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Assessment of liver function in COVID-19

Dipti Basavaraj Sanakal[1], Shankarsnehit B. Patil[2], Ravindra D. Totad[3] and Poojadevi Malipatil[4*]

[1]Department of Biochemistry, Ashwini Rural Medical College, Hospital & Research Centre, New Bypass Road, Kumbhari, Solapur-413006, Maharashtra, India, [2]Department of Radiology, Al Ameen Medical College and Hospital, Athani Road, Vijayapur-586108, Karnataka, India, [3]Department of Microbiology, Al Ameen Medical College and Hospital, Athani Road, Vijayapur-586108, Karnataka, India and [4]Department of Dermatology, Al Ameen Medical College and Hospital, Athani Road, Vijayapur-586108, Karnataka, India

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Abstract: *Introduction:* COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that commonly involved the respiratory system. However, the virus can affect any organ in the body including the liver. Hepatic involvement in COVID-19 could be related to the direct cytopathic effect of the virus, an uncontrolled immune reaction, sepsis, or drug-induced liver injury. *Objective:* The current study aims to evaluate the relevance of liver enzyme derangement in COVID-19. *Methods:* The sample size of 165 patients, tested positive for covid 19 and underwent liver enzyme testing. These patients were categorized into mild, severe, and critical diseases based on clinical evaluation, radiological findings, and biochemical parameters. *Results:* Of 165 patients selected 103 (62.4%) have mild disease, 40(24.2%) have severe and 12(7.2%) suffered from the critical disease. 48(29.1%) patients show deranged liver function. 83.3% of critical patients and 45% of severe patients show deranged liver function.9.09 %of patients died due to severe COVID – 19 infections showing moderately to severe liver function derangement. *Conclusions:* This study concludes that the severity of COVID-19 disease may increase due to chronic liver disease, particularly fatty liver. Atypical ALT and AST levels during hospitalization were indicative of liver injury and correlated with the severity of patients.
Keywords: COVID-19, Liver Injury, AST, ALT.

Introduction

China's Hubei province's capital Wuhan announced the first coronavirus epidemic case of 2019 in December. (COVID19), which is brought on by the severe acute respiratory illness coronavirus [1]. The gastrointestinal, hepatic, cardiac, neurological, and renal systems can all be affected by the COVID-19 virus, whereas the respiratory system is the most commonly affected organ [1-2]. Patients having a higher risk of developing serious problems or perhaps passing away once infected include those with diabetes, hypertension, cancer, cardiopathy, nephropathy, and liver disorders. Based on the lessons learned from the previous SARS pandemic, COVID-19 patients hospitalized with liver problems recently have drawn special attention [3]. According to earlier research, 2%–11% of COVID-19 patients also had underlying chronic liver disorders [4].

Accordingly, COVID-19 patients with liver problems should receive the appropriate therapy. The clinical impact of liver disorders, such as chronic hepatitis B or C, non-alcoholic fatty liver disease, liver cirrhosis, and liver transplantation, may differ based on specific clinical circumstances. There have been reports of liver abnormalities in about 60% of SARS patients. The incidence of liver damage and related clinical traits are yet unknown in the COVID-19 pandemic [5].

Patients with COVID-19 have reported deaths due to liver injuries, and COVID-19's consequences are worse in people who already have liver disorders and injuries, bringing on the impending financial crisis. The increases in ALT and AST levels during hospitalization are the main indicator of hepatic function injuries; however, the exact

mechanisms are still unknown and may include immune-mediated damage, direct cytotoxicity, anoxia, drug-induced liver injury, and reactivation of pre-existing liver disease [6].

Material and Methods

This retrospective and observational study were performed at Ashwini Rural Medical College Hospital & Research centre, Solapur, a designated hospital for COVID-19 patients. Permission and approval were taken from the Ethical committee before performing the study. The sample size was determined using Buderer's methods, with a reference study's estimated sensitivity and specificity of 92.3% and 83.3%, respectively [7]. Adults (at least 18 years old) who have had a positive report of reverse transcription polymerase chain reaction of COVID-19 (RT-PCR) with liver enzyme assay were selected for the study. The sample size calculated was 165.

These patients were categorized into mild, severe, and critical diseases based on clinical presentation, radiological findings, and biochemical parameter evaluation. The evaluation included blood routine, blood biochemistry, urine routine, stool routine, and chest X-ray, CT scans. All demographic, clinical, and outcome data were extracted from the patients.

Data collection: The research team collected and examined the medical records of 165 patients. Epidemiological, clinical, laboratory characteristics, and treatment and outcomes data were acquired by the hospitalization management system.

Laboratory Examination: All laboratory data were obtained from the medical record of patients. Data reveals that laboratory examination was conducted every 3 days. Complete blood count (CBC), absolute lymphocyte count, erythrocyte sedimentation rate, D-dimer, procalcitonin, and liver functions including alanine aminotransferase (ALT; 9–40 U/L), aspartate aminotransferase (AST; 13–35 U/L), γ-glutamyl transferase (7–45 U/L), ALP (35–100 U/L), and total bilirubin (3.4–20.5 μmol/L) were routinely measured using standard methods. We defined abnormal liver function as any parameter (ALT, AST, ALP, gamma-glutamyl transferase, and total bilirubin) more than the upper limit of normal value.

Therapeutic strategies: Patients with mild disease received symptomatic treatment in the form of nutritional support, antipyretics, and antibiotics if necessary. Antiviral therapy is tried in patients with severe and critical diseases.

Statistical Analysis: All analyses were performed using the SPSS software version 25.0. All the data was collected in an excel sheet and continuous variables were expressed as means ± SD, percentage, and p-value calculated. A *P* value of <0.05 was considered significant.

Results

165 suitable applicants in total were included in the study, 92 (55.7%) of them were men and 73 (44.2%) of them were women. Forty (40) participants between the ages of 18 and 40 had a mean age of 24.23 ± 8.8, while 125 patients ≥ 40 had a mean age of 46.74 ± 11.12. Fifteen patients (9.09%) passed away while they were hospitalized.

Table-1: Epidemiologic & Demographic characteristics of 165 COVID-19 patients

Variable	Frequency [N = 165]	Percentage (%)
Sex		
Male	92	55.8
Female	73	44.2
Age		
18 - 40	40 (24.23 ± 8.8)	24.2
≥ 40	125 (46.74 ± 11.12)	75.7
Basic Disease		
Diabetes Mellitus	87	52.7
COPD	78	47.2
Hypertension	76	46.0
Thyroid	63	38.1
Patients Status		
Discharged	150	90.91
Death	15	9.09

Variable	Frequency [N = 165]	Percentage (%)
Self-reported symptoms		
Fever	148	89.6
Cough	93	56.3
Chest distress	73	44.2
Gastrointestinal symptom	72	43.6
Pharyngeal symptoms	69	41.8
Muscle or joint pain	48	29.00
Other symptoms	81	49.0

Table-1 illustrates the Epidemiologic & Demographic characteristics of the 150 COVID-19 patients. The most common diseases that were reported during admission were diabetes mellitus in 87 (52.7%) patients, chronic obstructive pulmonary disease in 78 (47.2%) patients, hypertension in 76 (46.0%) patients, and thyroid illness in 63 (38.1%) patients. In the study of 165 patients selected for the study, 15 patients (9.09 %) patients died due to severe COVID – 19 infections. The self-reported symptoms which were reported in the study were fever in almost89.6 % of patients, 56.3 % of patients had to severe cough, 44.2 % of patients with chest distress, 43.6 % of patients complained of Gastro, 41.8 % of patients with pharyngeal symptoms, 29 % of patients had muscle and joint pain and 49 % patients had other symptoms.

Figure 1 & figure 2 illustrates the patient's status and associated comorbidities and diseases reported in the study.

Fig-1: Patients status

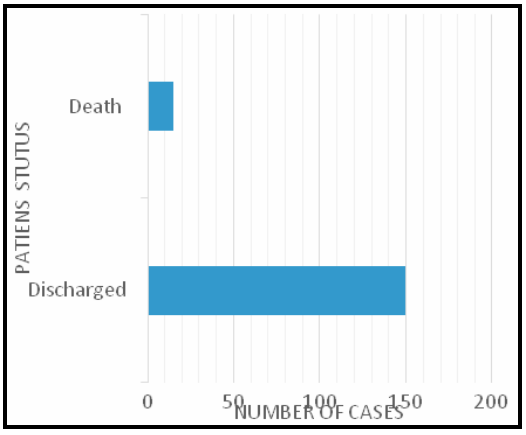
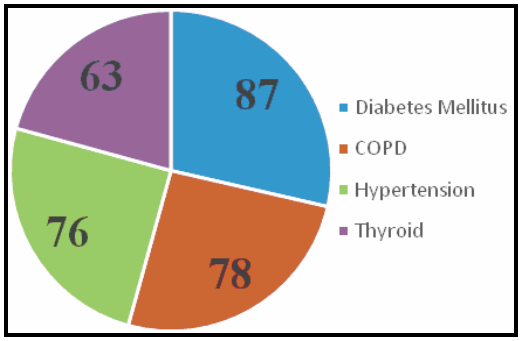


Fig-2: Associated co-morbities



Liver Function in COVID-19 Patients: There were 48 patients (29.1%) with abnormal liver function, including elevated ALT (n = 38; 41–115 U/L), AST (n = 36; 37–107 U/L), γ-glutamyl transferase (n = 30; 48–159 U/L), ALP (n = 8; 102–144 U/L), and total bilirubin (n = 10; 21–46.6 µmol/L). The proportion of patients with elevated AST, ALT, γ-glutamyl transferase, total bilirubin, and ALP was 23%, 21.8%, 18.1%, 4.8%, and 6%, respectively (Table 2 & Table 3).

Out of 48 patients, 18(37.5%) patients had abnormal liver function on admission; 30(62.5%) patients developed abnormal liver function during hospitalization.

Table-2: Liver function		
Liver Function	**Frequency (N=165)**	**Percentage (%)**
Normal	117	70.91
Abnormal	48	29.10
Total	165	100

Table-3: Abnormal Liver function		
Abnormal liver function	**Frequency (N=165)**	**Percentage (%)**
ALT	38	23.03
AST	36	21.82
γ-glutamyl transferase	30	18.18
Total bilirubin	10	6.06

Table 4 illustrates patients who have liver disease. Of the 165 patients,16(9.6%) had liver diseases before acquiring COVID-19, including hepatitis B (1.2%), fatty liver (7.2%), and Alcoholic liver disease (1.2%);

patients in serious condition during hospitalization had significantly higher probabilities to have liver diseases, especially the fatty liver, than compared with patients in the non-severe condition which is illustrated by table-4. Patients with liver illnesses were also seen to be substantially older and also have much longer hospitalization.

Table-4: Liver diseases		
Liver Disease	**Frequency [N =165]**	**Percentage (%)**
Fatty liver	12	7.2
Hepatitis B	2	1.2
Alcoholic liver disease	2	1.2

Table-5: Distribution of Covid-19 patients as per clinical severity concerning abnormal LFT & deaths			
	Mild / Moderate	**Severe**	**Critical**
Covid19 positive (n=165)	103(62.4%)	40(24.2%)	12(7.2%)
Deranged LFT (n=48)	20	18	10
Underlying Liver Disease (n=12)	02 (Fatty liver)	04 (3fatty liver +1 Hepatitis B)	06 (3fatty liver+1hepatitis B+2Alcoholic liver disease)
Death(n=15)	00	03	12

Table 5 illustrates the distribution of covid19 patients into three categories based on the clinical presentation, radiological findings, and various biochemical parameter levels. 62.4% of cases had mild to moderate disease and were treated symptomatically. All severe (24.2%) and critical (7.2%) disease patients were admitted to ICU. Out of 48 patients with deranged LFT, 12 patients had underlying liver disease. Most of the patients with underlying liver disease (83.3%) had severe to critical disease with higher mortality.

Discussion

The clinical characteristics of 165 COVID-19 patients at Ashwini Rural Medical College Hospital & Research Centre, Solapur, were examined in the current study. More than 50% of patients were male, and 75% of covid positive patients were in their 4^{th} to 6^{th} decade of life. These findings correlate with a study by Huang C et al [2]. Diabetes mellitus and COPD are the most commonly associated co-morbidities with 52.7% and 47.2% respectively. Among various symptoms fever and cough are the commonest. The study conducted by Ayusha Poudel et al [8]. reported similar findings.

On admission, liver function tests were part of the routine covid investigative protocol. There were 48 patients (29.1%) with abnormal liver function. Out of 48 patients, 18(37.5%) patients had an abnormal liver function on admission; which seems to have nothing to do with medication. 30 (62.5%) patients developed abnormal liver function during hospitalization. Abnormal liver function was in the form of raised ALT, and AST.GGT, ALP and total bilirubin. ALP was the least deranged parameter of LFT. A significant increase was seen in ALT & AST parameters followed by total bilirubin, many studies showed that ACE2 can be expressed in the liver, oesophagus, stomach, and colon, which suggests SARS-CoV-2 may enter the digestive system via ACE2 and cause liver and gastrointestinal tract injury [9].

In the liver, ACE2 is mainly located in the cytoplasm of hepatocytes followed by vascular endothelial cells and the lumen of the bile duct [9], which gives support to our findings which say ALT & AST parameters are most commonly severely deranged compared to ALP and total bilirubin. Similar findings were noted by Rundk Hwaiz et al [10] and Xiaoqiang chai LH et al [11].

Levels of ALT & AST are generally not high on admission, indicating in early SARS-CoV-2 infection, liver function tests are normal or minimally elevated. The frequency and severity of liver dysfunction increase with the severity of COVID-19. In early SARS-CoV-2 infection, liver function tests are normal or minimally elevated. In the severe acute respiratory syndrome (SARS) epidemic, severe acute respiratory syndrome coronavirus (SARS-CoV) viral particles and positive-

strand RNA with replicative intermediates were detected within hepatocytes, consistent with hepatocyte infection [12]. Evidence suggests that SARS-CoV-2 also replicates within hepatocytes [13].

We observe that 30 (62.5%) patients developed abnormal liver function during hospitalization. These patients received treatment in the form of antibiotics, antipyretics, interferon, and antiviral drugs during their hospitalization period. Antipyretic (acetaminophen) and antiviral drugs have adverse reactions, such as hepatotoxicity [14-17]. There is a possibility that various mechanisms play roles in liver derangement in covid-19. Although SARS-CoV-2 binds ACE2 with high affinity and ACE2 is located in the cytoplasm of hepatocytes followed by vascular endothelial cells and the lumen of the bile duct [9], the normal concentration of ALP in most patients with Covid-19 suggests that this is not the only mechanism underlying the association with liver derangement. Further analysis is required whether these patients with liver derangement are caused by SARS-CoV-2 infection or by the drugs.

Of the 165 patients, 16 (9.6%) had underlying liver conditions before infecting COVID-19, including hepatitis B (2, 1.2%), fatty liver (12, 7.2%), and alcoholic liver disease (2, 1.2%). Patients hospitalized in severe and critical conditions had a significantly higher probability of having liver conditions than those not hospitalized in severe conditions, especially fatty liver. Most cases of liver derangement will reflect either underlying chronic liver disease, sepsis-related inflammatory changes, or hepatotoxicity by concomitant medications. Because liver derangement might contraindicate particular medications, it is necessary to monitor liver function in hospitalized patients with covid 19 at regular intervals.

Patients with severe conditions also had a significantly higher risk of developing complications than those with non-severe conditions. These complications included steroid-induced diabetes, drug-induced liver injury, hematologic complications, cardiovascular injury, respiratory injury, infection, lung injury, and genitourinary injury. Hematologic problems, hypokalaemia, thrombus, cardiovascular injury, respiratory injury, and lung injury were all linked to liver disease. These issues were shown to be connected to COVID-19's fatal outcome [18-19]. The current findings indicate that COVID-19 individuals may be at risk for liver illness. Regardless of whether there is a link between abnormal liver enzymes and mortality, it is still crucial to improve detection and monitoring during the clinical and follow-up period [20].

The current study provides suggestions for the management& treatment of patients during hospitalization and can aid people in understanding the course of COVID-19, particularly the effects on liver function.

Conclusion

This study concludes that the severity of COVID-19 disease may increase due to chronic liver disease, particularly fatty liver. Atypical ALT and AST levels during hospitalization were indicative of liver injury, which may be related to epidemiological traits, clinical indicators, therapeutic agents, and other comorbidities. The variables influencing liver function were extremely intricate. Due to its size, this study cannot be concluded. More research is needed to improve patient care and protect them from pandemics.

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*All correspondences to: Dr. Poojadevi Malipatil, Associate Professor, Department of Dermatology, Al Ameen Medical College and Hospital, Athani Road, Vijayapur-586108, Karnataka, India. E-mail: pooja.malipatil@gmail.com