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Assessment of Liver Function and Its Correlation with Inflammatory Markers and Severity of Disease during COVID-19 Second Wave in a Tertiary Care Centre

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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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

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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.

ABBREVIATIONS

ACE-2 : Angiotensin-converting Enzyme 2
ALP : Alkaline Phosphatase
ALT : Alanine Aminotransferase
AST : Aspartate Aminotransferase
CRP : Creative Protein
ICU : Intensive Care Unit
IL-6 : Interleukin-6
LFT : Liver Function Tests
SARS-COV2 : Severe Acute Respiratory Syndrome Coronavirus 2

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].

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 Fig. 2. Amongst the patients who had deranged LFTs, 59.32% patients were males and 40.68% were females.

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].

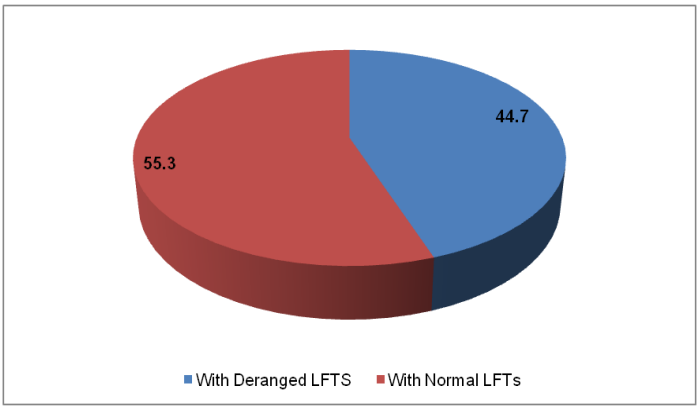

Fig. 1. Percentage of COVID-19 patients with and without deranged LFTs

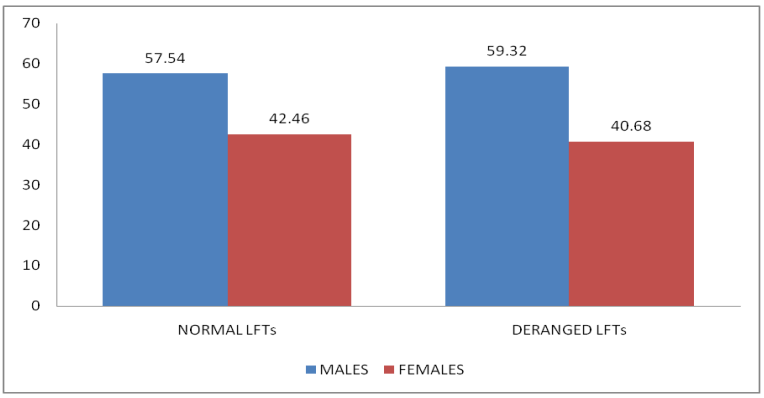

Fig. 2. Pattern of LFTs according to Gender

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 %. (Fig. 3).

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).

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].

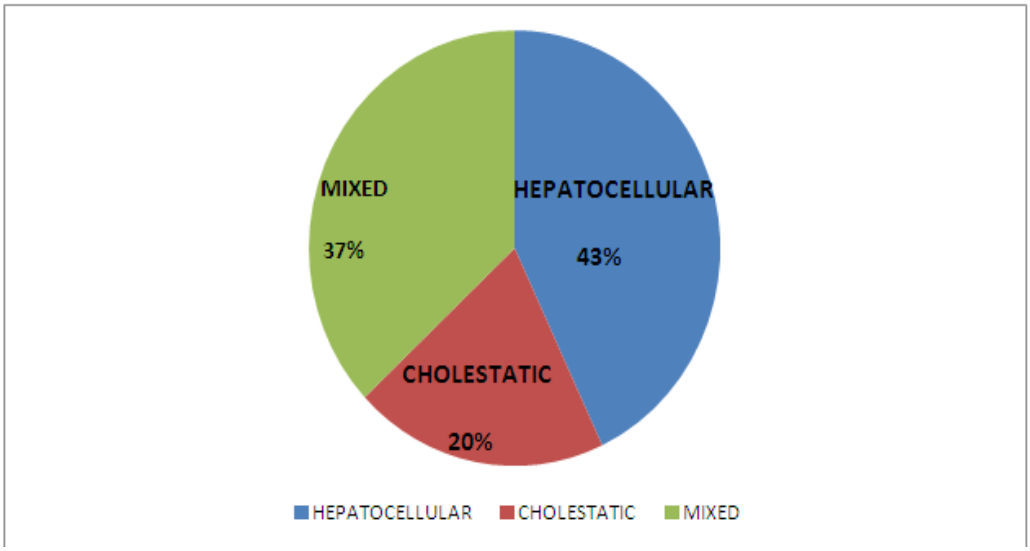

Fig. 3. Type of Liver injury

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)

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) (Fig. 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.

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) (Fig 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].

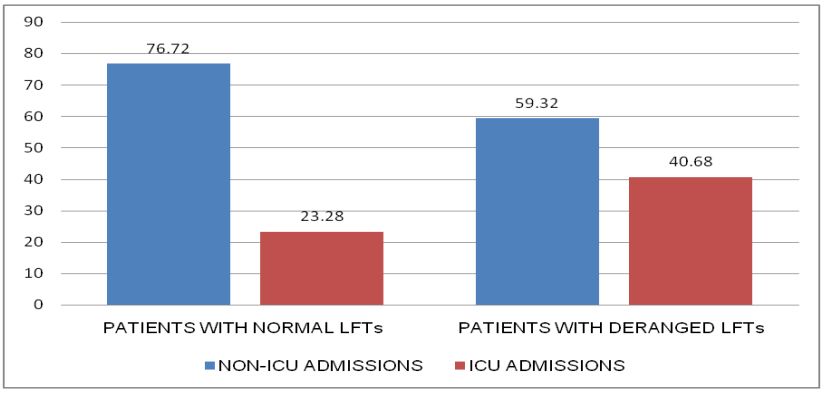

Fig. 4. Percentage of ICU admissions

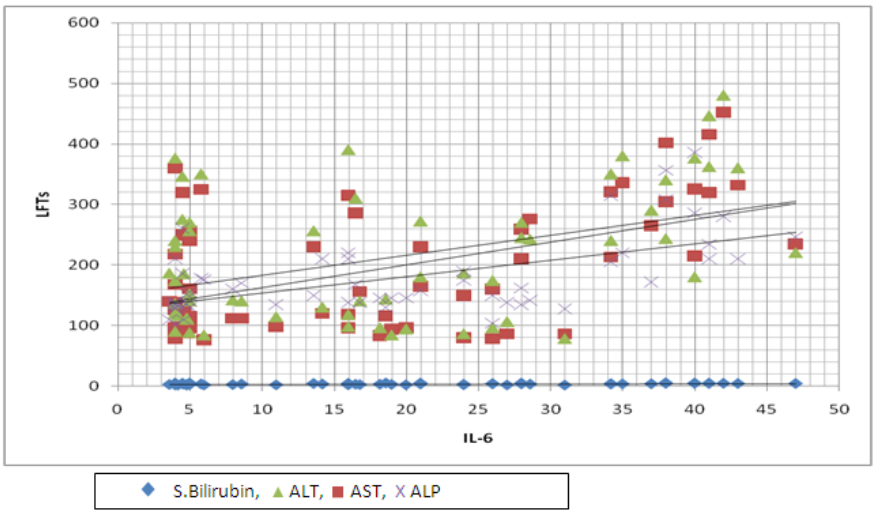

Fig. 5. Correlation of LFTs with IL-6

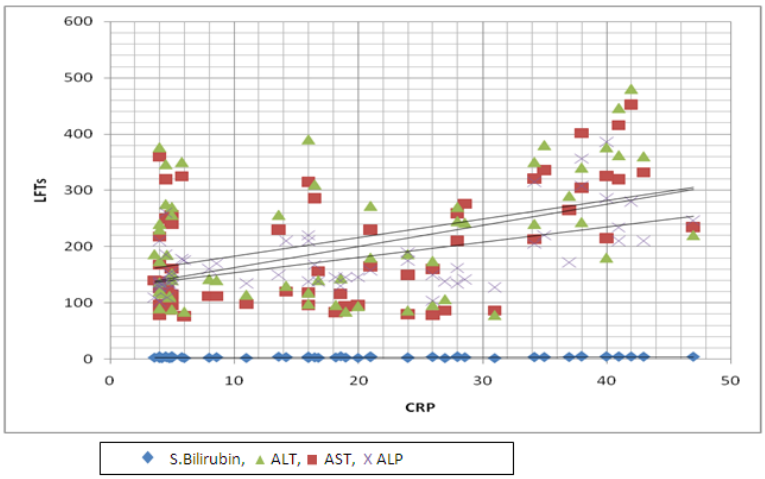

Fig. 6. Correlation of LFTs with CRP

4. MANAGEMENT

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

5. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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