality were previous comorbid conditions, SIRS, ICU admission, ferritin, albumin and serum creatinine. Therefore, the presence of other negative prognostic factors is crucial to increase the risk of mortality during SARS-CoV-2 inflammatory syndrome, of which abnormal liver test are a collateral manifestation.

Our study has a few limitations as data were collected from a single centre and the generic limitations related to the retrospective collection of the data. In particular, the prevalence of chronic liver disease was low in our study population. However, patients' records were accurately revised, and based on laboratory examinations, radiological findings and clinical data, we can reasonably rule out that patients with pre-existing advanced liver disease were included in the study group. Therefore, our conclusions can only be applied to patients with SARS-CoV-2 infection without severe chronic liver disease or cirrhosis, for whom high morbidity and mortality have been reported.^[30]

In conclusion this study suggests that SARS-CoV-2 infection is not associated with clinically meaningful liver injury in Indian patients without advanced chronic

liver disease. But further studies are needed to establish any causal association between SARS-CoV-2 infection and its association with abnormal liver function and mortality of patients.

Conflict of interests: All authors declare no conflict of interest.

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