Original Research Article

Assessment of Liver function and its correlation with inflammatory markers and severity of disease during COVID-19 second wave in a tertiary care centre

ABSTRACT

Aims: To assess the Liver function in COVID-19 infection and study its correlation with inflammatory markers and severity of disease.

Study design: A Retrospective Observational study.

Place and Duration of Study: Government Kilpauk Medical College, Chennai, India. Two month study period was taken during the second COVID wave (1st May 2021 to 30th June 2021).

Methodology: The study covered all COVID-19 positive individuals who were over the age of 19. Patients with any chronic liver disease, Hepatitis B or Hepatitis C were excluded. Data was collected from case files. Record was made of the liver function tests and inflammatory markers – C-Reactive Protein and Interleukin-6 (CRP, IL-6). Severe disease was defined as patients with respiratory rate > 30/min, SpO2 <90% on room air or requiring Intensive Care Unit (ICU) admission or mechanical ventilation. Collected data was analysed using appropriate statistical tests.

Results: 132 patients were included in the study. Out of these 59 patients (44.70%) had elevated Liver function tests (LFTs). Maximum patients (42.37%) had hepatocellular pattern. 59.32% patients were males. Mean age of patients with elevated LFTs was 51.03±13.03 years. ICU admission was required in 40.68% of patients with deranged LFTs compared to 23.28% in patients with normal LFTs, which was statistically significant (P <0.03). A positive correlation was found between deranged LFTs and inflammatory markers (CRP, IL-6). (P <0.001).

Conclusion: A significant number of COVID-19 positive individuals have abnormal liver function. Inflammatory indicators and elevated LFTs have a positive relationship. Patients with abnormal liver function tests were more likely to have severe illness.

Keywords: COVID-19, liver function test, severe disease, inflammatory markers.

1. INTRODUCTION

COVID-19 pandemic has afflicted nearly 350 million people around the world till now.[1] SARS-CoV-2 is a highly transmissible virus which can spread from person to person through respiratory droplets during sneezing and coughing. The incubation period of the disease is 2-14 days.

SARS-CoV-2 belongs to the family coronaviridae and belongs to the genus betacoronavirus. Coronavirus is single stranded RNA enveloped virus, of size 62-125 nm. It has four structural proteins known as S (Spike), E (envelope), M (membrane) and N (nucleic acid). [2]

Although COVID-19 patients typically experience respiratory symptoms, additional organ systems have been implicated, resulting in gastrointestinal problems [3] and abnormal liver functioning [4]. Few investigations have found a link between SARS-CoV-2 and liver dysfunction or injury. [4,5] The actual cause of liver impairment in people infected with SARS-CoV-2 is unknown. Direct virus-induced cytopathic effects, worsening of pre-existing liver disease, hypoxemia, drug-induced and overshooting inflammatory responses are all possible mechanisms.It has been postulated that the S protein of SARS-CoV-2 initially binds to the ACE-2 receptors which are found in epithelial cells and tissues of lung, heart, liver, blood vessels, GI tract and kidneys [6] inducing uptake of virus particles.[7,8] ACE-2 receptors are also present in central hepatic vein and portal vein endothelial cells. The binding of SARS-CoV-2 virus to ACE 2 receptors on cholangiocytes may lead to liver dysfunction. [9] Other potential mechanisms include hypoxic changes caused by respiratory failure and drug induced liver injury. [10].

Our study aims to assess the liver function in COVID-19 infection and to study its correlation with inflammatory markers and severity of disease.

2. MATERIALS AND METHODS

A retrospective observational study was carried out at Government Kilpauk Medical College and Hospital, Chennai, which is a tertiary care centre. The study was carried out over two months period (1st May 2021 to 30th June 2021), during the second COVID wave.

The study covered all COVID-19 positive individuals who were over the age of 19. The study excluded patients with chronic liver disease, hepatitis B, or hepatitis C.The COVID-19 infection cases were detected by real-time reverse transcriptase polymerase reaction (RT-PCR) from nasal or pharangeal swab. Data was collected from case files. Demographic data (age, gender) was noted. Record was made of the liver function tests and inflammatory markers [C-reactive protein (CRP) and interleukin -6 (IL-6)]. Aspartate aminotransferase (AST) value more than 40 U/L, Alanine aminotransferase (ALT) value more than 40 U/L, alkaline phosphate (ALP) value more than 120 U/L and total bilirubin value more than 1.5 mg/dl were taken as abnormal LFT values.[4] CRP value of more than 5 mg/dl and IL-6 value of 15 pg/ml were considered as elevated inflammatory markers. In the study liver injury was defined as hepatocellular, cholestatic or mixed type by calculating the R factor. Severe disease was defined as patients with respiratory rate > 30/min, SpO2 <90% on room air and requiring ICU admission or mechanical ventilation.

Collected data was tabulated in MS- Excel. The data was analysed using appropriate statistical tests. Demographic variables were expressed as percentage. Correlation analysis was done by using the Pearson correlation coefficient. *P* value of <0.05 was considered as statistically significant.

3. RESULTS AND DISCUSSION

132 patients were included in the study who fulfilled our inclusion criteria.

Out of these 59 patients (44.70%) had elevated Liver function tests and the rest 73 had normal LFTs. (Figure 1) Our findings were consistent to other studies like study by Saini RK *et al* [4] and Priyadarshini BP *et al* [11] which also suggest that COVID -19 is associated with liver dysfunction in a significant number of patients. According to another Indian study, more than half of COVID-19 patients have multiple liver function test anomalies. [12]

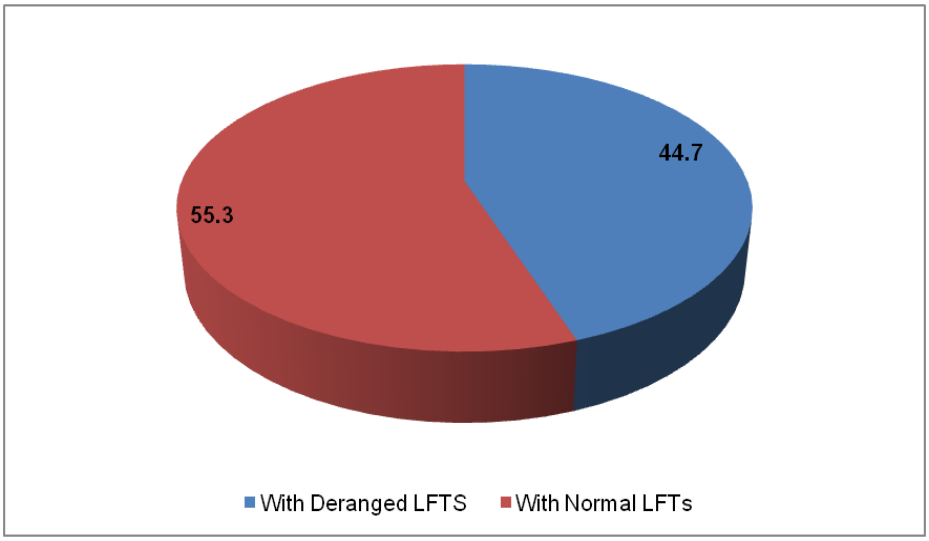

Figure 1 – Percentage of COVID-19 patients with and without deranged LFTs

3.1 Demographic profile

Of all the total patients included in the study, 58.33% were males and 41.67% were females.
The pattern of LFT profile amongst the males and females is shown in Figure 2. Amongst the patients who had deranged LFTs, 59.32% patients were males and 40.68% were females.

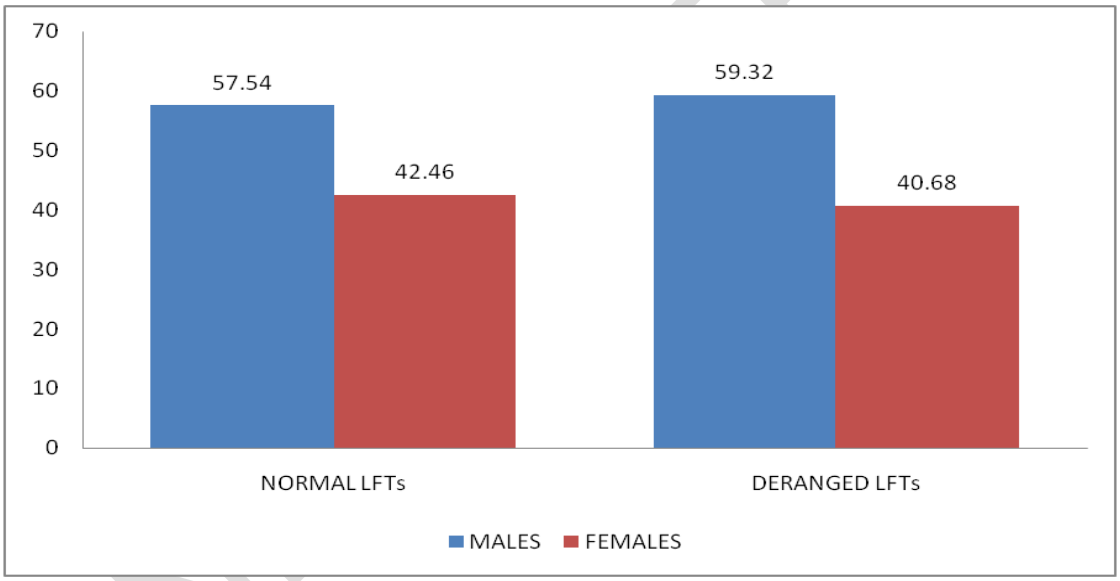

Figure 2- Pattern of LFTs according to Gender

Similar to our study, few other studies (Saini RK *et al.*[4] and Priyadarshini BP *et al.*[11]) also found a slight male preponderance for COVID-19 infection. Another study done in India by Kaushik A et al reported the percentage of male and females were 60.9% and 39% respectively.[12] A slightly increased predominance amongst the males according to some studies in Wuhan is attributed to higher expression of ACE-2 receptors in males. [13,14]

In a study of 148 individuals with COVID-19, Fan et al found that the average age was 50 years old. [15]
In our study, mean age of patients was 47.52 ± 12.06 years in those with normal LFTs and 51.03 ± 13.03 years in those with elevated LFTs.

3.2 Liver injury in COVID-19 infection

Amongst the patients with deranged LFTs, maximum patients (42.37%) had hepatocellular pattern of type of liver injury, followed by mixed pattern in 37% and cholestatic pattern was seen only in 20 %. (Figure 3)

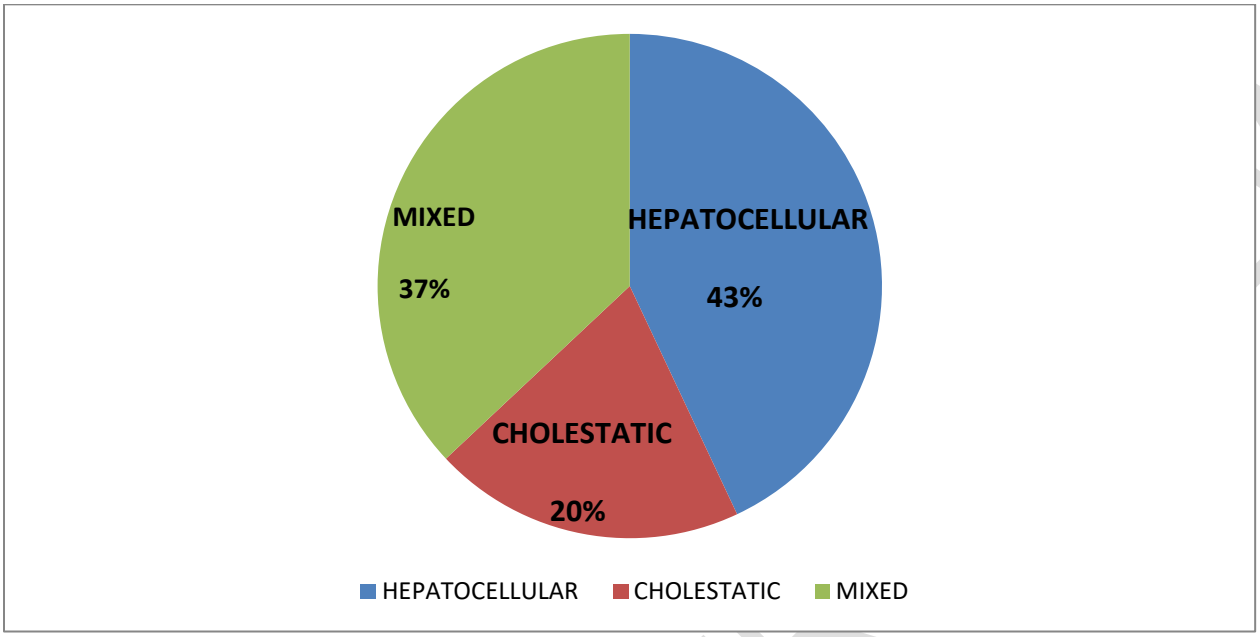

Figure 3 – Type of Liver injury

A study by Xu W et al also showed that the pattern of abnormal liver function tests is predominantly hepatocellular.[16] Cai Q *et al* however found mixed type of liver injury to be most common.[17]
Mean LFTs values amongst those with elevated LFTs were as follows- Mean S. Bilirubin = 3.26 ± 1.03 mg/dl, Mean AST = 195.29 ± 102.71 IU/L, Mean ALT = 211.75 ± 106.89 IU/L, Mean ALP = 177.51 ± 61.42.
On calculating the mean values of the different parameters of LFTs in the 2 groups, it was observed that the elevation in the liver function tests was significant (Table1)

Table 1- Comparison of normal LFTs and Deranged LFTs group in COVID-19 patients

PARAMETERS	**NORMAL LFTs GROUP (N=73)**	**DERANGED LFTs GROUP (N=59)**	***P*-value**
MeanS.Bilirubin (mg/dl)	0.80 ± 0.18	3.26 ± 1.03	<0.001
Mean AST (IU/L)	29.14 ± 6.48	195.29 ± 102.71	<0.001
Mean ALT (IU/L)	32.68 ± 6.15	211.75 ± 106.89	<0.001
Mean ALP	77.37 ± 15.70	177.51 ± 61.42	<0.001

P<0.001 suggests that LFTs are significantly increased in the deranged liver function group
(AST **-** Aspartate aminotransferase**,** ALT - Alanine aminotransferase, ALP **-** Alkaline Phosphatase **)**

When compared to patients with lesser forms of COVID-19, patients with severe COVID-19 have greater bilirubin levels. [18] Total bilirubin was found to be significantly increased (*P* <0.001) in patients with abnormal liver enzyme levels and liver injury as compared to patients with normal liver enzyme levels [4]
In study by Saini RK *et al*., he found, median values of AST, ALT, ALP were found to be 95.0 U/L, 127.7 U/L, 142.0 U/L. [4].

The inflammatory markers were raised significantly. Mean IL-6 was 17.07 ± 13.16 pg/ml and Mean CRP was 18.7 ± 13.7 mg/dl in patients with deranged LFTs.

3.3 Correlation of LFTs with severity of disease and inflammatory markers

Severe disease was defined as patients with respiratory rate > 30/min, SpO2 <90% on room air and requiring ICU admission or mechanical ventilation. ICU admission was required in 40.68% of patients with deranged LFTs compared to 23.28% in patients with normal LFTs, which was statistically significant (*P* <0.03) (Figure 4).
Among the patients with deranged LFTs, 4 patients expired (6.7%), whereas only 2 deaths (2.7%) were reported in patients with normal LFTs.

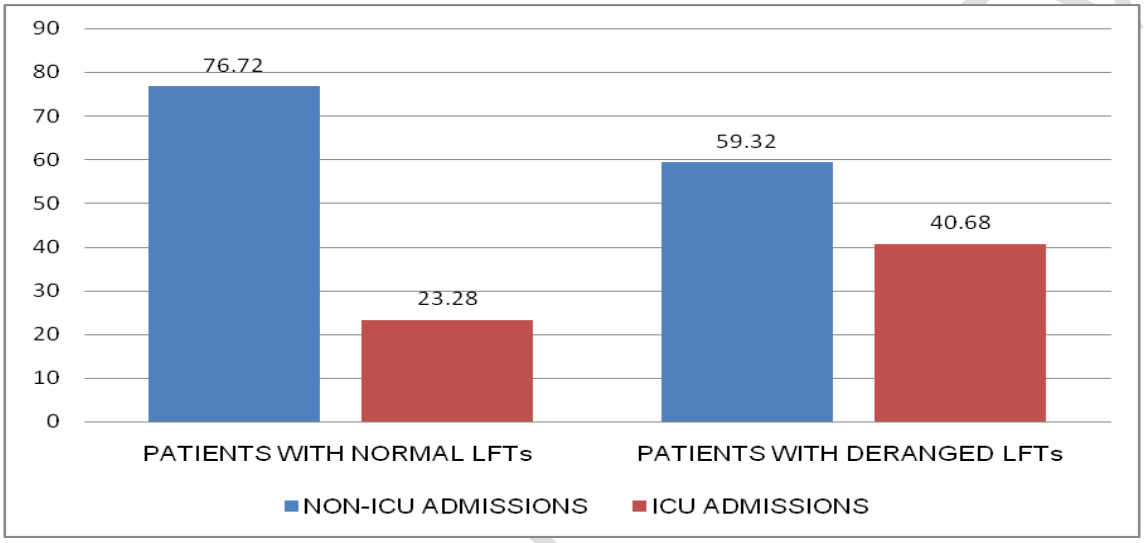

Figure 4 – Percentage of ICU admissions

RK Saini also conducted a study in which he found 37.07% patients with elevated LFTs and 21.15% with normal LFTs required ICU admissions. [4]

On calculating the *P*-values amongst the different liver function tests and the CRP and IL-6 values in the group with deranged LFTs, a positive correlation was found between deranged LFTs and inflammatory markers (CRP, IL-6). (*P*<0.001). (Figure 5,6)

Our results were consistent with studies by Saini RK et al and Xu W et al who also concluded that patients with abnormal LFTs are at an increased risk of severe disease.[4,16] Also Saini RK et al in their study concluded that patients with abnormal LFTs were associated with raised levels of inflammatory markers and they found a positive correlation between elevated LFTs and CRP.[4]

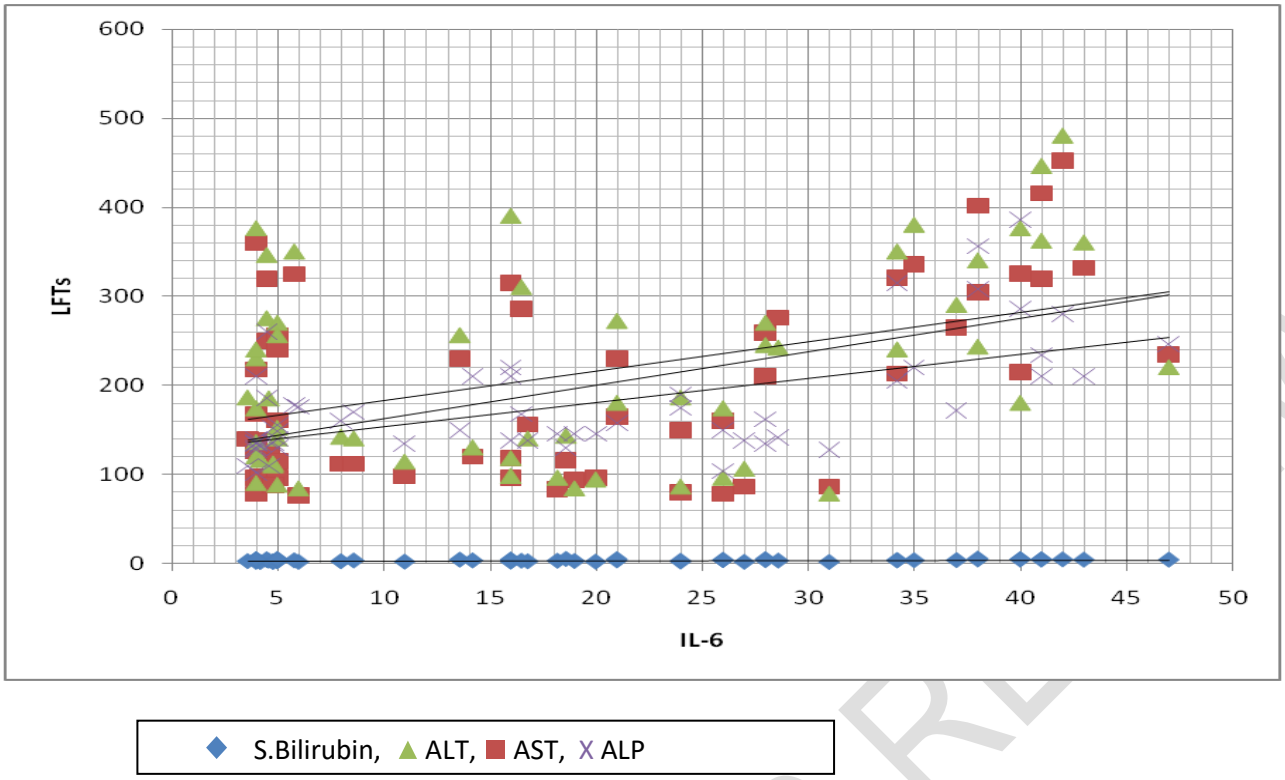

Figure 5- Correlation of LFTs with IL-6

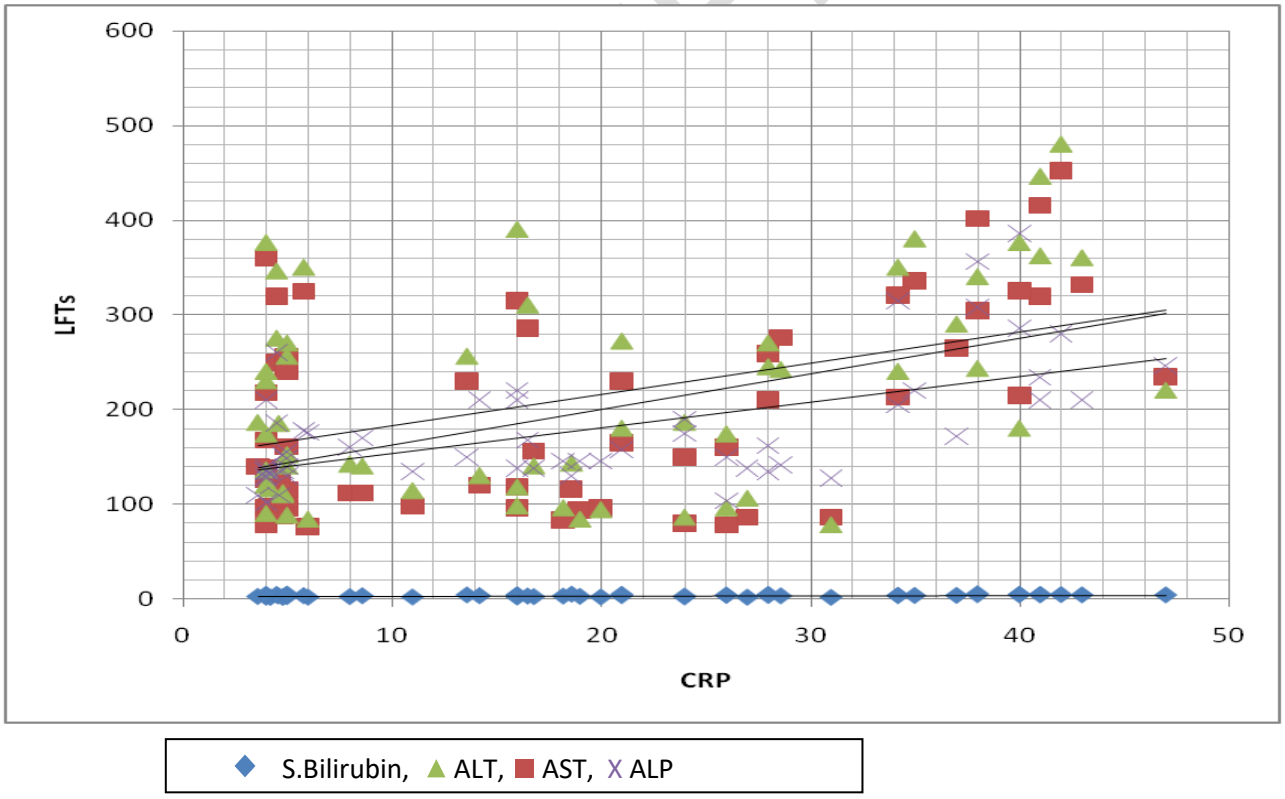

Figure 6- Correlation of LFTs with CRP

Management

All the patients were treated according to the COVID-19 protocol guidelines issued by ministry of health and family welfare, Government of India.

4. CONCLUSION

COVID-19 individuals typically have respiratory symptoms, although other organ systems have also been implicated.

A significant number of COVID-19 positive individuals have abnormal liver function. Inflammatory indicators and elevated LFTs have a positive relationship. Patients with abnormal liver function tests were more likely to have severe illness necessitating ICU hospitalisation.

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ABBREVIATIONS

ACE-2	ANGIOTENSIN-CONVERTING ENZYME 2
ALP	ALKALINE PHOSPHATASE
ALT	ALANINE AMINOTRANSFERASE
AST	ASPARTATE AMINOTRANSFERASE
CRP	C REATIVE PROTEIN
ICU	INTENSIVE CARE UNIT
IL-6	INTERLEUKIN-6
LFT	LIVER FUNCTION TESTS
SARS-COV2	SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2