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# LIVER INJURY IN COVID-19 INFECTION: A CROSS SECTIONAL STUDY IN TERTIARY CARE CENTRE.

**Gastroenterology**

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## ABSTRACT

**Introduction** The novel coronavirus disease 2019 (COVID-19) unquestionably changed the world and provided a fresh perspective on respiratory tract illness. However, coronavirus (COVID-19) cannot be viewed as a condition restricted to pneumonia of varying severity. Numerous reports have shown a variety of potential systemic symptoms, including liver issues. The pathogenesis of liver injury in COVID-19 individuals may include viral immunologic injury, drug-induced liver injury, the systemic inflammatory response, hypoxia hepatitis, and worsening of pre-existing liver disease. We must distinguish between the onset of aberrant liver function, which can happen either at the time of diagnosis or while receiving treatment. **Methods:** 580 patients were admitted with COVID-19 between August 2020 -December 2020 in SUNSHINE HOSPITALS, SECUNDERABAD. A COVID-19 diagnosis was confirmed with a positive RT-PCR test.LFT was performed in all patients undergoing admission (DPD with sample blank,IFCC AMP method) in a standard laboratory. **Results:** In our observation only 34%(n=580) of patients had altered LFT in which majority are mixed type (51%), rest all were hepatocellular (39%) and cholestatic type (10%). Though mixed & hepatocellular pattern commonly seen in men, cholestatic pattern is significantly seen in women($p<0.05$), but there was no association found between BMI ($p=0.10$), other comorbidities and inflammatory markers($P=0.10$) in relation to altered LFT. Though 23% of the patients had altered LFT at the time of discharge, Majority (49%) got discharge with normalized LFT,but 28% of patients had worsening LFT with majority of them are in ICU. Most of the ICU admitted patients with altered LFT were elderly, obese with mixed type of altered LFT. 21 patients died in our series, but known of them had isolated liver injury. **Conclusions:** In covid patients all types of LFT changes were observed, most of the changes were resolved at the time of discharge. Persistent altered LFT was not a hindrance for the discharge. We could not notice isolated liver injury as causative factor for death in covid patients.

## KEYWORDS

Coronavirus-COVID 19, Liver Function Test - LFT

## INTRODUCTION

A pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or novel coronavirus disease (COVID-19) began in the Chinese province of Wuhan in December 2019 and spread throughout the world. In sufferers with COVID-19, the liver is the second one maximum typically affected organ after the lungs (1).

The first publication reported COVID-19-related liver injury. This manifested as increased serum aminotransferase and/or cholestatic enzyme activity in her 32.6% of patients [2]. However, other authors report that this rate is 50% at admission and he exceeds 75% during admission. In patients from China, liver damage was associated with increased severity of COVID-19 [3]. In addition, underlying liver disease, including metabolic disease, has been shown to worsen the prognosis of COVID-19 patients [4], especially those younger than her 60 years [5].

The angiotensin-converting enzyme 2 (ACE2) receptor, which allows virus entry into cells, plays an important role in the pathogenesis of COVID-19. ACE2 receptors are most commonly found on intestinal mucosa, testis, adipose tissue, and vascular endothelium. It is also present in the liver, mainly cholangiocytes, although it is slightly less abundant in the lung (density increases in smokers) [6]. An RNA-sequencing study performed in COVID-19 patients showed significantly higher ACE2 receptor expression in cholangiocytes (59.7%) compared to hepatocytes (2.6%), demonstrating that SARS-Cov-2 may directly affect the internal bile duct. However, a transmembrane serine protease (TMPRSS2) present in hepatocytes facilitates the fusion of SARS-CoV-2 to the cell membrane [7].

SARS-CoV-2 has been shown to have direct cytopathic effects on lung cells. In clinically severe cases, COVID-19 causes immune dysregulation, leading to widespread release of pro-inflammatory cytokines and activation of immunosuppression. Lung injury is accompanied by endothelial inflammation of various organs with a propensity for intravascular thrombus formation [8]. The mechanism of liver injury due to SARS-CoV-2 infection is highly complex. SARS-CoV-2 has been shown to upregulate hepatocyte apoptosis, reduce regenerative capacity, and affect immune dysfunction [9]. Some patients may develop cholestatic liver injury due to the presence of high densities of ACE2 receptors on cholangiocytes. Liver injury as a result of COVID-19 can be caused by pneumonia-related hypoxia, drug-induced (e.g., by remdesivir or other antiviral drugs), Other factors that can lead to liver damage include gut microbiota and hepato-intestinal damage, vascular lesions (endotheliitis), and right ventricular failure. However, exacerbation of existing liver disease is

also possible. Arguably, all the above mechanisms of liver injury by COVID-19 coexist and overlap [10].

If clinically indicated, they were administered antibiotics (i.e., cephalosporins and macrolides) and low molecular weight heparin. A few patients were administered lopinavir/ritonavir, ribavirin, or chloroquine, while some were treated with tocilizumab and glucocorticosteroids in the ICU setting.

The aim of this study was to identify the type, frequency and severity of de novo liver injury in COVID-19 and its association with liver injury.

## MATERIALS AND METHODS

580 patients were admitted with COVID-19 between August 2020 - December 2020 in SUNSHINE HOSPITALS, SECUNDERABAD.

A COVID-19 diagnosis was confirmed with a positive RT-PCR test.LFT was performed in all patients undergoing admission (DPD with sample blank,IFCC AMP method) in a standard laboratory.

**Inclusion Criteria:**
All Patients with positive RT-PCR test with age group 18-80 years.

**Exclusion Criteria**:
Pt with baseline liver pathology
- Age <18,>80
- Hepatitis B infection, hepatitis C infection, autoimmune, hepatitis
- Hepatocellular carcinoma
- Chronic inflammation as well as cirrhosis of other aetiologies such as alcoholic liver disease, NAFLD.

The following laboratory assays were performed along with oxygen saturation (SpO2) measurements using continuous 24-hour recording:

1. Complete Blood Picture,
2. C-reactive protein (CRP), procalcitonin,
3. D-dimers,
4. LFT.

Based on severity of the inflammatory response in lungs, classified as:
- **Mild**—where the patient did not need oxygen therapy;
- **Moderate**—patient needed conventional oxygen therapy;
- **Severe**—patient needed high-flow nasal cannula oxygen or mechanical ventilation;

Patients were divided into three groups:
- **Parenchymal Injury**—showing an isolated increase in transaminases activity;
- **Cholestatic Injury**—showing an isolated increase in GGT and/or bilirubin activity;
- **Mixed Types of Injury.**

**Statistical Analysis**:
- Subject Comparisons: ANOVA (for more than two groups).
- The Chi-Squared Test: distributions for contingency tables larger than 2 × 2,
- Additionally, all statistical tests were performed with significance level equal to 0.05 ($p < 0.05$).

## RESULTS

We found 198 incidences of liver injury among the 580 individuals admitted with covid-19 (Pie Chart-1). These included 102 women with an average age of 67 and 96 men with average age 60 years (Pie -2). 49% (67 women and 30 men) of the cases, did not require oxygen therapy at admission.

Another 10% of the individuals (12 women and 8 men) required immediate HFNC therapy, while another 41% of the subjects (43 women and 50 men) required low-flow oxygen therapy.

175 patients had liver damage when they were admitted, while the other 23 cases developed while the patients were being treated at the hospital (mostly women).

Patients with (123, 62%) and without (75, 38%) comorbidities both demonstrated altered LFT.Table 1 displays the fundamental demographic and clinical characteristics of the study group.

**Table-1:**

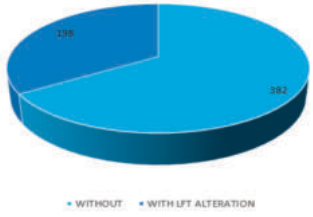
Baseline characteristics of the study group.

| | | Female | | Male | | Total | |
|---|---|---|---|---|---|---|---|
| Number of cases | | 42 | minimum/ maximum | 56 | minimum/ maximum | 98 | minimum/ maximum |
| Age | mean | 67 | 26/80 | 65.1 | 29/80 | 60 | 25/80 |
| Age | <50 | 10 | | 8 | | 18 | |
| | 50-60 | 8 | | 8 | | 18 | |
| | 60-70 | 22 | | 13 | | 33 | |
| | >70 | 13 | | 11 | | 26 | |
| BMI | mean | 27.2 | 19.5/36.8 | 29.5 | 20.9/36.3 | | |
| Number of cases | | 96 | | 102 | | 198 | |
| Duration of hospitalization (days) | mean | 17.8 | 0/39 | 20.8 | 0/69 | 19.5 | 69 |
| Symptom duration (days) | mean | 13.2 | 0/34 | 15.1 | 0/43 | 14.3 | 0/43 |

**Table -1 cond.,**

| | | Female | | Male | | | Total | |
|---|---|---|---|---|---|---|---|---|
| Comorbidities | | | | | | | | |
| Diabetes | 5 | 14% | 12 | | 24% | 17 | | 19% |
| Cancer (lung, colorectal, and breast) | 7 | 19% | 6 | | 12% | 13 | | 15% |
| Hypertension | 16 | 43% | 27 | | 53% | 43 | | 49% |
| Ischemic heart disease | 4 | 11% | 4 | | 8% | 8 | | 9% |
| Valvular disease | 2 | 5% | 0 | | 0% | 2 | | 2% |
| Artificial heart valve | 0 | 0% | 3 | | 6% | 3 | | 3% |
| Stroke | 1 | 3% | 1 | | 2% | 2 | | 2% |
| Arrhythmias | 4 | 11% | 4 | | 8% | 8 | | 9% |
| Myocardial infarction | 0 | 0% | 1 | | 2% | 1 | | 1% |
| Lung cancer | 1 | 3% | 1 | | 2% | 2 | | 2% |
| COPD | 1 | 3% | 3 | | 6% | 4 | | 5% |
| Pneumothorax | 0 | 0% | 1 | | 2% | 1 | | 1% |
| Obstructive sleep apnea | 0 | 0% | 1 | | 2% | 1 | | 1% |
| Asthma | 1 | 3% | 1 | | 2% | 2 | | 2% |
| Hepatocellular | 14 | 38% | 14 | | 27% | 28 | | 32% |
| Cholestatic | 3 | 8% | 3 | | 6% | 6 | | 7% |
| Mixed | 16 | 43% | 29 | | 57% | 45 | | 51% |

PIE CHART-1 TOTAL NUMBER OF PATIENTS WITH AND WITH OUT LFT ALTERATION




In comparison to men, women under 60 tend to have lower ALT, AST, ALP, and GGT activity. During hospitalisation, women older than 60 years old eventually suffered hepatocellular liver damage. The sole female fatalities in our sample, however, occurred in this specific subset.

PIE CHART-2:SEX RATIO WITH LFT ALTERATION


**Cholestatic Liver Injury**

Cholestasis was present in only 20 patients (10%) and was more frequent among woman than man (6% of men and 8% of women). The association between sex and cholestatic liver injury was significant ($p < 0.05$). All affected men and most women (all except for one) were at least 60 years old. In this group, we observed normal baseline ALT (29 U/L) and AST (32 U/L) values, and the values remained within the reference range during the hospitalization and at its end. Cholestatic enzyme (i.e., GGT and ALP) and bilirubin levels were consistently elevated throughout the hospitalization (Table 2) (BAR CHART-1).

**Table:2- Pattern Of LFT On Admission And Upon Discharge**

| | | | UPON ADMISSION | | | UPON DISCHARGE | | |
|---|---|---|---|---|---|---|---|---|
| | | No Liver Injury | Cholestatic Liver Injury | Hepatocellular liver injury | Mixed-Pattern Liver Injury | Cholestatic Liver Injury | Hepatocellular liver injury | Mixed-pattern Liver injury |
| ALT | Minimum | 12.0 | 7.0 | 17.6 | 19.2 | 16.0 | 12.4 | 35.7 |
| | Mean | 20.4 | 31.1 | 55.0 | 86.5 | 33.0 | 68.0 | 101.5 |
| | Maximum | 42.1 | 40.4 | 107.1 | 341.0 | 70.0 | 134.3 | 792.0 |
| AST | Minimum | 19.7 | 21.0 | 27.1 | 23.9 | 17.0 | 25.0 | 1.6 |
| | Mean | 29.4 | 32.8 | 52.3 | 87.0 | 45.3 | 50.8 | 64.9 |
| | Maximum | 39.7 | 44.0 | 251.0 | 413.0 | 72.0 | 73.0 | 338.0 |
| GGT | Minimum | 17.0 | 46.6 | 22.4 | 46.3 | 33.6 | 34.1 | 47.0 |
| | Mean | 26.2 | 61.0 | 31.6 | 134.5 | 41.2 | 42.1 | 120.0 |
| | Maximum | 37.7 | 144.7 | 36.0 | 863.0 | 65.3 | 87.0 | 654.0 |
| ALP | Minimum | 39.0 | 46.0 | 42.0 | 39.0 | 96.0 | 58.0 | 48.0 |
| | Mean | 63.0 | 73.0 | 73.0 | 89.5 | 96.0 | 68.0 | 98.0 |
| | Maximum | 78.0 | 202.0 | 133.0 | 516.0 | 96.0 | 78.0 | 478.0 |

**Hepatocellular Liver Injury**

77(39%)-37women and 40 men had elevated ALT and AST levels. The ALT values normalized towards the end of hospitalization in 47 cases from an initial mean level of 80 U/L. The same 10 patients had either normal or mildly elevated AST levels throughout the entire hospitalization

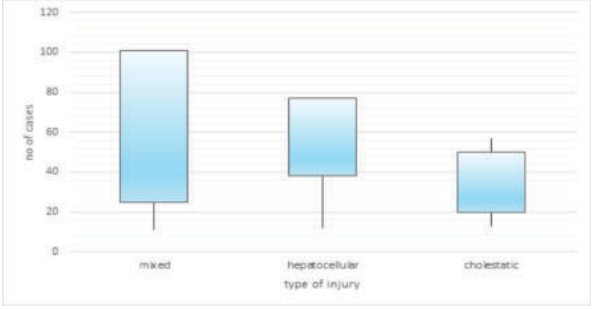
The ALT and AST values, elevated at baseline, did not normalize until the end of hospitalization in another 20 patients with the same liver injury pattern. In those patients, the mean ALT level on admission was 65 U/L. It increased further to 120 U/L on day eight, reaching 150 U/L at discharge. The AST level on admission was 88 U/L. Although it decreased to 77.75 U/L, the value by the end of hospitalization did not return to the normal range.

**Mixed-type**

The predominant type of liver injury secondary to COVID-19 in the study cohort. It was shown in 101 patients (51% of the study group, 36 women and 65 men). The laboratory biomarkers of that subgroup are summarized in Table 2. The elevated parameters normalized towards the end of the inpatient treatment in only 14 female and 15 male patients.The levels of ALT and CRP in this subgroup had an intriguingly high connection ($p = 0.003$).

The length of hospitalisation for all 101 patients (excluding the 21 deaths) did not differ significantly from that of patients without clinically obvious liver disease, regardless of the type of liver injury.

In 36% of patients, the ALT/AST levels and 22% of patients, the GGT levels recovered to normal.

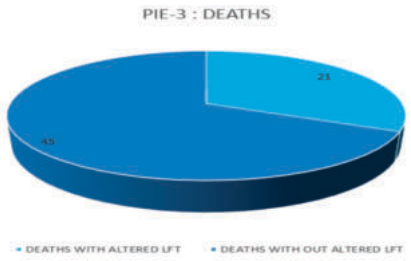



**Bar chart 1:types of altered LFT**

**Mortality:**

Out of 580 patients 66 were died.21 out of the 198 cases of liver injury secondary to COVID-19 (10 %, 13 men and 8 women) died (PIE-3). According to the baseline assessment, this group included 8 patients in moderate clinical condition, 5 in moderate to severe clinical condition, and 8 in severe clinical condition. Interestingly, all women who died were over 60 years of age. For a comparison, the mortality rate in patients with COVID-19 without liver pathology was 20%. The cause of death in all cases was the progression in lung disease, with zero cases where death would be caused by liver failure.

During hospitalization, we observed a progressive increase in AST, ALT, GGT, and ALP levels, which reached very high values (over ten-fold the upper normal range) in those patients who required ICU treatment due to the fact of multiple organ failure and subsequently died. The duration of inpatient treatment did not differ significantly between those who died of COVID-19 and those who were discharged home.




**DISCUSSION**

In our study, 198 (34%) of 580 patients hospitalized for COVID-19 presented with altered LFT.The rate is very similar to the results of the meta-analysis done by Mao et al (27%), and Chen et al. (29%) [11,12,13].

Surprisingly, we observed a return to normal of previously elevated LFT (i.e., GGT, ALP, AST, and ALT) in 41% of patients, particularly those with isolated hepatocellular and cholestatic liver injury. This could indicate that the liver injury caused by SARS-CoV-2 infection was mild. This finding is consistent with Gopal R et al, & Orlay et al, observations [11,12,14,15].

In our study we have majority of patients had hepatocellular (39%) and mixed-type of pattern (51%), cases of isolated cholestatic liver injury were very rare (10%). Our observations are matching with results reported by Lie F et at all, [16].In our study, no correlation was found between the baseline AST and ALT levels and the risk of death due to COVID-19.

This observation, however, contradicts the results of other studies, where a positive correlation was demonstrated between ALT levels, levels of inflammatory markers as CRP, D-dimers, ferritin and interleukin-6 (IL-6) and covid-19. The IL-6 level, on the other hand, correlates with disease severity [17,18].

We additionally ascertained that the AST, ALT, ALP, and GGT levels didn't come back to normal values throughout the course of hospitalization within the 21 patients who died of COVID-19.This supports the view that liver injury in the patients was part of multiple organ failure, aggravated by hypoxia [19].

Our observations do not confirm previous suggestions that altered LFT of any kind is associated with a higher risk of COVID-19 mortality (3). And there are other authors who seem to agree with us. A study by Yang et al., carried out in 52 critically ill patients treated in an ICU setting for COVID-19 pneumonia, demonstrated that altered LFTwas not associated with a higher risk of death (20).

In Summary the pathological mechanism of liver damage resulting from COVID-19 is undoubtedly very complex and its potential clinical consequences require further follow-up and research [21].

**Limitations: -**

- Small size of our study group.
- Treatment included neither routine abdominal ultrasound checks nor all biochemical tests that could reveal even minor cases of fatty liver.

**CONCLUSION:**

Altered LFT secondary to COVID-19 is common, presents mainly as a mild mixed-type injury, and affects patients regardless of their pre-existing liver disease status.

In covid patients all types of LFT changes were observed, most of the changes were resolved at the time of discharge. Persistent altered LFT was not a hindrance for the discharge. We could not notice isolated liver injury as causative factor for death in covid patients.

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**Institutional Review Board Statement:** Ethical review and approval were performed for this study.

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Conflicts of Interest**: The authors declare no conflict of interest.

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