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ORIGINAL ARTICLE

Prevalence of liver injury in 445 patients with Corona Virus Disease-19-Single-centre experience from southern India

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Abstract

Background Abnormal liver function tests (LFT) are common in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and vary from 15% to 53%. There are scanty data from India on the prevalence of liver injury in corona virus disease 2019 (COVID-19) patients.

Methods We did this retrospective study in a tertiary care hospital, Chennai, India. Patients aged >18 years admitted with COVID-19 from May 1, 2020, to May 31, 2020, were included. We noted the demographic details, symptoms at presentation, history of pre-existing illnesses, and laboratory tests. We also recorded the patient's clinical course and outcome.

Results We took 445 patients for final analysis. Aspartate transaminase (AST) was borderline elevated in 47.5%, mildly elevated in 11.2%, moderately elevated in 2% and severely in 0.7%. Alanine transaminase (ALT) was borderline elevated in 28.7%, mildly elevated in 11.4%, and moderately elevated in 1.3%. Bilirubin and alkaline phosphatase were abnormal in only 19 (4.2%) and 15 (3.3%) patients, respectively. Patients with abnormal LFT were more likely to be symptomatic (90.3% vs. 80.6%, p 0.002). Respiratory symptoms (43.5% vs. 29.7%) and loose stools (11.4% vs. 3.4%) were also more common among them. Patients with abnormal LFT were more likely to have severe disease (25.2% vs. 13.6%, p value 0.003) and mortality (8.8% vs. 0.7%).

Conclusion Liver test abnormalities were widespread in patients with COVID-19. Most of the patients had borderline or mild transaminase elevation. Despite only mild changes, patients with abnormal LFT were more likely to be symptomatic and had more severe disease and mortality.

Keywords ACE 2 receptor · Acute respiratory distress syndrome · Alanine transaminase · Aspartate transaminase · COVID-19 · Liver dysfunction · Liver function tests · Liver injury · Liver test abnormalities · SARS-CoV-2

Introduction

Coronavirus, an enveloped single-stranded Ribonucleic acid (RNA) virus, is commonly seen in mammals and birds. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current corona virus disease 2019 (COVID-19) pandemic. As of 27/7/2020, there have been 16,096,741 confirmed cases of COVID-19, including 646,384 deaths, reported on WHO Dashboard.

The clinical spectrum of COVID-19 ranges from mild asymptomatic cases to full-blown respiratory illness, acute respiratory distress syndrome (ARDS), or multi-organ dysfunction [1, 2]. The infection is particularly severe in patients with underlying comorbid conditions, such as diabetes, hypertension, and coronary artery disease. The typical clinical symptoms are fever, dry cough, and tiredness. In addition to that, breathlessness or chest pain are the serious complaints. In the previous severe acute respiratory syndrome outbreak in 2002, liver impairment was reported in up to 60% of patients [3]. Whereas, in the current COVID-19 pandemic, Zhang et al. reported hepatic dysfunction in 14% to 53% of the patients [3].

There is limited information describing the liver-related abnormalities in COVID-19 patients from India. This study presents the clinical data and analysis of 445 patients with

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Bullet points of the study highlights

What is already known?

- The current Coronavirus pandemic has predominantly respiratory symptoms.
- Liver tests are abnormal in 15% to 53 % of the patients suffering from corona virus disease 2019 (COVID-19).
- Most of the patients have mild elevations in liver tests.

What is new in this study?

- It is the one of the initial study looking into the prevalence of liver abnormalities in Indian patients affected with COVID-19.
- More than half of the patients have transaminases above the normal limits
- Only a small number of patients have moderate to severe transaminase elevation based on the criteria defined by the American College of Gastroenterology.
- Patients with abnormal liver function tests are more likely to have severe disease and mortality.

What are the future clinical and research implications of the study findings?

- More research will be required to study whether the liver injury is due to the direct cytopathic effect of the virus or is due to the damage from systemic inflammation and cytokine storm.

COVID-19. They were admitted at a tertiary hospital in Chennai (India), in May 2020.

Methods

Patients admitted and treated for COVID-19 in MIOT International Hospital, Chennai, between 1st and 31st May, 2020 were included in the study. Reverse transcriptase polymerase chain reaction (RT- PCR) for SARS-CoV-2 RNA from a nasopharyngeal and oropharyngeal swab confirmed COVID-19. The institutional ethical committee approved the study and exempted the patients' informed consent because of its retrospective nature.

Data collection

We collected the medical records of the patients from the hospital's information system. The information collected included demographic details, main symptoms at presentation, and any history of pre-existing illnesses like diabetes, hypertension, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease and chronic liver disease. We also recorded the patients' clinical course, laboratory investigations, and outcome.

Definitions

Cut-off values for normal and abnormal LFT varies between various published studies. In this study, we have taken the cut-off values recommended by the American College of Gastroenterology (ACG) on the abnormal evaluation of liver tests [4]. As per the ACG guidelines, the upper limit of normal (ULN) for transaminases is considered 33 IU/L for males and 25 IU/L for females. Their guidelines define

- borderline elevation as less than two times ULN
- mild elevation as two to five times the ULN
- moderate elevation as five to ten times the ULN
- and severe elevation as levels more than ten times the ULN

Additionally, any serum bilirubin and alkaline phosphatase values above the ULN was considered to be abnormal. Patients with abnormal LFT were considered to be Group 1, and those with normal LFT were considered to Group 2.

Based on the 2019 American Thoracic Society guidelines on community-acquired pneumonia [5, 15], patients with mild symptoms (i.e. fever, cough, expectoration, and other upper respiratory tract symptoms) were classified as

non-severe types. Patients with imaging feature suggestive of pneumonia and any of the following were classified as severe.

i) Significantly increased respiration rate (RR): RR > 30 times/min;
ii) Hypoxia: oxygen saturation (resting state) </= 93%;
iii) Blood gas analysis: partial pressure of oxygen/fraction of inspired oxygen (PaO2) /FiO2) </= 300 mmHg or
iv) the occurrence of respiratory or another organ failure that required intensive care unit (ICU) monitoring and treatment, or shock.

All symptoms, comorbid disease, laboratory parameters, clinical severity, and outcome were compared between group 1 and 2.

Laboratory investigations

All suspected patients underwent nasopharyngeal and oropharyngeal swabs for SARS-CoV-2 RNA. Baseline laboratory tests, including complete blood count, renal function tests, liver function tests, prothrombin time, international normalized ratio (INR), blood sugar, thyroid stimulating hormone (TSH), glycosylated hemoglobin (HbA1c), chest X-ray, and electrocardiogram (ECG) were done for all the patients. All the patients underwent hepatitis B and C markers to rule out any concurrent viral infection. Subsequent repeat tests and markers of severity like C-reactive protein (CRP), procalcitonin, interleukin 6, D – dimer were done based on the patient's clinical course. The tests were usually not repeated in uncomplicated and mild cases except for blood sugars and electrolytes.

Management strategy

The Intensivists managed the patients as per the guidelines available in May 2020 from the International societies and the Government of Tamil Nadu. Non-severe patients were managed in the ward, and severe patients were treated in the ICU or step-down units. For the purpose of this study, we used the LFT done at admission. Repeat LFTs were done at treating physician's discretion. Generally, it would be repeated for moderate to severe elevation in LFTs. However, repeat tests, if done were not part of the analysis in this study. No specific treatment was given for elevated liver enzymes.

Tocilizumab was sparsely available during the later part of the study period and was administered to a small number of patients as per the intensivist's advice. Remdesvir was not available during the study period.

Statistical analysis

For our study, we entered the data in Epi Data 3.1 and analyzed using the Statistical Package for the Social Sciences (SPSS) 20.0 software (IBM Corp., Armonk, NY, USA). Our calculations included descriptive statistics like percentages and mean. In addition to that, we did the comparative analysis using the Chi-squared test for categorical variables and Student *t*-test for continuous variables. A *p* value of less than 0.05 was taken as statistically significant.

Results

During the study period of one month from 1st to 31st May, 2020, a total of 515 patients were admitted with positive RT-PCR for SARS-CoV-2 RNA. Of them, we excluded 27 patients who were below 18 years of age and 21 others who left the hospital against medical advice. Moreover, we also excluded patients with incomplete data. As a result, 445 patients were included in the final analysis. Among the 445 patients, two thirds ($n = 292$) of the patients were male. The mean age of presentation was 49.5 years and our oldest patient was 94 years (Table 1).

Clinical features, severity, and the outcome are given in Table 2. Fever was the most common presenting symptom, followed by cough, sore throat, and breathlessness. About one-tenth of the patients had abdominal symptoms of pain and loose stools as the initial presentation. 22% (i.e. 96 patients) had severe disease.

In our analysis of serum aspartate transaminase (AST) and alanine transaminase (ALT), we found that the values were abnormal in 63.9% ($n = 283$) and 42.4% ($n = 189$) of the patients, respectively. AST was borderline elevated in 47.5%, mildly elevated in 11.2%, moderately elevated in 2%, and severely in 0.7%.

ALT was borderline elevated in 28.7%, mildly elevated in 11.4%, and moderately elevated in 1.3%.

Serum bilirubin and alkaline phosphatase were above the upper limit of normal in only 19 and 15 patients, respectively. Table 1 shows the baseline laboratory findings. The number of patients with various degrees of transaminase elevation, the severity of COVID-19, and mortality are given in Table 3. (During the study period there was no patients with pre-existing liver disease based on history and hepatitis B and C were negative in all the study subjects).

Asymptomatic patients were more likely to have normal LFTs. On the other hand, respiratory symptoms and loose stools were more common in patients with abnormal LFT. The patients with abnormal LFT were more likely to have severe disease (25.2% vs. 13.6%).

Table 1 Demographic features and investigations of the 445 patients with Corona Virus Disease-19

	All (Mean±2 SD) *n* =445	Group 1 (Mean±2 SD) *n* =298	Group 2 (Mean±2 SD) *n* =147	P value
Age (Years)	49.6 ± 2.2	51.5±1.8	45.5±2.n	0.01
Investigations				
WBC count-per mm^3	7428 ± 517	8074±y 824	6126±418	0.001
Hb (Gm/dL)	12.2 ± 1.4	11.8±1.0	12.6±1.8	0.204
Platlet (10^9/dL)	1.96 ± 0.23	1.96±0.18	1.94±0.28	0.891
INR	1.0 ± 1.4	1.03±0.1	1.00±2.6	0.139
Creatinine-mg/dL	0.7 ± 0.35	0.8±0.3	0.8±0.4	0.101
RBS mg/dL	145 ± 10	151±9.8	134±11.2	0.02

SD Standard deviation, *WBC* white blood cell, *Hb* hemoglobin, *INR* international normalized ratio, *RBS* random blood sugar. Group 1 (abnormal LFT),Group 2 (normal LFT)

Overall, mortality in our study was 6% (27 patients). Mortality was higher in group 1 compared to group 2 (8.8% vs. 0.7%). Even among patients with abnormal LFT, mortality was 5% in those with a borderline elevation of enzymes compared to 33% among those with a moderate and severe elevation of transaminases (Table 3).

Discussion

SARS-CoV-2 primarily causes respiratory illness manifesting as mild upper respiratory symptoms to severe pneumonia, acute respiratory distress syndrome, and death. However, extrapulmonary manifestations involving almost all organ

Table 2 Clinical features, severity and outcome of 445 patients with Corona Virus Disease-19

	All patients *n*=445(%)	Group 1 *n*=298	Group 2 (%) *n*=147	*P* value
Males	293 (66)	197 (66%)	96 (65)	0.47
Symptoms				
Asymptomatic	59 (13.5)	29 (9.7)	30 (20.4)	0.002
Fever	327 (73.3)	239 (73)`	88 (60)	0.001
Sore throat	55 (12.3)	31 (10.4%)	24 (16.3)	0.05
Cough	158 (35.4)	120 (43.5%)	38 (29.7)	0.005
Breathlessness	80 (17.9)	67 (22.5%)	13 (8.8)	0.001
Myalgia	42 (9.4)	24 (8.1%)	18 (12.2)	0.10
Loose stools	39 (8.7)	34 (11.4%)	5 (3.4)	0.003
Abdominal pain	12 (2.7)	11 (3.7%)	1 (0.7)	0.614
Headache	30 (6.7)	18 (6%)	12 (8.2)	0.55
Pre-existing disease				
Diabetes-*n* (%)	166 (37)	122 (40.9%)	43 (29.3)	0.01
HT	131 (29)	93 (31.2%)	37 (25.2)	0.11
CAD	30 (6.5)	21 (7.1%)	9 (6.1)	0.44
COPD/BA	9 (2)	7 (2.3%)	2 (1.4)	0.38
Disease severity				
Not severe	350 (78.7)	223 (74.8%)	127 (86.4)	
Severe	95 (22.3)	75 (25.2%)	20 (13.6)	0.003
Outcome				
Survived	418 (94)	272 (91.2%)	146 (99.3)	
Death	27 (6)	26 (8.8%)	1 (0.7)	0.001

HT hypertension, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *BA* bronchial asthma

Table 3 Severity of transaminase elevation among patients with Corona Virus Disease-19 (COVID-19) included in this study

Severity of transaminase elevation	Number of patients (%)	Severe COVID-19 - *n* (%)	Number of deaths (%)
Normal	147 (33)	21 (14.8)	2 (1)
1-2ULN	220 (49.4)	47 (21.6)	12 (5)
2–5 ULN	66 (14.8)	23 (34)	9 (13)
5–10 ULN	9 (2)	3 (33)	3 (33)
>10 ULN	3 (0.6)	1 (33)	1 (33)
Total	445	95	27

ULN upper limit of normal

systems have also been described [6]. COVID-19 has been detected in non-respiratory specimens, including stool, blood, ocular secretions, and semen. Viral RNA could be detected in stool samples even after the clearance of viral RNA from respiratory secretions.

Coronavirus spike protein facilitates the entry of the virus into the cell by engaging the angiotensin converting enzyme 2 (ACE2) receptor. SARS-CoV-2 can cause liver injury by binding to the ACE 2 receptors expressed on biliary ducts. Other postulated liver injury mechanisms include inflammatory damage from cytokine storm and hypoxia-associated damage [6]. In addition, various drugs used in managing these patients like Remdesvir, Tocilizumab, Lopinavir, etc. can cause drug-induced liver injury. Histopathological changes noted during autopsy included kupffer cell proliferation, chronic hepatic congestion, hepatic steatosis, portal fibrosis, lymphocytic infiltrates, and ductular proliferation [6, 7].

The prevalence of liver abnormalities in COVID-19 varies in different published studies. Cut-off for abnormal values differed in most studies [14]. In the study published by Guan et al., out of 1099 patients from 552 hospitals in 30 provinces, AST, ALT and bilirubin were elevated in 22%, 21%, and 10.5% of patients, respectively [1]. In a large retrospective cohort study from United States involving more than three thousand patients, transaminases were noted to be above the ULN in 70% of the patients. However, it was more than five times the ULN in only 6.4% [8]. In another study published from China, out of 417 patients, 76.3% had abnormal liver tests [5]. COVID-19 is also known to present as severe acute hepatitis with transaminases in thousands [11]. In patients with pre-existing liver disease, SARS-CoV-2 infection can have a poor outcome with up to 43% mortality [12, 13].

In our study, transaminase elevation was very common. However, most of them have only borderline to mild elevation as per by the ACG's criteria on evaluation of abnormal liver tests [4]. Transaminases were more than five times the ULN in only 2.6%. In our study only 3 patients had transaminase values more than ten times the ULN. Of them, one patient was also positive for dengue fever. So a clinical possibility of dengue hepatopathy was also considered in that patient.

In spite of mild elevation of transaminases, patients with liver injury had more severe disease [1, 2]. In our study, about one third of the patients had severe disease if it was more than two times the ULN.

Similar to the observations made in other studies [9], AST was more commonly elevated than ALT in our patients. AST is found in multiple tissues apart from liver and hence it can be more elevated in those with severe systemic illness. Elevation of AST > ALT and presence of severe disease with transaminase elevation suggest a possibility that in SARS-CoV-2 infection, more than the direct cytotoxic effects, liver injury from systemic cytokine storm can also play a major role causing transaminase elevation.

Serum bilirubin and alkaline phosphatase were above the ULN in a very small number of patients. This was surprising, given that bile ductular cell is considered to be the primary site of attachment of SARS-CoV-2. This was noted in other studies too [9].

We also noticed that diabetes was more common in patients with abnormal LFT. Some of these patients can have underlying non-alcoholic steatohepatitis (NASH). Due to logistic restrictions during the pandemic, ultrasound abdomen was not done in our patients to rule out fatty liver. Patients with diabetes are known to have more severe disease and mortality [10].

Our study's main strength is the large number of patients. Main limitations of our study are non availability of ultrasound and not having taken the history of alcohol consumption.

In conclusion, abnormal liver tests are common in patients with COVID-19. Most of the patients had borderline or mild transaminase elevation with normal bilirubin and alkaline phosphatase. Despite mild transaminase elevation, it is associated with more severe disease and mortality. An in depth prospective study to validate these findings and correlation with markers of disease severity are needed.

Compliance with ethical standards

Conflict of interest HVS, MM, and MA declare that they have no conflict of interest.

Ethics statement The study was performed conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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