

COVID-19 associated variations in liver function parameters: a retrospective study

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ABSTRACT

Background Characteristics of laboratory findings of COVID-19 patients are of great significance for diagnosis and treatment. Studies that have analysed the variations in hepatic profile in correlation with the inflammatory markers in SARS-CoV-2 are limited.

Methods We retrospectively analysed liver function tests and inflammatory markers of 170 admitted patients with confirmed COVID-19 in the tertiary care centre, Post Graduate Institute of Medical Education and Research (PGIMER), India, using Roche Cobas Autoanalyzer.

Results Number of patients with normal liver enzyme levels were 63 (41.5%), while with raised levels of any of the liver enzymes were 89 (58.5%), out of which 43 (48.31%) had liver injury which manifested as increased severity in terms of intensive care unit (ICU) requirement ($p=0.0005$). Significantly raised levels of liver enzymes and liver injury were observed with age ($p<0.0001$) and in males ($p=0.004$). Significantly decreased levels of albumin and total proteins and increased levels of total bilirubin ($p<0.0001$) were seen in patients with abnormal liver enzyme levels and liver injury as compared to patients with normal levels. Significant increase in the levels of alanine transaminase and gamma-glutamyl transferase was seen on the 7th day, CRP and ferritin ($p<0.0001$) peaks were observed on 2nd and 3rd day respectively. A significant positive correlation was found between the levels of these inflammatory markers and liver function parameters.

Conclusions More than half of patients admitted to the hospital with SARS-CoV-2 infection had an abnormal liver function which was found to be associated with raised levels of inflammatory markers. Significantly higher proportions of patients with abnormal liver function were elderly and males and were at higher risk of progressing to severe disease.

INTRODUCTION

In December 2019, an infectious severe acute respiratory syndrome was reported in China, found to be caused by a coronavirus.¹ Initially named as 2019 novel coronavirus (2019-nCoV), the virus was later termed as SARS-CoV-2.² This virus has been reported to have some features of SARS-CoV reported in 2003 and MERS-CoV reported in 2012. On 11 March 2020, the WHO declared COVID-19 (Coronavirus disease 2019) as a pandemic, which has resulted in more than 22 million infections with 781 932 deaths worldwide until 19 August 2020.^{3 4} Currently, the primary diagnostic tool to detect cases of SARS-CoV-2 infections is real-time reverse

transcriptase polymerase reaction (RT-PCR) from nasopharyngeal swabs and bronchoalveolar lavage fluids. Rapid antigen testing and measurements of antibody titre are also conducted for surveillance testing. Additionally, some haematology and biochemistry parameters complement the diagnosis.⁵

The primary organ targeted in SARS is the lung, hence designated as ‘Severe Acute Respiratory Syndrome’ and ‘SARS atypical pneumonia’.⁶ However, other organ dysfunctions, including gastrointestinal symptoms,⁷ abnormal liver functions,⁸ lymphadenopathy⁹ and splenic atrophy, have also been observed in patients. These occurrences reflect widespread immunopathology or extrapulmonary dissemination and replication of SARS-coronavirus (CoV).¹⁰ Partial autopsies also indicate multiple organ infection by the virus.¹¹ The pathological changes can be attributed either to the direct cytotoxic effect by local replication of the virus or indirectly due to immune response induced by the viral infection. There are certain reports on the impact of COVID-19 on other organs, including varying levels of liver disease in patients.¹² A recent study found the binding of SARS-CoV-2 virus to ACE 2 (ACE2) on cholangiocytes leading to its dysfunction, which may result in liver injury through inducing a systemic inflammatory response.¹³ Several hospital-based studies have reported liver damage in patients with COVID-19 in terms of elevated levels of liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with 14% to 53% rise in comparison to their normal levels.^{14–17} Further, moderate microvesicular steatosis, mild lobular and portal activity found in the liver biopsy specimens of a dead COVID-19 patient indicated the involvement of SARS-CoV-2 in liver damage.¹⁸

However, only a few studies have broadly analysed all the liver enzymes and also the variations in the liver function tests with inflammatory markers along with the characteristics of liver failure among patients with COVID-19. Hence, the study aims to report the variations in liver test parameters in correlation with the inflammatory markers in patients with COVID-19.

METHODS

Study design and participants

We retrospectively evaluated and analysed the liver function test results and inflammatory marker levels along with the medical history obtained from 170 adult patients of both genders with confirmed COVID-19 from 15 March 2020 to 15 June 2020



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All COVID-19 positive patients of 15 years of age and above were included in the study. Patients suffering from chronic liver diseases, alcoholism, hepatitis, pregnant women and children (below 15 years) were excluded from the study. The study has been cleared by the Institutional Ethics Committee (INT/IEC/2020/000765).

Laboratory examination

The COVID-19 positive status was confirmed by RT-PCR analysis of nasal swab samples in the Department of Virology, PGIMER, Chandigarh, India, as per guidelines of Indian Council of Medical Research (ICMR), New Delhi, India.

Following standard operating procedures, the blood samples were handled by a designated technician with proper safety gear. The sample tubes were decontaminated by wiping and spraying with 0.1% hypochlorite solution, which was followed by placing the vacutainers under UV-C Biosafety Cabinet for 15 min. The samples were then centrifuged for 10 min at 3500 RPM; the lid of the centrifuge was kept closed for the next 15 min for the aerosols to settle down. The serum samples for liver function tests were analysed after maintaining proper quality control check in Roche Diagnostics International Ltd, Switzerland, Cobas: 8000 Autoanalyser. Analysis of C reactive protein (CRP) and ferritin was done in Roche Cobas: E-411 Autoanalyser. All tests were performed according to standard protocols and procedures provided by Roche company.

Liver function tests parameters and inflammatory markers

Abnormality in liver tests was defined as: Alanine transaminase (ALT) >40 U/L, aspartate transaminase (AST) >40 U/L, alkaline phosphatase (ALP) >128 U/L, gamma-glutamyl transferase (GGT) >61 U/L, total bilirubin (T.Bil) >1.2 mg/dl, total protein <6.5 g/L and albumin <3.4 g/L at any given time point during the hospitalisation. COVID-19 is a new, emerging infectious disease and liver injury classifications have not been clearly defined. In this study, liver injury was thus classified as hepatocellular, cholestatic or mixed type. Hepatocellular injury was defined in patients who had raised ALT and/or AST more than 3× the upper limit unit of normal (ULN); cholestatic injury in patients with raised ALP or GGT 2× ULN; and mixed liver injury included those having a combination of both ALT/AST elevated more than 3× ULN and ALP/GGT twice ULN.¹⁷

Increase in inflammatory markers was defined as CRP >5 mg/dl, ferritin >400ng/dl in males and >150ng/dl in females.

Statistical analysis

Categorical variables were expressed as percentages. The difference between categorical variables was examined with the χ^2 test or Fisher's exact test with median (IQR). Unpaired t-test was used to compare day-wise differences in the levels of liver enzymes and inflammatory markers. Correlation analysis was done using the Pearson correlation coefficient. A p value <0.05 was considered as statistically significant. All statistical analysis was performed using Graph Pad Prism8.

RESULTS

COVID-19 positive patients with raised liver enzymes levels

Out of the 170 COVID-19 positive patients admitted, 18 were excluded according to the selection criteria. Recruited patients for study were 152 who were analysed for their liver function enzyme levels (ALT, AST, ALP and GGT), based on which 63 (41.5%) were found with enzyme levels within the normal range

throughout their stay in hospital. Eighty-nine (58.5%) patients had raised levels of any of these enzymes at any time point during their hospitalisation (figure 1A). In these patients, the median values of AST, ALT, ALP and GGT were found to be 57.0 U/L, 64.65 U/L, 122.0 U/L and 61.50 U/L, respectively, as compared to 24.60 U/L, 24.80 U/L, 86.0 U/L and 20.0 U/L, respectively, in patients with normal liver enzymes (table 1). Out of these 89 patients, abnormal liver enzyme levels up to 2× ULN were observed in 42 patients whereas 47 patients had abnormal liver enzyme levels higher than 2× ULN.

The study population of 152 included 89 males and 63 females. Elevated levels of liver enzymes (above ULN) were found to be significantly higher in males (67.4%, $p=0.004$) as compared to females (46.03%) (figure 1B). Moreover, the percentage of males with raised liver enzymes beyond 2× ULN was 38.2%, while in females it was 20.6%. Classification of these subjects in different

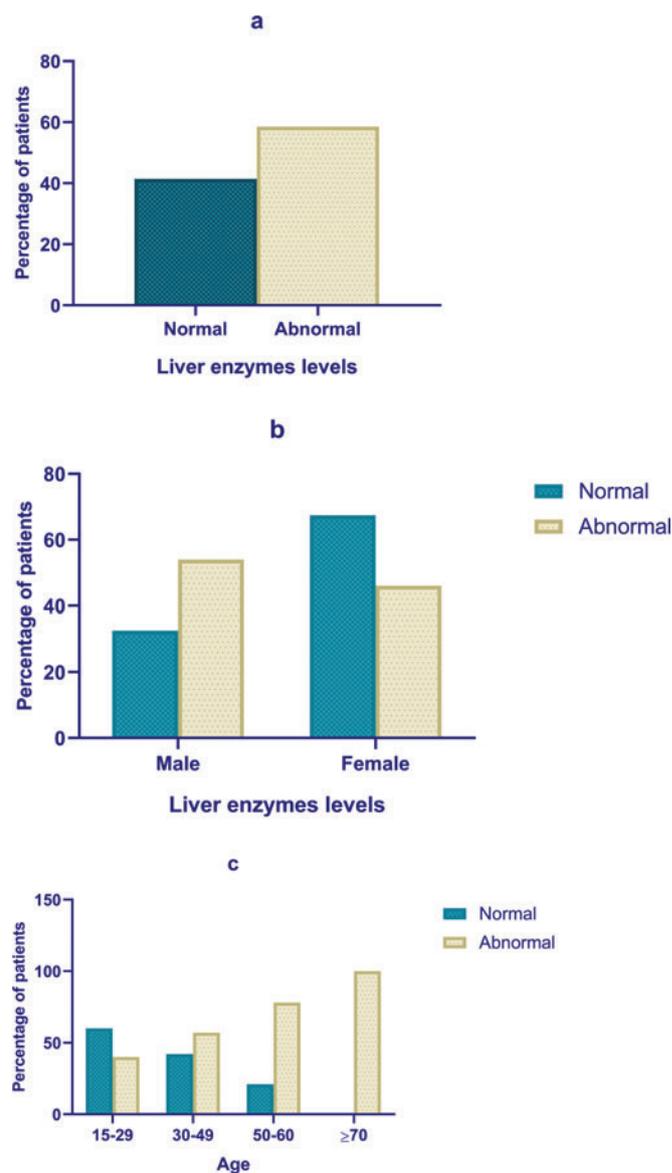


Figure 1 (A) Percentage of patients having normal and abnormal levels of liver enzymes in study population, with respect to (B) gender ($p=0.004$) and (C) age ($p<0.0001$). Abnormal levels of liver enzymes indicate any value of ALT, AST, ALP and GGT above ULN. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit unit of normal.

Table 1 Table showing the median values of liver function parameters

	Range of normal liver parameters	Range of abnormal liver parameters	Range in patients with liver injury
	Min-Max (Median)	Min-Max (Median)	Min-Max (Median)
Total Protein (g/dl)	5.41–8.15 (07.18)	3.7–8.6 (06.80)	3.7–7.9 (06.40)
Albumin(g/dl)	1.9–3.4 (04.27)	1.54–5.02 (03.80)	1.58–4.96 (03.20)
T.Bil (mg/dl)	0.11–1.5 (00.52)	0.32–20.78 (00.70)	0.43–20.78 (00.82)
AST (U/L)	15–44 (24.60)	19.8–2175 (57.00)	19.8–2175 (95.00)
ALT (U/L)	6.8–58.5 (24.80)	13.2–854.4 (64.65)	4.1–854.4 (127.70)
ALP (U/L)	48–302 (86.00)	13.7–323 (122.00)	78–824 (142.00)
GGT (U/L)	8–106 (20.00)	11–566 (61.50)	13–688 (101.50)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; T.Bil, total bilirubin.

age groups showed a direct correlation of abnormal liver enzyme levels with age as 40%, 57.9%, 78% and 100% of the COVID-19 patients falling in the age group 15–29, 30–49, 50–69 and ≥ 70 , respectively ($p < 0.0001$, [figure 1C](#)).

COVID-19 patients with liver injury

Out of the 89 patients with abnormally raised liver enzymes, liver injury was seen in 43 patients (48.31%). Hepatocellular injury (ALT and/or AST more than $3 \times$ ULN) was seen in 23 (53.48%), whereas cholestatic (ALP or GGT $2 \times$ ULN) and mixed (combination of both) type of injury were seen in 12 (27.9%) and 8 (18.6%) patients, respectively ([figure 2A](#)). The median values of AST, ALT, ALP and GGT were found to be 95.0 U/L, 127.7 U/L, 142.0 U/L and 101.50 U/L in these patients ([table 1](#)). Of these 43 patients with liver injury, 31 were males and 12 were females. No significant difference was found in the incidence of liver injury in males and females ([figure 2B](#)). However, we found a significant effect of age on the prevalence of these injuries. Below age 50, more percentage of patients had hepatocellular and cholestatic liver injury whereas in 50 years and above patients, there was more occurrence of mixed type of liver injury ($p < 0.0001$, [figure 2C](#)).

Out of the total recruited subjects, three died during the study. These dead patients displayed different liver profiles. In one to them, highly raised levels of AST ($55 \times$ ULN) and ALT ($21 \times$ ULN) were found, indicating hepatocellular injury. Only a mild rise in AST and ALT levels (up to $2 \times$ ULN) was observed in another patient. The third dead patient displayed significantly elevated GGT ($11 \times$ ULN) and ALP ($6 \times$ ULN) levels, indicating more of cholestatic type of liver injury. Levels of CRP and ferritin were highly raised in all three patients. Incidentally, abnormal renal function was also detected in these patients (data not shown).

Severity in COVID-19 patients in terms of intensive care unit (ICU) requirement

Severity in COVID-19 patients was assessed in terms of their ICU requirement during hospitalisation. Out of the 89 patients with raised liver enzymes, ICU care was required for 33 patients (37.07%), while in patients with normal liver enzymes only 21.15% required ICU care. ICU requirement was found to be more pronounced in patients with liver injury, where 23 out of 43 (52.48%) were admitted in ICU ($p = 0.0005$, [figure 3](#)).

Total proteins, albumin and total bilirubin

Levels of total proteins, albumin and total bilirubin were compared between patients with normal liver enzyme levels, abnormal liver enzyme levels and liver injury. Protein levels were found

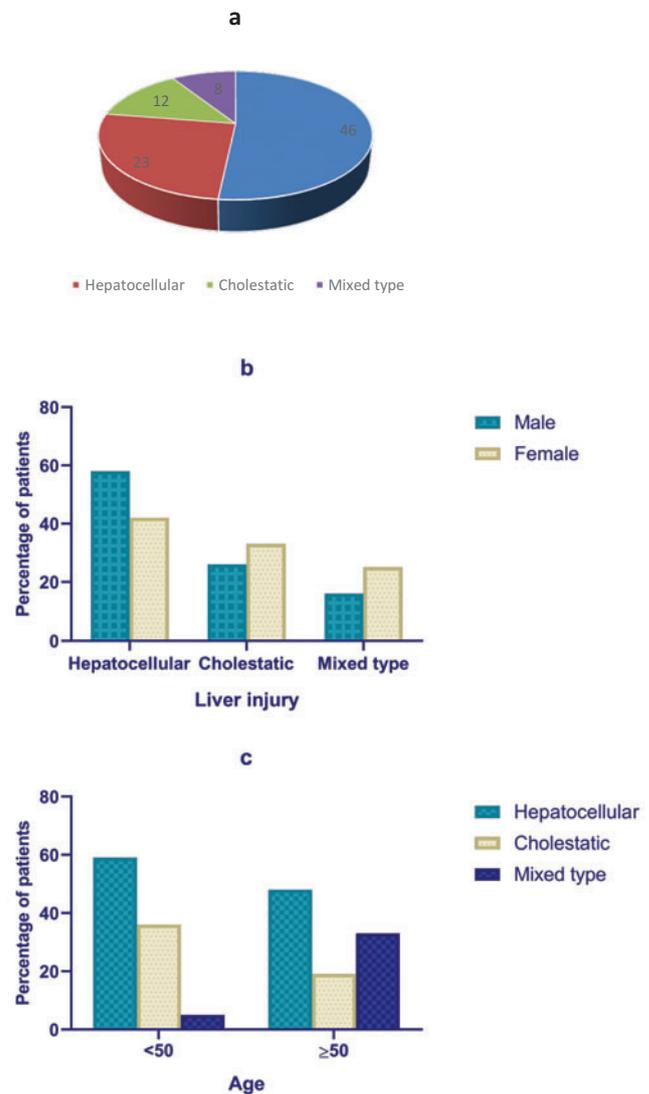


Figure 2 (A) Patients with Hepatocellular, Cholestatic and Mixed type of liver injury, (B) percentage of these patients with respect to gender (p value ns) and (C) age ($p < 0.0001$).

to be significantly reduced in patients with abnormal liver enzymes with median value 6.80 g/L ([table 1](#)) and patients with liver injury, median value 6.40 g/L ([table 1](#), $p = 0.003$, [figure 4A](#)) as compared to patients with normal liver enzymes with median value 7.18 g/L ([table 1](#)). A similar decrease was also observed in the levels of albumin in patients with abnormal liver enzymes (median value 3.80 g/L ([table 1](#))) and patients with liver injury ($p < 0.0001$, [figure 4B](#) with median value 3.20 g/L, [table 1](#)) as compared to patients with normal liver enzymes having median value 4.27 g/L ([table 1](#)). Levels of total bilirubin were found to be significantly increased in patients with abnormal liver enzymes and in liver injury patients ($p < 0.0001$, [figure 4C](#)), as compared to the patients with normal liver enzyme levels, with median values 0.70 mg/dl, 0.82 mg/dl and 0.52 mg/dl, respectively ([table 1](#)).

Serial changes in liver enzymes and inflammatory markers

Levels of liver enzymes and inflammatory markers (CRP and ferritin) were analysed on each day after the admission of patients. Considering day of admission as Day 1, no significant increase in the levels of AST, ALT, ALP, GGT, CRP and ferritin was observed in

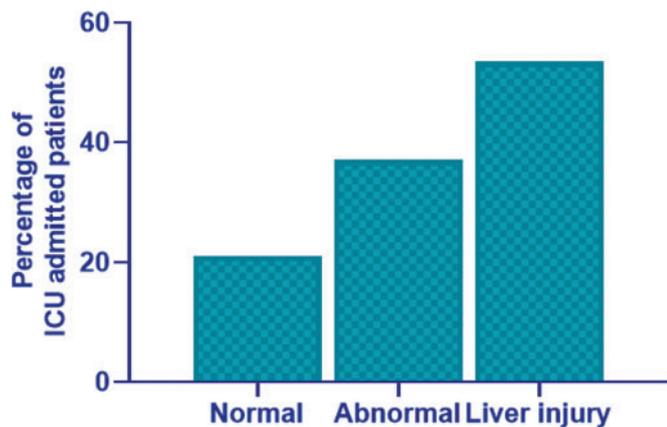


Figure 3 Figure showing the percentage of patients admitted in ICU in normal, abnormal and liver injury patients ($p=0.0005$). ICU, intensive care unit.

patients having normal liver function enzyme level (data not shown) throughout the study. In patients with raised liver enzyme levels, a significant increase in the levels of ALT ($p=0.02$) and GGT ($p=0.04$) was found on 7th day (figure 5A,B). However, no significant increase in the levels of ALP and AST was observed at any of the days as compared to Day 1. In these patients, peaks of CRP ($p<0.0001$) and ferritin ($p<0.0001$) were observed on 2nd and 3rd day, respectively (figure 5C,D).

Correlation between liver function tests parameters and inflammatory markers

The liver function test parameters were correlated with the inflammatory markers using Pearson coefficient (r) and p values. A positive correlation was found between the levels of CRP with AST, ALT, GGT, total protein and albumin in the patients with raised liver enzymes. Similarly, a positive correlation was found between ferritin with AST, ALT, ALP, GGT, total protein and total bilirubin. In patients with normal liver enzymes, no correlation was found between the inflammatory markers and liver function test parameters except for ferritin with GGT and ALP (table 2).

DISCUSSION

The present study was retrospectively carried out in 170 COVID-19 positive patients admitted to Nehru Hospital Extension, PGIMER, Chandigarh, India. Following the selection criteria, 18 patients were excluded from the study. Patients included in the study were 152, out of which majority of the patients, that is, 89 (58.5%), had raised liver enzyme levels as compared to 63 (41.5%) with normal liver enzyme levels. This suggests the presence of liver damage in patients with coronavirus infection. Earlier studies have reported similar findings, suggesting liver damage may be directly caused by the viral infection.¹⁹ Few studies have indicated that ACE2 is the key receptor for the entry of SARS-CoV-2 into the cells^{20 21} and the direct binding of SARS-CoV-2 to ACE2 receptors in cholangiocytes might result in the liver damage.²²

We observed noticeable elevated liver enzyme levels in males (67.4%) as compared to females (46.03%). This higher predisposition could be attributed to the higher expression of ACE2 receptors in males, as reported from a study in Wuhan.^{23 24} Moreover, there was a direct positive correlation of abnormal liver enzyme levels with increasing age ($p<0.0001$), which is consistent with a previous report.²⁵

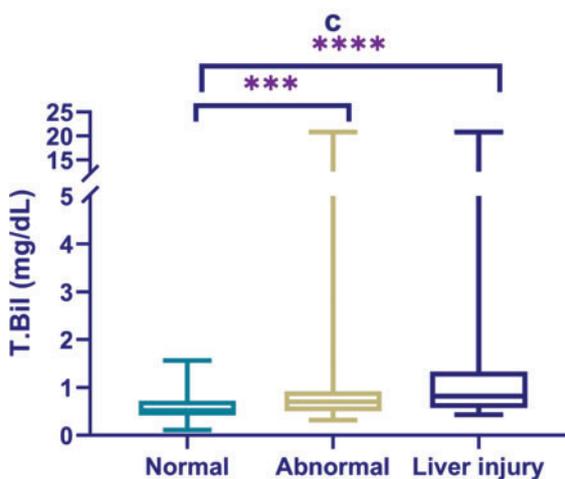
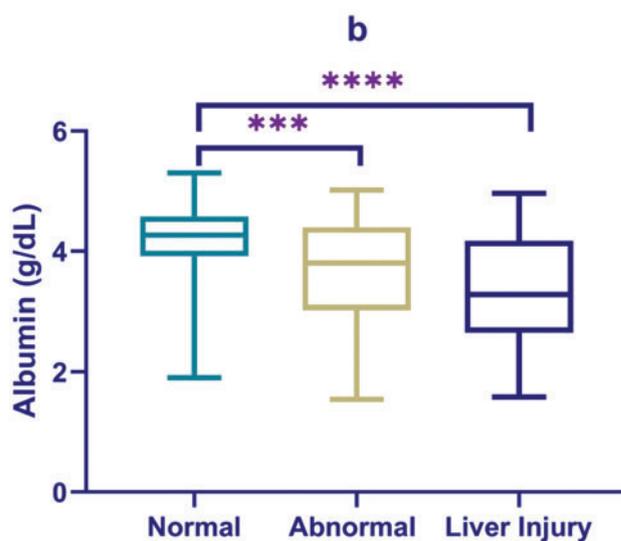
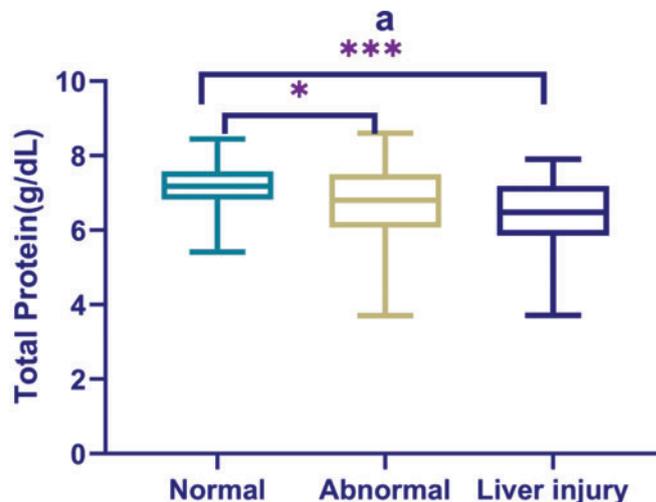


Figure 4 Figure showing the levels of (A) total protein, (B) albumin and (C) T.Bil in normal, abnormal and liver injury patients. T.Bil, total bilirubin.

Notably, approximately half of the patients with raised liver enzyme levels (43 out of 89 patients) were found to have occurrence of some liver injury (AST and/or ALT $>3\times$ ULN and/or ALP and/or GGT $>2\times$ ULN), which was again more prevalent in

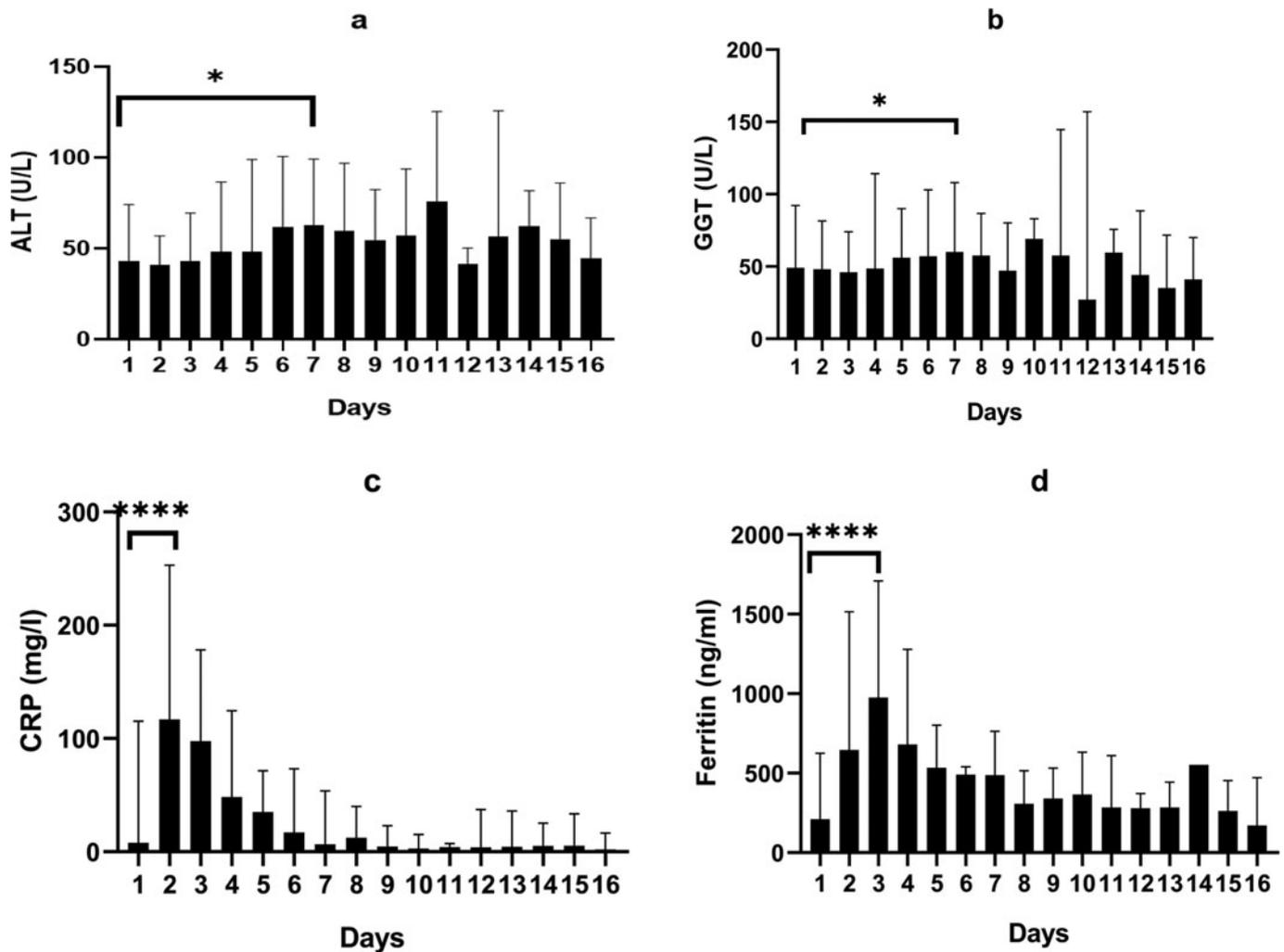


Figure 5 Serial study of the levels of liver enzymes. (A) ALT, (B) GGT and inflammatory markers, (C) CRP and (D) Ferritin in patients with abnormal liver enzyme levels. ALT, alanine aminotransferase; CRP, C reactive protein; GGT, gamma-glutamyl transferase.

Table 2 Table showing the correlation between inflammatory markers with liver function parameters

	Patients with normal liver enzyme levels		Patients with abnormal liver enzyme levels	
	r	P	r	P
CRP vs.				
AST	-0.01	ns	0.323	0.0022
ALT	-0.07	ns	0.346	0.0010
GGT	0.10	ns	0.444	<0.0001
ALP	0.16	ns	0.186	ns
Total protein	-0.065	ns	-0.299	<0.005
Albumin	-0.1451	ns	-0.523	<0.0001
Total Bilirubin	0.0103	ns	0.0235	ns
Ferritin vs.				
AST	-0.12	ns	0.39	0.0002
ALT	-0.2	ns	0.43	<0.001
GGT	0.32	0.01	0.56	<0.001
ALP	0.43	0.0004	0.31	<0.003
Total protein	-0.0097	ns	-0.42	<0.0001
Albumin	0.086	ns	0.07	ns
Total Bilirubin	0.027	ns	-0.04	0.0068

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C reactive protein; GGT, gamma-glutamyl transferase.

male as compared to female. In patients with liver injury, hepatocellular injury was seen in 53.5%, followed by cholestatic in 28% and mixed (combination of both) in 18.5% patients. Patients above the age of 50 years had more of mixed type of liver injury as compared to those below 50 years ($p < 0.0001$), substantiating the reports that disease severity is more pronounced in elderly patients.

ICU requirement during hospitalisation was assessed to determine the severity of disease in COVID-positive patients. In patients with normal liver enzymes, only 21.15% required ICU admission, 37.07% in patients with raised liver enzymes, while maximum requirement of 52.48% was observed in patients with liver injury. This observation indicates severe manifestations of SARS-CoV2 infection in patients with liver injury, thereby requiring ICU care. There are studies reporting similar findings that patients in intensive care units and critical states are more likely to have their liver biochemical markers deranged denoting the severity of infection.²⁵

Patients with abnormal liver enzyme levels and liver injury had significantly decreased values of albumin and total proteins ($p < 0.0001$) as compared to patients with normal liver enzyme levels. This could be attributed, possibly to the poor nutritional intake and the role of 'cytokine storm' with the release of major acute-phase cytokines, in downregulating the albumin synthesis in liver, after the onset of COVID-19.²⁶ Total bilirubin was found

to be significantly increased ($p < 0.0001$) in patients with abnormal liver enzyme levels and liver injury as compared to patients with normal liver enzyme levels. A recent study in a pooled analysis showed that bilirubin levels were significantly increased in patients with mild and severe COVID-19 which corroborates our results.²⁷

Many studies have reported mild, transient and clinically non-significant liver dysregulation which displayed minimal impact on COVID-19 outcomes.²⁸ However, patients with hepatocellular type or mixed type liver injury at the time of admission were at a higher risk of developing severe disease during hospitalisation²⁹ which was also observed in our study.

On analysis of serial changes in the levels of liver enzymes and inflammatory markers, in patients with abnormal liver enzyme levels, peaks of ALT and GGT were observed on 7th day whereas CRP and ferritin were raised to maximum levels on 2nd and 3rd day, respectively, indicating that the rise in levels of inflammatory markers preceded the rise in liver enzyme levels. As liver function tests are routine investigations carried out at the time of admission, liver function test abnormalities could, therefore, be used as a predictor for the severity of the disease. Significant increase in levels of CRP and ferritin is indicative of immune-mediated damage to the liver as a result of the severe inflammatory response following COVID-19 infection.¹⁴ This is with accordance with another study that showed that the inflammatory biomarkers including CRP, LDH, serum ferritin, D-dimer, IL-2 and IL-6 are significantly elevated in patients with severe COVID-19.³⁰

A positive correlation was observed between the inflammatory indices CRP, ferritin with liver function parameters in patients with abnormal liver enzyme levels indicating potential virus replication induced immune response. In patients with severe pneumonia, elevated levels of transaminase are known to be associated with inflammatory cytokines.³¹ Altered inflammatory cytokine expression profile was likewise seen during SARS-CoV and MERS-CoV infections that were concomitant with disease severity and poor prognosis.³² There are plausible parallels between the SARS-CoV2 and SARS-CoV outbreaks as evidenced in the autopsy analysis of patients who died of severe acute respiratory syndrome of SARS-CoV, with the liver affected by fatty degeneration and central lobular necrosis.³³ It can thus be inferred that SARS-CoV-2 may also affect the human liver.

This study has a few limitations. First, it is a retrospective study carried out using the data collected from a single centre with lack of complete records of patients' history. Second, the medication history of the patients was not available. Third, we examined only the association between COVID-19 and abnormal liver function, therefore, could not highlight the exclusive role of liver damage resulting in casualties. Although three patients who died during this study had highly raised liver enzyme levels, their renal function tests were also highly elevated. Therefore, further studies are required to explore the mechanisms of COVID-induced liver injury.

In conclusion, abnormal liver profile is present in COVID-19 patients. SARS-CoV-2 may possibly cause liver damage. Abnormal liver function is associated with elevated levels of inflammatory markers. Elderly and male patients with abnormal liver function were at higher risk of developing severe disease. These findings may help to elucidate the role of liver function tests on COVID-19 prognosis and provide a scope for improvement in the clinical treatment of patients during this current pandemic.

Main messages

- ▶ Out of the 152 COVID-19 positive patients, 89 (58.5%) had abnormal liver tests, out of which 43 (48.31%) had liver injury during hospitalisation.
- ▶ Severity in terms of ICU requirement was more pronounced in patients with raised liver enzymes and liver injury where 37.07% and 52.48% were admitted in ICU, respectively, as compared to 21.15% in patients with normal liver enzymes.
- ▶ Raised liver function parameters were predominantly observed in males and elderly patients.
- ▶ Elderly patients had preponderance towards severe liver injury.
- ▶ Peaks of inflammatory markers preceded the peaks of liver function enzymes.
- ▶ A significant positive correlation was observed between liver function parameters and inflammatory markers.

Current research questions

- ▶ Does COVID-19 liver involvement play a causal role in disease pathogenesis?
- ▶ Whether patients with pre-existing liver disease are more susceptible to COVID-19?
- ▶ Is COVID-19-induced liver injury reversible?

What is already known on the subject

- ▶ Severe inflammatory response following COVID-19 infection results in organ immune-mediated damage.
- ▶ Besides other organs, ACE-2 is also known to be abundantly expressed in biliary epithelial cells of the liver and SARS-CoV-2 binds to target cells through these receptors therefore making liver a potential target for direct infection.

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