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Original Article

Liver function tests in COVID 19: A retrospective record-based study from a tertiary care centre in urban Maharashtra, India

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ABSTRACT

Background: COVID-19 is a multi system disorder and causes various abnormalities in liver function tests. The aim of this study was to estimate the prevalence of abnormal liver function tests in patients of COVID-19 and to describe the association of liver function tests with clinical features and disease severity in these patients.

Methods: We retrospectively evaluated and analyzed the liver function tests of all real-time polymerase chain reaction (RT-PCR) positive COVID-19 patients admitted to a tertiary care hospital in Western Maharashtra. The Institutional Ethics Committee of our hospital approved the study.

Results: Of the 533 patients included in our study, 50% had abnormal albumin levels while 40.1%, 43.5%, 9.3%, and 6.3% patients had deranged alanine transaminase (ALT) aspartate transaminase (AST), total protein and bilirubin levels, respectively. Hepatocellular injury was observed in 21 (3.9%) patients, and cholestatic liver injury was observed in seven (1.3%) patients. Abnormal liver function test (LFT) was significantly associated with disease severity but not with mortality.

Conclusion: Abnormal LFT in patients of COVID-19 is associated with severe disease but not mortality. Liver injury is common in patients of COVID-19.

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Introduction

Coronavirus disease 19 (COVID-19) was first identified in Wuhan Province of China in December 2019 as pneumonia of unknown etiology.[1] A new strain of coronavirus known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was later identified as the causative agent.[2] The pandemic has had a heavy toll on human life, health resources, and the world economy, despite most cases being either asymptomatic or mildly symptomatic.[3] Though COVID-19 is an airborne infection[4] that begins from the respiratory system, it evolves into a systemic infection affecting the lungs, kidneys, liver, and almost every other organ.[5]ACE II receptors serve as the receptor on the cell surface, facilitating the entry of SARS-CoV-2.[6] These receptors are variably expressed in respiratory, gastrointestinal, and hepatobiliary cells.

Abnormal liver function tests (LFT) have been associated with COVID-19 infection. Abnormal LFTs were reported in 4%–58% of Chinese cohorts[7] and 39%–58% in US cohorts.[8]The possible pathogenic mechanisms postulated for liver injury in COVID-19 include either direct cytopathic damage or indirectly due to the inflammatory response initiated by hepatic Kupfer cells in response to the presence of SARS-COV-2 and inflammatory mediators in portal circulation from the intestine.[9] Studies have reported severe illness and higher mortality risk in COVID-19 patients with abnormal LFT.[10,11] There is limited data from India on LFT in COVID-19 patients,[12–16] and most of the studies have been carried out on a small subset of patients, thus limiting their generalisability. We planned this study with the following objective: (a) To estimate the prevalence of abnormal liver function tests in COVID 19 and (b) To describe the association of liver function tests with clinical features and disease severity in these patients.

Material and methods

Study design

This retrospective study was carried out in a tertiary care hospital in Western Maharashtra. We retrospectively screened the medical records of all COVID-19 patients admitted to our hospital between September and November 2020. All patients were classified (mild/moderate/severe) investigated and treated according to the prevalent Ministry of Health and Family Welfare, India (MOHFW) standardised management protocol.[17] The Institutional Ethics Committee approved the study.

Patient selection

We included all patients above 18 years of age who were real-time polymerase chain reaction (RT-PCR) positive for SARS-COV-2.The following patients were excluded: patients with preexisting liver disease and those undergoing chemotherapy for any malignancy.

Data collection

The following information was extracted from the medical records of the patients: basic demographic details, comorbidities, disease severity, progression of the disease and liver biochemistry (serum bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), total protein, albumin, alkaline phosphatase (ALP)). Liver function tests of all patients were carried out at admission. Abnormal values were defined as, serum bilirubin > 1.2 mg/dL, ALT and AST > 40 U/L, ALP > 128U/L, total protein < 6.5 g/dl and albumin < 3.4 g/dl at any point of time during the period of hospitalisation. Abnormal liver function tests were defined as an elevation of any liver enzymes OR reduced total protein and albumin levels OR raised total bilirubin more than the upper limit of normal value.[12]Liver injury was defined as hepatocellular if ALT and or AST were more than three times the upper limit of normal (ULN) and cholestatic if ALP was more than two times the ULN.[12] Patients were classified as mild, moderate, and severe according to MOHFW standardized management protocol (ver. four).[17]Mild disease included patients with uncomplicated upper respiratory tract infection with mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache with SpO2 levels $\geq$ 94% at room air, respiratory rate $\leq$ 24/min, and no evidence of hypoxemia or breathlessness; moderate disease: pneumonia and no signs of severe illness, SpO2 90%–94% on room air, respiratory rate 24–30/min; severe disease: severe pneumonia with signs of respiratory distress, respiratory rate > 30/min or SpO2 < 90% on room air.

Statistical analysis

Data were summarized as numbers and percentages with mean and standard deviation (SD) and 95% confidence interval (95% CI) where applicable. Bivariate analysis was carried out to determine the association between clinical parameters and abnormal liver enzymes. Chi-square test and Student T-test/Mann–Whitney U were done as applicable. P-values less than 0.05 were considered significant. SPSS ver 21 was used for statistical analysis.

Results

Out of the 533 patients of COVID-19 admitted to our hospital, 417 (78.2%) were males with a mean age of 55.58 ± 16.7 years, while 116 (21.8%) were females with a mean age of 53.92 ± 19.41 years (Table 1). Fever was the most common presenting symptom (68.6%), followed by cough (57.7%). We observed type 2 diabetes melletus in 27% (146) of our patients, and hypertension and chronic kidney disease in 189 (35.4%) and 18 (3.3%) patients, respectively. Overall, 148 (27.7%) of our patients had mild disease, and 52 (9.7%) had severe disease, while the majority (61.3%) had a moderate illness. We report mortality in 9.7% of our patients (Table 1).

The prevalence of abnormal liver chemistry is depicted in Fig. 1. In our study, 394 patients (74.2%; 95% CI = 69–77) had at least one abnormal LFT value. Proportion of patients with deranged albumin (50%; CI = 45.7–54.4) AST (43.5%; CI = 39.1–47.6), ALT (40.1%; CI = 35.9–44.4) and ALP (2.62%; CI = 1.5–4.3) is also depicted (Fig. 1). Deranged serum bilirubin was noted in 6.3% of patients (CI = 4.4–8.8) and abnormal protein levels in 9.3% of patients (CI = 7–12.1). We report hepatocellular injury in 21 (3.9%; CI = 2.4–5.9) patients and cholestatic liver injury in seven (1.3%; CI = 0.5–2.6).

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Table 1 – Baseline characteristics of patients (n = 533).

Characteristics	Frequency (%)
Gender	
Male	417 (78.2)
Female	116 (21.8)
Mean Age ± SD years	55.22 ± 17.31
Male	55.58 ± 16.7
Female	53.92 ± 19.41
Additional ventilation	
Oxygen supplementation	128 (24)
Mechanical ventilation	28 (5.2)
Disease severity	
Mild	148 (27.7)
Moderate	327 (61.3)
Severe	58 (9.7)
Presenting complaints	
Breathlessness	275 (51.6)
Cough	308 (57.8)
Fever	366 (68.7)
Outcome	
Alive	481 (90.3)
Dead	52 (9.7)

Table 2 – Distribution of clinical parameters and abnormal liver tests.

	Normal liver tests	Abnormal liver tests	P-value
Number (%)	139 (25.8)	394 (74.2)	**0.009**
Gender			
Females	47 (34.1)	69 (17.6)	**<0.001**
Males	92 (65.2)	325 (82.4)	
Age			
< 50 years	57 (40.6)	117 (29.6)	**0.02**
>= 50years	82 (59.4)	277 (70.4)	
Fever present	80 (58)	286 (72.5)	**0.004**
Cough	69 (50)	239 (60.6)	0.071
Breathlessness	51 (37)	224 (56.8)	**0.018**
Severity			
Mild	57 (41)	91 (23)	**< 0.001**
Moderate/Severe	66 + 15 (47.3)	261 + 42 (66.2)	
Oxygen supplementation	15 (10.7)	113 (28.6)	**< 0.001**
Mechanical ventilation	1 (0.7)	27 (6.8)	**< 0.001**
Outcome			
Alive	130 (93.5)	353 (89.5)	0.061
Dead	9 (6.4)	41 (10.4)	
Comorbid			
Diabetes	33 (23.7)	113 (28.6)	0.44
Hypertension	47 (33.8)	142 (36.4)	0.86
Chronic kidney disease	02 (1.4)	16 (4)	

Table 2 lists the distribution of clinical parameters and LFT in the study participant. Older age ($p = .02$) and the presence of fever ($p = .004$) were significantly associated with abnormal liver tests. Abnormal LFT was significantly associated with moderate or severe disease ($p < .001$). Patients with abnormal liver tests had 2.3 times higher odds (CI-1.5–3.5) of having severe or moderate disease than those with normal LFTs (not in Table). The requirement of mechanical ventilation ($p = .<0.001$) and oxygen supplementation ($p < .001$) was also significantly associated with abnormal LFT. Table 3 compares the mean LFT values in the two categories of patients (mild versus moderate/severe). Mean albumin, ALP, and transaminases were significantly different in the two groups.

Overall, the prevalence of deranged LFT in our study participants was 74.2%. We observed a higher prevalence of deranged transaminases compared to other LFTs. We also report an association of abnormal LFT with older age, male sex, and a more severe course of illness.

Discussion

The present study was carried out in 533 COVID-19 patients admitted to a tertiary care hospital attached to a Medical College in Western Maharashtra. We observed that 74.2% of our patients had at least one abnormal liver test. In our study, 50% of patients had abnormal albumin levels, while 43.5%, 40.1%, and 2.62% had deranged AST, ALT, and ALP, respectively. Raised serum bilirubin (6.3%) and deranged protein levels (9.3%) were also reported.

Varying estimates of the prevalence of abnormal LFT in COVID-19 have been reported. Some of the studies are summarised in Table 4. Prevalence of elevated LFT has been reported from as low as 9.6%[18] to as high 93%[19] in patients admitted with COVID-19. Similarly, the proportion of patients with elevated AST, ALT, and ALP shows marked variation between studies (Table 4). We report higher prevalence of elevated transaminases as compared to other liver tests. Most studies also reported a higher prevalence of abnormal AST than ALT. We report hepatocellular injury in 21 (3.9%) patients and cholestatic liver injury in seven (1.3%) patients.

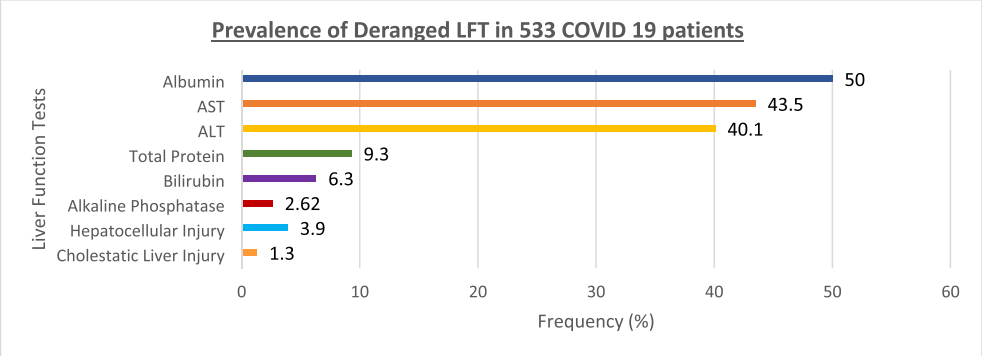

Fig. 1 – Prevalence of abnormal liver tests in COVID-19 patients.

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Table 3 – Comparison of average value of liver function tests in COVID-19 patients.

Liver Functions	Mild	Moderate and severe	Total 533 (100%)	P-value
AST U/L				
Mean ± SD	37.78 ± 25.8	52.75 ± 49.3	48.94 ± 44.9	**0.001**[a]
Median (IQR)	30.50 (23.7–58.6)	42 (28.8–76.1)	39.50 (27–55.7)	**< 0.001@**
ALT U/L				
Mean ± SD	41.20 ± 22.3	52.12 ± 39.2	49.35 ± 41.1	**0.02**[a]
Median (IQR)	37 (26.1–56.25)	39 (27.2–88.6)	38 (28.2–77.6)	**0.036@**
Total protein g/dl				
Mean ± SD	7.3 ± 0.6	7.2 ± 0.8	7.24 ± 0.84	0.366[a]
Median (IQR)	7.7 (6.2–7.5)	7.2 (6.6–7.9)	7.31 (6.7–7.8)	0.75@
ALP U/L				
Mean ± SD	95.24 ± 49.175	179.64 ± 112.8	148.7 ± 120.2	**< 0.001**
Median (IQR)	82.5 (62–128)	99.50 (84.4–218.7)	90.6 (73.7–159.7)	
Albumin g/dl				
Mean ± SD	3.42 ± 0.7	3.21 ± 0.67	3.26 ± 0.68	**0.013**[a]
Median (IQR)	3.30 (2.9–3.8)	3.10 (2.7–3.6)	3.20 (2.8–3.7)	**0.004@**
Bilirubin mg/dl				
Mean ± SD	1.08 ± 0.23	1.26 ± 0.60	1.21 ± 0.4	0.856[a]
Median (IQR)	1.0 (0.8–1.2)	1.1 (0.9–1.6)	1.1 (0.9–1.4)	0.604@

[a] Students T test @ Mann Whitney U test.

Saini et al (using similar criteria to define liver injury as this study) reported hepatocellular injury in 55.3% of patients and cholestatic injury in 27% of patients. In another study from India, Saithanyamurthi et al[16] reported transaminases elevated above five times the upper limit of normal in 2.6% of COVID-19 patients. Cai et al[7] defined liver injury as any elevation of enzymes over three times and bilirubin over twice the upper limit of normal and reported liver injury in 21.5% of COVID-19 patients. Richardson et al reported acute liver injury in 1.96% of patients when using the criteria of elevation in aspartate aminotransferase or alanine aminotransferase of more than 15 times the upper limit of normal.[20] ACE2 receptors are predominantly expressed in the biliary tree. However, we report a higher prevalence of abnormal transaminase in our study participants. This points to hepatocellular liver injury rathe than injury to the biliary tree in patients of COVID-19. Our results align with findings from similar studies that reported a higher prevalence of deranged transaminases, which points to hepatocellular injury in these patients.[21]

We report higher odds of abnormal LFT in males and those above 50 years of age. Several published studies have reported similar findings.[18,22,23] We found the disease severity to be significantly associated with abnormal liver chemistry ($p < .001$) but not with mortality ($p > .05$). The association of abnormal LFT with adverse outcomes in patients with COVID-19 seems consistent across studies. Most authors have reported increased risk of ICU admissions,[12,24,25] mechanical ventilation,[24] longer duration of hospital stay,[15,26] and mortality.[11,15,24] However, a few studies did not find any increased risk of mortality[9,25] in patients with abnormal LFT.

We observed that mean albumin, AST and ALP varied significantly between the mild and the moderate/severe patients. Certain studies have found hypalbumi-naemia as a significant independent risk factor for severe illness[23] and mortality.[27]Kumar et al. [14]reported statistically different mean AST and ALP levels among different severity groups of ninety-one patients of COVID-19. Still, they reported no significant difference in the mean ALT and total bilirubin levels in these two groups.

Our study has certain limitations. Firstly, it is a single-center retrospective record-based study limited to admitted patients; we did not measure GGT levels, and inflammatory markers and LFT analyzed in the study were measured only at

Table 4 – Comparison of prevalence of abnormal LFT reported in COVID-19 patients in different studies.

Study	Abnormal LFT	AST	ALT	ALP	Bilirubin	Albumin
This study	74.2%	43.5%	40.1%	2.62%	6.3%	50%
Lv et al.[24]	48.6%	7.6%	22.7%	4.6%	1.8%	25.3%
Xie et al.[28]	–	35.4%	31.6%	NR	5.1	NR
Cai et al.[7]	76.3%	47%	57%	NR	11.5%	64%
Kaushik et al.[15]	NR	54%	74%,	NR	93%	NR
Saithanyamurthi et al.[16]	NR	63%	42%	3.3%	4.2%	NR
Kulkarni et al.[11]	47.6%	22.5%	20.1%	6.1%	13.4%	55.5
		95% CI = 18.1–27.6	95% CI = 16.8–23.8	95% CI = 2.4–14.2	95%CI = 09–19.4	95% CI = 42.8–67.6
Wijarnpreecha et al.[21]	NR	23.2%	21.2%	4.0%	9.7%	4.0%
		95% CI 19.8–27.1	95% CI 17.2–25.9	95%CI 2.5–6.3	95% CI 6.8–13.8	95% CI 2.5–6.3

NR: Not reported

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the time of admission/initial presentation. Analysis of serial measurement of LFT would have provided more information regarding the progression of infection and outcome. However, one of the strengths of this study is its large sample size; we feel that this is possibly one of the largest studies in India estimating the prevalence of abnormal LFT and measuring the association of LFT with severity and outcomes in COVID-19 patients.

Abnormal LFT is associated with a severe course of illness in COVID-19. Prospective studies are needed to validate these findings and identify the specific mechanism of liver injury in these patients.

Disclosure of competing interest

The authors have none to declare.

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