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Hepatic and Pancreatic manifestations of COVID-19

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ABSTRACT

Background: Since its first detection in November 2019, the outbreak of severe acute respiratory syndrome coronavirus 2 has influenced over 200 countries, areas or territories worldwide. The virus was initially thought to be a primary respiratory pathogen, but has been reported to have multisystem involvement, including cardiovascular, neurological and gastrointestinal manifestations. The manifestations of liver damage are usually mild and generally asymptomatic. While abdominal symptoms such as pain and diarrhoea are a known presentation, little is known about pancreatic injury as a complication of COVID-19 infection. **Aims and Objectives:** The aim of the study was to describe the abnormality in liver enzymes and pancreatic enzymes and to correlate it with the severity and outcome of COVID-19 patients. **Materials and Methods:** A total of 200 patients were enrolled during the study period from August-2020 to July-2021. Data were collected from case files of patients fulfilling the inclusion criteria. **Results:** A cross sectional study conducted among 200 patients showed that the mean aspartate transaminase and alanine transaminase values were 41.89 ± 50.22U/L and 37.69 ± 41.41U/L respectively and mean amylase and lipase levels were 97.77 ± 126.42U/L and 90.34 ± 127.76U/L. The percentage of transaminitis that was present in patients who were discharged was 29.41% when compared to those who died which was 53.33% and this difference is statistically significant(P = 0.02).However, there was no statistically significant difference observed in patients with elevated pancreatic enzymes with their outcomes. **Conclusion:** Hepatic injury is more commonly associated with an increased severity of the disease and also as a contributor for the greater mortality of the COVID-19 patients.

Key words: ALT; Amylase; AST; Lipase; Liver enzymes; Outcome; Pancreatitis; Transaminitis

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic with over 251 million cases identified worldwide and more than 5 million deaths (as of November 2021)[1]. There is evidence of human-to-human transmission among close contacts of patients with COVID-19. Although considerable efforts have been made to curb the transmission, the overall upward trend of COVID-19 is continuing around the world. Although the most frequent and critical clinical presentation is secondary to the involvement of the lungs (fever, cough, breathlessness, chest pain) the infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus may lead to a systemic and multi-organ disease,[2] also involving the gastrointestinal tract (nausea/vomiting, or diarrhea).[3,4] The liver appears to be the second most frequently involved organ, after the lung.[5-7] Mechanisms of damage are complex and include direct cholangiocyte damage and other coexisting conditions such as the use of antiviral drugs, systemic inflammatory response, respiratory distress syndrome-induced hypoxia, sepsis, and multiple organ dysfunction. Liver injury may be observed during new COVID-19 infections. If liver involvement appears during COVID-19 infection - attention is required. This is particularly true if patients are older or have a pre-existing history of liver diseases. During COVID-19 infection, the onset of liver damage impairs the prognosis, and prolongs the hospital stay. Few patients can still develop severe liver

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problems, and therapeutic options can be limited. Liver dysfunction may affect about one-third of the patients, with prevalence greater in men than women, and in the elderly.

Viral diseases such as Human Immunodeficiency Virus, Mumps, Cytomegalovirus, Coxsackievirus B and Influenza A (H1N1), have been reported to cause acute pancreatitis.[8] The SARS-CoV-2 that causes COVID-19 uses angiotensin-converting enzyme 2 (ACE2) receptors for invading the tissue cells and primarily spreads through the respiratory tract. The clinical signs of patients with COVID-19 usually include fever, cough and fatigue and some patients have shown symptoms of gastrointestinal disturbances such as pain and diarrhea.[9] Autopsy reports from four patients with COVID-19 infection identified SARS-CoV RNA (Ribo nucleic acid) in pancreatic tissues.[10] Very little is known about the pancreatic manifestations in COVID-19 as well. Thus, in this study we describe the abnormality in liver enzymes and also study the effect of COVID-19 disease on markers of exocrine pancreatic injury that is serum amylase and lipase and correlate it with the severity and outcome of COVID-19 patients.

Aims and objectives

The objectives of the study are as follows:

1) To describe the abnormality in liver enzymes and to correlate it with the severity and outcome of COVID-19 patients.
2) To study the levels of pancreatic enzymes (Serum amylase and serum lipase) in COVID-19 patients and to correlate the levels of pancreatic enzymes (Serum amylase and serum lipase) with severity of COVID-19.

MATERIALS AND METHODS

This study has been conducted in a hospital in Bangalore, Karnataka, India after obtaining ethical clearance from the Institutional Ethics Committee (No:532/L/11/12/Ethics/ESICMC&PGIMSR/Estt.vol...IV) in accordance with the guidelines issued by the Indian Council of Medical Research.

The case files of the 200 patients admitted to the Department of General Medicine Triage and COVID Ward/ICU at ESIC MC and PGIMSR during the period of August 2020 - July 2021, fulfilling the inclusion criteria were analyzed and appropriate data were collected after obtaining consent from these patients.

Case record form with follow-up chart was used to record the duration of disease, history of treatment and complications. COVID-19 infection was be diagnosed by either Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or Rapid Antigen Test (RAT) technique. Patients underwent biochemical investigations which included complete blood count, liver function test, renal function test, serum electrolytes, serum amylase, serum lipase, serology, C-reactive protein, lactate dehydrogenase, D-dimer and serum ferritin, ABG and chest X-ray. Co-morbid conditions such as metabolic disorders, endocrine disorders, renal disorders, cardiac disorders, respiratory disorders, pancreatitis and chronic liver disease were confirmed with medical history.

Inclusion criteria

The following criteria were included in the study:

1. Adult patients (18 years and above) with either RT-PCR or RAT positive for COVID-19.
2. Patients willing to consent for participation in the study.

Exclusion criteria

1. Patient not willing to give informed consent.
2. Age <18 years.
3. Known case of chronic liver disease.
4. Known case of pancreatitis secondary to Gall stones, alcoholism, and hypertriglyceridemia.
5. Drug-induced pancreatitis, for example, azathioprine, sulfonamide, valproic acid, didanosine and estrogens.

The patients were monitored and the outcome was measured either as improved (clinical improvement, decreasing trend of inflammatory markers and discharge) or deteriorated (clinically worsening, increasing trend of inflammatory markers and death of the patient). The patients were discharged as per the discharge policy of the Government of Karnataka after 10 days of symptom onset with no fever or symptoms for 3 consecutive days, maintained oxygen saturation above 95% for 4 consecutive days, showed improvement clinically with no breathlessness, showed a decreasing trend of inflammatory markers and repeat RT-PCR test turned negative.

Method of Statistical analysis

Data were entered into Microsoft Excel data sheet and were analyzed using SPSS 22 version software. Categorical data were represented in the form of frequencies and proportions. Chi-square test was used as a test of significance for qualitative data. Continuous data were represented as mean and standard deviation. Pearson correlation was done to find the correlation between two quantitative variables and qualitative variables, respectively. $P<0.05$ was considered to be a significant.

RESULTS

As shown in Table 1, the majority of the study population are above the age of 50 years that is 57%.

Moreover, of the 200 included for the study, 117 are male and 83 are female. One hundred and seventy of the 200 COVID-19 patients were discharged in hemodynamically stable condition whereas the remaining 30 succumbed to death as per Table 2.

Hypertension and diabetes are the major co morbidities in the study population as depicted in Table 3.

In the present study, the mean aspartate transaminase (AST) levels were 41.89±50.22 U/L, mean alanine transaminase (ALT) levels were 37.69±41.41 U/L, mean amylase levels were 97.77±126.42 U/L, and mean lipase levels were 90.34±127.76 U/L as shown in Table 4.

Table 5 shows us the comparison of the laboratory parameters among the two groups, that is, discharged and those who died. The LDH levels were 406.46±223.8 U/L among the discharged ones and 556.26±256.81 U/L among the deceased, p-value being 0.00 which is statistically significant. Neutrophilia and lymphocytopenia were also significant among the two groups with p-value being <0.05 as well thus marking a greater severity of the disease.

In Table 6, we see that the percentage of transaminitis that was present in patients who were discharged was 29.41% when compared to those who died which is 53.33% and this difference is statistically significant with p-value of 0.02.

However, there was no statistical significance seen among the patients with elevated pancreatic enzymes when compared to their outcomes.

Table 1: Demographic data

	Mean±SD
Age (years)	
18-30	18 (9.05%)
30-50	68 (34.0%)
> 50	114 (57.0%)
Gender	
Male	117
Female	83

Table 2: Demographic data

Predictors N = 200	Discharge N = 170	Death N = 30
Age (years)		
18-30	15 (8.82%)	3 (10.0%)
30-50	58 (34.12%)	10 (33.33%)
more than 50	97 (55.29%)	17 (53.33%)
Gender		
Male	99	
Female	71	
Male	18	
Female	12	

Table 3: Co morbidities

Co morbidities	Discharge N = 170	Death N = 30	p-value
Hypertension	68 (40.0%)	11 (36.67%)	0.89
Cardiac Disorder	13 (7.65%)	4 (13.33%)	0.30
Diabetes Mellitus	69 (40.59%)	10 (33.33%)	0.61
Thyroid Disorder	14 (8.24%)	2 (6.67%)	0.92

Table 4: Laboratory parameters

Descriptive Statistics N = 200	
Predictors	**Mean±SD**
TLC (x 10^3 cells/cu mm)	9.88±5.25
N (%)	77.96±15.17
L (%)	13.38±10.21
NLR	11.71±12.65
AST (U/L)	41.89±50.22
ALT (U/L)	37.69±41.41
AMYLASE (U/L)	97.77±126.42
LIPASE (U/L)	90.34±127.76
D-DIMER (mg/L)	8.3±52.15
LDH (U/L)	417.22±231.74
CRP (mcg/ml)	
< 1.2	65 (32.5%)
1.2-10	128 (64%)
>10	7 (3.5%)
Outcome	
Discharge	170 (85.0%)
Death	30 (15.0%)

ALT: Alanine Transaminase, AST: Aspartate Transaminase, CRP: C-reactive Protein, L: Lymphocyte, LDH: Lactate Dehydrogenase, N: Neutrophil, NLR: Neutrophil-Lymphocyte Ratio, TLC: Total Leukocyte Count

Table 5: Comparison of the parameters among those who were discharged to those who expired

Variables	Discharge	Death	p-value
TLC (x 10^3 cells/cu mm)	9.65±5.03	10.32±3.64	0.26
N (%)	76.83±16.01	84.66±7.65	0.02
L (%)	14.03±10.75	10.13±5.89	0.04
NLR	11.68±13.44	11.07±6.57	0.41
AST (U/L)	41.13±53.14	46.63±33.03	0.31
ALT (U/L)	37.1±42.42	43.59±39.2	0.24
AMYLASE (U/L)	99.64±133.80	72.77±68.47	0.17
LIPASE (U/L)	82.40±109.36	120.87±204.21	0.08
LDH (U/L)	406.46±223.8	556.26±256.81	0.00
D-DIMER (mg/L)	7.08±51.23	3.01±2.98	0.35
CRP (mcg/ml)			
< 1.2	52 (31.71%)	9 (37.5%)	0.74
1.2-10	107 (65.24%)	14 (58.33%)	0.66
>10	5 (3.05%)	1 (4.17%)	0.56

ALT: Alanine Transaminase, AST: Aspartate Transaminase, CRP: C-reactive Protein, L: Lymphocyte, LDH: Lactate Dehydrogenase, N: Neutrophil, NLR: Neutrophil-Lymphocyte Ratio, TLC: Total Leukocyte Count

Table 6: Liver and pancreas involvement

Variables	Discharge N = 170	Death N = 30	p-value
Transaminitis	50 (29.41%)	16 (53.33%)	0.02
Pancreatitis	51 (30%)	8 (26.67%)	0.92

DISCUSSION

The liver function abnormalities in COVID-19 patients were mainly manifested as abnormal levels of ALT or AST, with a slight increase in bilirubin levels. In a study of 69 patients by Wang et al.,[11] 23 had elevated ALT (33%) and 19 had elevated AST (28%). In the study by Cai et al.,[12] 44 of 298 patients (14.8%) had liver injury and those with severe liver injury (36.2%) were more prone to these elevations than patients with mild liver injury (9.6%). According to the study by Zhang et al.,[13] the incidence of liver injury may be as high as 78% among 82 deaths of laboratory-confirmed SARS-CoV-2 infection. In the present study, transaminitis was present in 29.41% of the total cases who were discharged and among 53.33% of the patients who died and the difference between them was statistically significant with *P*-value of 0.02.

Abnormalities in liver function led to a longer hospital stay. Chronic liver disease in the absence of immunosuppressive therapy is not known to be associated with an increased risk of acquiring COVID-19.[14] However, the liver may be susceptible to SARS-CoV-2 virus because of ACE2 receptors in the biliary and liver epithelial cells.[15]

A study conducted by Nurshad Ali concluded that abnormal liver function test markers were more common in patients with severe COVID-infection and these COVID-19 patients were advised to be treated with drugs that are able to inhibit inflammatory responses and protect liver functions.[16]

However, the major studies clearly indicated increased liver dysfunctions in severe COVID-19 patients, though clinically significant liver failure has rarely been described.

Speaking of the involvement of pancreas in COVID-19, it has been found that in patients with severe COVID-19, the expression of ACE2 in the pancreas during SARS-CoV-2 infection can result in acute inflammation which caused acute pancreatitis.[17] A study conducted by Alves et al., in December 2020 concluded that SARS-CoV-2 seems to have some tropism for pancreatic (exocrine and endocrine) cells, causing acute pancreatitis.[18] A study conducted by Barlass et al., in July 2020 concluded that higher lipase levels were significantly associated with admission to the ICU and rate of intubation in COVID-19 patients.[19] Kumaran et al., in August 2020 concluded that COVID-19 is a potential cause in patients presenting with idiopathic pancreatitis.[20]

In the present study, the pancreatic enzymes were elevated only in 30% of the cases who were discharged and among 26.67% of the cases who succumbed to death and this was not statistically significant. Sathik et al., in September 2020 concluded that the incidence of pancreatitis in patient having COVID-19 infections is relatively uncommon and in patients having pancreatitis the susceptibility to SARS-COV-2 infection are more than the normal public.[21] A study conducted by Patnaik et al., in July 2020 found out that although no causal relationship had been established, a temporal association between pancreatitis and COVID-19 was strongly indicative of SARS-CoV-2-induced injury.[22]

Limitations of the study

The study has its limitations like the sample size is small and it being a single center study.

CONCLUSION

Although COVID-19 has established itself as a respiratory pathogen, it is also responsible for hepato-pancreatic manifestations. Hepatic injury and pancreatic injury have been evident in the subset of patients ranging on a spectrum with the severity of the disease. In the present study, we see that hepatic injury is more commonly associated with an increased severity of the disease and also as a contributor for the greater mortality of the COVID-19 patients.

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AHR – Conceptualization, data curation, methodology, and validation; **VSB –** Conceptualization, data curation, investigation, software, Writing – original draft, and Writing – review and editing; **AU –** Project administration, formal analysis, and Visualization

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