



Clinical Significance of Liver Function Abnormality in Symptomatic – Mild, Moderate, Severe and Asymptomatic COVID-19 Patients

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Abstract

Background: According to initial findings, the infection of SARS-CoV-2 causes the alteration in the liver functions as disease progression. Hepatic dysfunction is more common in patients with severe COVID-19.

Aim: The study was designed to determine the clinical significance of liver functions abnormalities in mortality risk.

Methods: A retrospective study was conducted to evaluate the level of liver function parameters in 185 asymptomatic and 215 symptomatic (mild, moderate, and severe) patients from March 2021 to April 2022 during second and third wave of COVID-19 in India. Blood samples drawn and assessed for LFT parameters analysis including bilirubin direct, globulin, albumin, SGPT (ALT), SGOT (AST), bilirubin total, bilirubin Indirect, and alkaline phosphatase.

Results: A total of 400 patients with COVID-19 were included in the analysis. Of these, 185 (46.3%), 63 (15.8%), and 51 (12.8%) patients had asymptomatic, mild, and moderate COVID-19 respectively, while 101 (25.3%) had severe COVID-19. The median age was 52.25 years, 157 (39.2%) patients were female and 243 (60.6%) were male. The median age, and LFT were significantly higher in asymptomatic vs. symptomatic severe infection ($P < 0.0001$). The laboratory examination revealed significant higher levels of LDH ($p < .0001$), while a lower level of albumin (Hypoalbuminemia) in asymptomatic and symptomatic patients ($p < .0001$). The LFT shows comparable aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which were both statistically and clinically insignificant. Elevation of bilirubin indirect levels were also observed in COVID-19 patients with mild and moderate disease.

Conclusion: The abnormal liver function should be common in all symptomatic and asymptomatic COVID-19 patients. Patients with severe COVID-19 had a greater incidence of abnormal liver function e.g., LDH, albumin. The severity of COVID-19 also linked to mortality in these patients. It is essential to carefully monitor the liver function indicators in patients with COVID-19 admitted to the hospital to rule out the possibility of liver damage.

Keywords: COVID-19, Liver function, Symptomatic, Asymptomatic, LDH, Albumin

Introduction

Every society is still being impacted by the ongoing COVID-19 (coronavirus disease 2019) pandemic, which has now spread to practically all parts of the world. Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-CoV-2) is the culprit responsible for it. It was first discovered in China in late 2019 but has since expanded fast, posing a large global burden of morbidity and mortality.^{1,2} Overall,

COVID-19 patients are more likely to experience multi-organ failure, which may be linked to a high mortality rate.³ Across the globe, COVID-19 patients' poor results have been linked to older age and higher comorbidities.⁴ On the other hand, impaired liver function has also gained attention as one of the key predicted risk factors for COVID-19 development and subsequently poor outcomes.⁵⁻⁷

The potential impact of severe liver injury in raising the mortality risk among COVID-19 patients has been highlighted in numerous hospital-based investigations carried out globally.⁸ Additionally, it has been demonstrated that hepatic impairment in severe COVID-19 patients is connected to a fatal outcome.⁹ Studies have shown that individuals with severe COVID-19 have a higher incidence of raised levels of the enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and hypoalbuminemia than patients with non-severe COVID-19.¹⁰ The emergence of aberrant liver function may be caused by a variety of different processes. These include inflammation that is immune-mediated, hypoxic injury brought on by acute pneumonia, and inflammation brought on by drugs that results in hepatic injury.^{11,12}

The correlation between abnormal liver function and COVID-19 has been the subject of very few Indian studies.^{13,14} Better understanding of the pathogenesis could lead to the development of more focused treatments and integrative care paradigms, which may help to prevent severe liver injury or failure in patients with COVID-19. The present study aimed to retrospectively evaluate the impact of COVID-19 on liver function of patients admitted at Pacific Institute of Medical Sciences (PIMS) Hospital, Udaipur, Rajasthan, India and its clinical significance in determining the mortality risk.

Methods

Study Design and Participant

This retrospective study includes patients with confirmed COVID-19 infection, hospitalized for acute complications between March 2021 and April 2022, at Pacific Institute of Medical Sciences hospital, Udaipur, Rajasthan, during second and third wave of COVID-19 in India.

The DTprime real-time PCR instrument (Genetix Biotech Asia Pvt. Ltd., India) was used for qualitative and quantitative analysis of RNA targets in rRT-PCR reactions from throat/nose swabs samples. Nasopharyngeal or oropharyngeal samples were collected from patients for the detection of SARS-CoV-2 RNA. The COVISure is Single Tube Multiplex Assay SARS-CoV-2 real-time RT-PCR assay was performed to achieve qualitative detection of SARS-CoV-2 RNA.

The swabs were collected in Virus Liquid Transport Medium-VTM as per manufacture instruction for collection and handling (COVISure, India). Prior to RNA extraction, collection tubes were vortexed; 200 or 400 µl of VTM were transferred to 2 ml tubes for RNA extraction (Genetix Biotech Asia Pvt. Ltd., India). Finally, RNA extraction was done in automated RNA extractor and 5 µL of extracted RNA was used as template for the rRT-PCR.

Data from hospitalized patients were initially screened for inclusion in the study. The patients classified into two groups according to their symptoms: group A, COVID-19 asymptomatic (185 patients), and group B, COVID-19 infection symptomatic (215 patients). The clinical data and laboratory tests were collected from the patients' hospital electronic medical records (EMR).

Laboratory Procedures

Blood and plasma samples drawn and assessed immediately for LFT parameters analysis includes bilirubin direct, globulin, albumin, SGPT (ALT), SGOT (AST), bilirubin total, bilirubin Indirect, and alkaline Phosphatase using the EM-360 and EM-200 Analyzer.

Liver function tests

Liver function test indicators including SGPT [ALT] (normal range: 9–40 U/L), SGOT [AST] (normal range: 13–35 mg/dl), alkaline phosphatase [ALP] (normal range: 38–126 mg/dl), and serum bilirubin (normal range: 0.2–1.0 mg/dl), LDH (normal range: 225–450 U/L), Bilirubin Total (normal range: 0.2–1.0 mg/dl), Globulin (normal range: 2.0–3.9 g/dl), Bilirubin Direct (normal range: 0.2 mg/dl), Albumin (normal range: 1.1–2.2 mg/dl), Bilirubin Indirect (normal range: 0.2–0.8 mg/dl), and Total Protein (normal range: 6.4–8.3 g/dl) were analyzed using the

EM-360 and EM-200 Analyzer (ERBA Mannheim, London, TW8 9DF, United Kingdom).

Lactate dehydrogenase (LDH), C-reactive protein (CRP) were examined using a clinical chemistry analyzer (XL-640, Erba Global, Mumbai, Maharashtra, India). D-dimer, IL-6, and ferritin were measured using the MAGLUMI – 2000 Plus, Shenzhen, P.R. China.

Statistical analysis

Data were analyzed using Statistical Package for The Social Sciences (SPSS) software, version 27.0 (IBM Corp., Armonk, NY, USA). Qualitative data were presented as number and percentages, while quantitative data were presented as mean (standard deviation) or median (range), depending on the normal or skewed distribution of data. Online statistical tool Social Science Statistics (www.socscistatistics.com) were also used for the calculation of Standard error, 95% CI, t-statistic, and significance level (p value). A p-value of less than 0.0001 was considered statistically significant.

Results

Baseline clinical characteristics

A total of 400 patients with COVID-19 were included in the analysis. Of these, 185 (46.3 %), 63 (15.8%), and 51 (12.8%) patients had asymptomatic, mild, and moderate COVID-19 respectively, while

101 (25.3%) had severe COVID-19. The median age was 52.25 years, 157 (39.2%) patients were female and 243 (60.8%) were male. The most common symptoms at the initial stage of illness were fever, cough, breathlessness, and sore throat. While other less common symptoms reported were generalized weakness, loss of appetite, headache, vomiting, nausea, acute weakness, unconsciousness, insomnia, loose motions, and pain in the abdomen.

Biochemical characteristics

Table 2-4 illustrates the baseline mean values of variables in the whole population and the statistical comparison between asymptomatic and symptomatic patients. The laboratory examination revealed higher levels of globulin ($p=0.1406$), LDH ($p < .0001$) [Fig 2], while a lower level of albumin in asymptomatic and symptomatic patients ($p < .0001$) [Fig 3]. Specifically, the liver function tests showed comparable aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, which were both statistically and clinically insignificant [Fig 3]. To monitor liver damage, bilirubin levels are a universally accepted marker. Elevation of bilirubin indirect levels has been observed in COVID-19 patients with mild and moderate disease (Fig 1). Table 5 explain the Liver function test (mean, standard deviation (SD), coefficient of variation (CV) of symptomatic-mild, moderate, severe, and asymptomatic COVID-19 patients.

Table 1: Characteristics of patients with COVID-19 by severity

| Parameters | Total (n=400)* | Asymptomatic (n=185)** | Symptomatic (n=215)** | | | p value |
|------------------------------|-------------------|------------------------|-----------------------|------------------|------------------|---------|
| | | | Mild (n=63)*** | Moderate (n=51)# | Severe (n=101)## | |
| Age in years, median (range) | 52.25 (20.0–80.0) | 50 (46.3) | 50 (15.8) | 55 (12.8) | 57.2 (25.3) | <0.0001 |
| Sex | | | | | | <0.0001 |
| Male | 243 (60.8) | 109 (58.9) | 35 (55.5) | 31 (60.7) | 68 (67.3) | |
| Female | 157 (39.2) | 76 (41.1) | 28 (39.7) | 20 (39.2) | 33 (32.7) | |

Data shown as n (%), unless otherwise specified. *n=400; **n=185; ***n=63; #n=51; ##n=101, unless otherwise specified.

Table 2: Mean values of Liver functions - Bilirubin Direct, Bilirubin Indirect, and Bilirubin Total

| Parameters | Asymptomatic | Symptomatic (Mean) | p value |
|------------|--------------|--------------------|---------|
|------------|--------------|--------------------|---------|

| | (Mean) | Mild | Moderate | Severe | |
|--------------------|--------|------|----------|--------|--------------------------------|
| Bilirubin Direct | 0.21 | 0.38 | 0.28 | 0.59 | 0.0667* , 0.0061** , 0.0085*** |
| Bilirubin Indirect | 0.42 | 0.77 | 1.33 | 0.54 | 0.1875* , 0.0645** , 0.3325*** |
| Bilirubin Total | 0.53 | 0.78 | 0.64 | 1.38 | 0.1542* , 0.1727** , 0.0011*** |

Fig 1. Liver function - Bilirubin Direct, Bilirubin Indirect, and Bilirubin Total

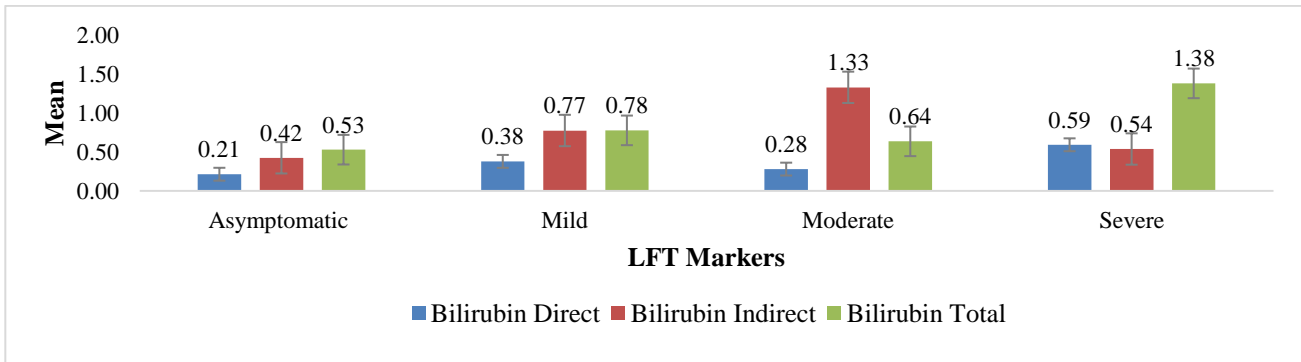


Table 3: Mean values of Liver function – Globulin, Albumin and Total Protein

| Parameters | Asymptomatic (Mean) | Symptomatic (Mean) | | | p value |
|----------------------|---------------------|--------------------|----------|--------|---|
| | | Mild | Moderate | Severe | |
| Globulin (g/dl) | 3.02 | 3.03 | 3.31 | 4.88 | 0.9210* 0.0122** 0.1406*** |
| Albumin (g/dl) | 3.34 | 3.07 | 2.95 | 2.92 | < 0.0001* , < 0.0001** , < 0.0001*** |
| Total Protein (g/dl) | 6.30 | 6.10 | 6.25 | 6.05 | 0.1551* , 0.7450** , 0.0368*** |

Fig 2. Liver function - Globulin, Albumin and Total Protein

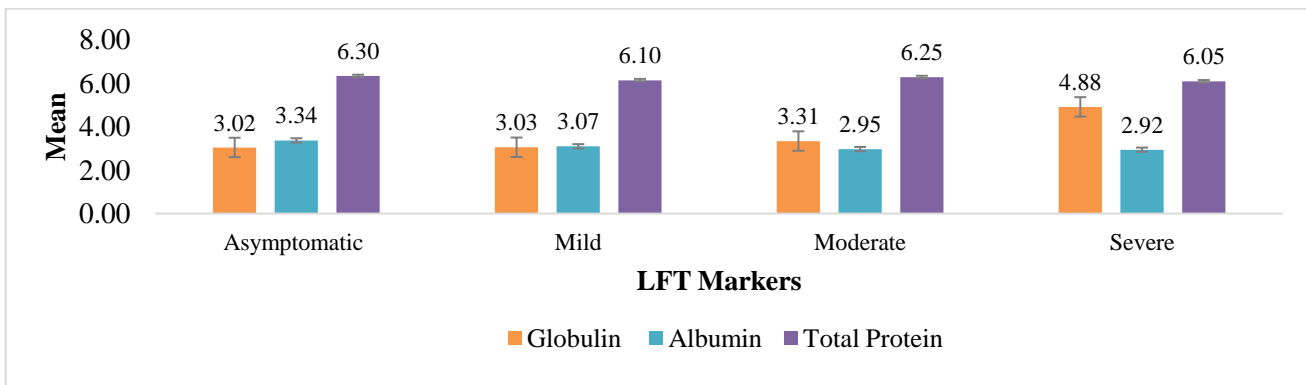


Table 4: Mean values of Liver function - Alkaline Phosphates, SGOT (AST), SGPT (ALT)

| Parameters | Asymptomatic (Mean) | Symptomatic (Mean) | | | p value |
|-------------------------|---------------------|--------------------|----------|---------|---------|
| | | Mild | Moderate | Severe | |
| SGPT (ALT) [U/L] | 51.09 | 63.70 | 87.87 | 51.80 | 51.09 |
| SGOT (AST) [U/L] | 52.52 | 71.27 | 119.26 | 58.43 | 52.52 |
| Alk Phosphatase (mg/dl) | 78.25 | 71.95 | 106.80 | 108.97 | 78.25 |
| LDH (U/L) | 557.81 | 745.76 | 891.78 | 1164.16 | 557.81 |

Fig 3. Liver function - SGOT (AST), SGPT (ALT), Alkaline Phosphates and LDH

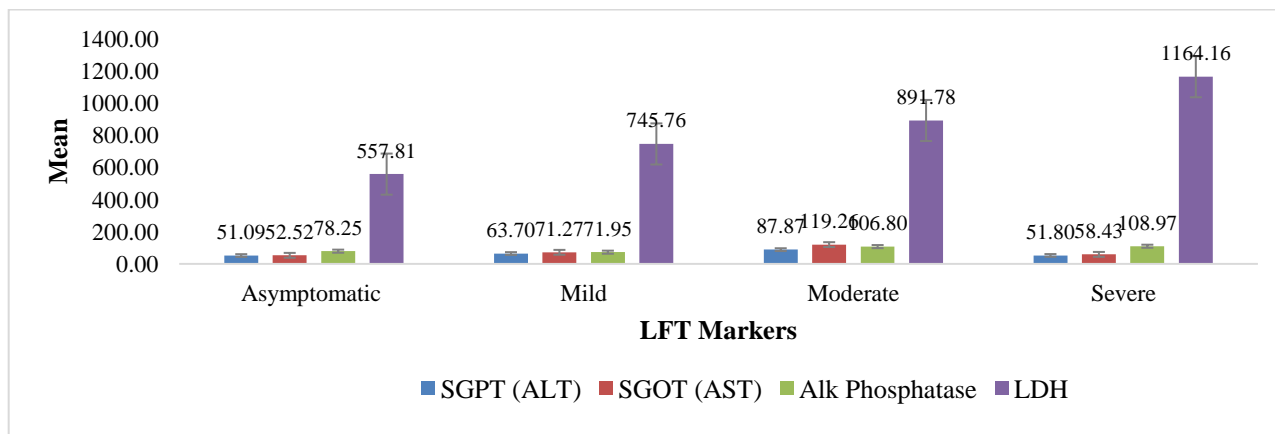


Table 5: Comparative all Liver function test (mean, standard deviation (SD), coefficient of variation (CV) of symptomatic-mild, moderate, severe, and asymptomatic COVID-19 patients

| Parameters | Asymptomatic | | | Symptomatic | | | | | | | | | p-value |
|----------------------|--------------|--------|--------|-------------|--------|--------|----------|--------|--------|---------|--------|--------|------------------------------------|
| | | | | Mild | | | Moderate | | | Severe | | | |
| | Me an | SD | CV | Me an | SD | CV | Me an | SD | CV | Mea n | SD | CV | |
| SGPT (ALT) | 51.09 | 55.35 | 108.34 | 63.70 | 50.77 | 79.71 | 87.87 | 162.94 | 185.44 | 51.80 | 33.62 | 64.92 | 0.1122*, 0.0103**, 0.9065 *** |
| SGOT (AST) | 52.52 | 50.42 | 96.00 | 71.27 | 94.57 | 132.70 | 119.26 | 359.02 | 301.03 | 58.43 | 41.28 | 70.64 | 0.0473*, 0.0148**, 0.3144 *** |
| Alkaline Phosphatase | 78.25 | 43.89 | 56.09 | 71.95 | 29.62 | 41.16 | 106.80 | 98.67 | 92.39 | 108.97 | 101.53 | 93.17 | 0.2905*, 0.0029**, 0.0004*** |
| LDH | 557.81 | 222.45 | 39.88 | 745.76 | 330.18 | 44.27 | 891.78 | 380.10 | 42.62 | 1164.16 | 689.83 | 59.26 | < 0.0001*, < 0.0001**, < 0.0001*** |
| Bilirubin Direct | 0.21 | 0.16 | 75.52 | 0.38 | 1.23 | 325.58 | 0.28 | 0.16 | 57.92 | 0.59 | 1.94 | 327.94 | 0.0667*, 0.0061**, 0.0085*** |
| Bilirubin | 0.4 | 1.1 | 259 | 0.7 | 3.0 | 397 | 1.3 | 6.3 | 478 | 0.54 | 0.7 | 145 | 0.1875*, 0.0645**, |

| | | | | | | | | | | | | | |
|-----------------|------|------|--------|------|------|--------|------|------|-------|------|-------|--------|--------------------------------------|
| Indirect | 2 | 0 | .58 | 7 | 8 | .68 | 3 | 6 | .39 | | 8 | .22 | 0.3325*** |
| Bilirubin Total | 0.53 | 0.54 | 102.49 | 0.78 | 2.20 | 282.97 | 0.64 | 0.37 | 58.38 | 1.38 | 3.44 | 249.33 | 0.1542* , 0.1727** , 0.0011*** |
| Globulin | 3.02 | 0.71 | 23.45 | 3.03 | 0.63 | 20.63 | 3.31 | 0.78 | 23.47 | 4.88 | 17.12 | 350.83 | 0.9210* , 0.0122** , 0.1406*** |
| Albumin | 3.34 | 0.45 | 13.38 | 3.07 | 0.40 | 13.04 | 2.95 | 0.45 | 15.14 | 2.92 | 0.40 | 13.80 | < 0.0001* , < 0.0001** , < 0.0001*** |
| Total Protein | 6.30 | 1.01 | 15.97 | 6.10 | 0.80 | 13.17 | 6.25 | 0.81 | 12.91 | 6.05 | 0.87 | 14.33 | 0.1551* , 0.7450** , 0.0368*** |

The p-value of less than 0.0001 considered statistically significant

| | |
|-------------------------------------|-----|
| Asymptomatic vs. Mild - P Value | * |
| Asymptomatic vs. Moderate - P Value | ** |
| Asymptomatic vs. Severe - P Value | *** |

The significantly higher levels of LDH in Asymptomatic patients than Symptomatic (severe) patients (560.428 U/L vs 1164.16 U/L, $p=0.0001$). Since significantly high levels of LDH continued in the symptomatic mild, moderate, and severe patients (745.76 U/L, 891.77 U/L and 1164.16 U/L, $p=0.0001$), LDH may be a predictive biomarker of severe disease.

Discussion

The present retrospective study assessed the liver function abnormalities in patients with symptomatic and asymptomatic COVID-19 to elucidate if there is any association of liver injury with mortality of patients. A previous study found significantly higher levels of LDH in ICU patients than non-ICU patients.¹⁵ When LDH levels were correlated with CT scans, significantly higher levels reflected the severity of pneumonia.¹⁶ The significantly lower levels of Albumin in Asymptomatic patients than Symptomatic (severe) patients (3.34 g/dl vs 2.92 g/dl, $p < 0.0001$). Since significantly high levels of LDH continued in the symptomatic mild, moderate, and severe patients (3.07 g/dl, 2.95 g/dl and 2.92 g/dl, $p < 0.0001$), Albumin may also be a predictive biomarker of severe disease.¹⁷ Lower albumin level is seen in severe COVID-19 and is not parallel to the changes in alanine aminotransferase (ALT) and

aspartate aminotransferase (AST) levels. The difference in albumin between the survival group and the non-survivor group was considerable (37.6 ± 6.2 vs 30.5 ± 4.0 $P < .001$).¹⁸ Although ALT and AST slightly increased in COVID-19 patients, they were not of predictive value for the outcome.¹⁹ Increased LDH activity may be indicative of cellular damage, hypoxia, or death. It should also be considered that elevated LDH activity may be associated with other conditions, including those associated with cardiac ischemia and pathological processes. Often, this process is caused by hypoxia due to the disproportionate transfer of oxygen to the cells, the cause of which is, among others, SARS-CoV-2 infection.²⁰ Previous studies have proposed a link between bilirubin levels and disease severity, but they have had relatively small sample sizes and have not explored the relationship between bilirubin levels and the survival of patients with COVID-19. Moreover, continuously monitoring to the changes of bilirubin levels may be of great value²¹⁻²³.

Conclusion

The COVID-19-associated liver function abnormalities in the level of bilirubin, globulin, albumin, ALT, AST, LDH and alkaline phosphatase, is generally mild but it is more obvious in

symptomatic severe cases, especially change in the level of albumin and LDH.

Overall findings indicate that abnormal liver function was more common and was linked to a longer hospital stay in patients with severe COVID-19. Mortality was also linked to the severity of COVID-19. Therefore, it is essential to carefully monitor the liver function indicators in patients with COVID-19 who have been hospitalized to the hospital to rule out the possibility of liver damage.

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