http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v9i1.49

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

# Hepatic Impacts of COVID19: Raised GGT is an Indicator of Severity of Disease

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**Abstract**
**Introduction:** *The Coronavirus disease of 2019 (COVID19) is highly contagious disease of Coronaviridae family which mainly targets upper and lower respiratory tracts. But other organs like liver, gastrointestinal tract, heart, brain, kidneys, and vessels are also involved. The data regarding the effects of COVID19 on the liver is limited. We highlighted the impacts of COVID19 on the liver in the mild to moderate and the severe to critical groups of the patients.*
**Materials & Methods:** *This study was conducted at Department of Internal Medicine of the Capital Hospital, Islamabad, Pakistan, from March 1 to July 14, 2020, on 100 confirmed cases of the COVID19. The study group categorized into mild to moderate (mild symptoms to mild pneumonia, and SpO2 >93%), and severe (respiratory rate >30, SpO2 <93%, and/or >50% lung involvement on the imaging studies) to critical (respiratory failure, shock, and/or multi organ dysfunction syndrome) group. Liver function tests, serum albumin, PT, APTT were compared in groups; p-value less than 0.05 was considered significant.*
**Results:** *In our study 67% vs 33% are male and female, respectively. Major symptoms were fever (96%), fatigue (88%), myalgia (86%), cough (80%). The 76% vs 24% patients are categorized in mild to moderate group and in severe to critical group, respectively. Serum total bilirubin levels are increased in 12.5% vs 4% in the mild to moderate group and in the severe to critical group, respectively, with p-value 0.248; ALT level between 10-40IU/L in 36% vs 0% patients; 41-100IU/L in 60% vs 54%; >100IU/L in 2.6% vs 46% with p-value 0.000; AST level between 10-40IU/L in 51% vs 8.4%; 41-100IU/L in 48% vs 50%; >100IU/L in 0 vs 41.6% with p-value 0.000; ALP >130IU/L in 14.4% vs 16.7% with p-value 0.000; and the GGT level between 10-40IU/L in 29% vs 0; 49-100IU/L in 44.7% vs 8.3%; >100IU/L in 26% vs 91.3%; >200IU/L in 0% vs 51.1% with p-value 0.000 in mild to moderate and severe to critical group, respectively.*
**Conclusion:** *The GGT is the main enzyme affected in the severe to critical condition of COVID19. Thus, it can be used as an indicator of the severity of the disease and also very useful in assessing the recovery phase.*
**Keywords**: *Coronavirus disease, COVID19, Gamma-Glutamyl Transferase, GGT, Hepatic disease.*

## Introduction and Background

Coronavirus disease 2019 (COVID19) is highly contagious disease. This virus is also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was first time diagnosed in seafood market's worker of Wuhan city of China in December 2019. This novel infection has produced disastrous effects on human health and transmitted from bats to humans, mainly involves the respiratory system but also target the other organs of body. It transmits from person to person by respiratory droplets during cough, sneeze, talking, close contact (within ~2 meters, ~6 feets), as well as by touching a contaminated surface[1].

World Health Organization (WHO) declared it an outbreak as health emergency and pandemic in march 2020 because of its rapid spread in 188 countries of the world with more than 5,75,000 deaths, 13.2 million people have been infected with this novel viral disease and 7.33 million have recovered till July 14th, 2020[2].

The Coronavirus belongs to Coronaviridae and Orthocoronavirinae family and subfamily respectively. It is RNA virus having characteristic appearance of crown or solar corona. There are alpha, beta and gamma groups. Most of these infections transmitted from animals to human. Corona virus was first time diagnosed in 1930 and presented with mild symptoms of upper and lower respiratory tracts. In the year 2002 one of the virus of this family caused Severe Acute Respiratory Syndrome (SARS-1) was reported. It was also originated from china and spread in the nearest countries within few days. High mortality rate was associated with this disease. The year of 2013 another virus of this family Middle East Respiratory Syndrome (MERS) was diagnosed in Gulf States and transmitted from camel to human, it had less mortality rate and was easily treated [3].

The presentation of COVID19 is variable from mild to moderate and severe to critical. Most of the patient have good prognosis but some developed multi organ failure (MOF), and mortality can occurred. People of any age group can be effected but vulnerable age groups are 60 years and above, and patients with co-morbidities. Mostly patients present with high grade fever, headache, myalgia, fatigue, loss of sense of smell and taste, cough, shortness of breath, severe pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS). The gastrointestinal and hepatic involvement are not of serious nature, but symptpms include anorexia, diarrhea, nausea, vomiting, and the abdominal pain along with the abnormality in the liver functions test as well as in serum albumin, prothrombin time (PT), activated partial prothrombin time (APTT)[4,5,6].

In this study we assessed the hepatic impacts of COVID19 and observed the liver enzymes derangement in mild to moderate and severe to critical groups.

## Material and Methods

This cross-sectional study was conducted in the emergency department and the isolation wards of the Department of Internal Medicine of the Capital Hospital, a tertiary care hospital in Islamabad, Pakistan from March 1 to July 14, 2020. After taking permission from the concerned authorities data collection phase was started by using non-probability convenient sampling. One hundred confirmed COVID19 patients on the basis of real-time polymerase chain reaction (RT-PCR) of more than 18 years of age were included. The RT-PCR was done on the nasopharyngeal sample of the respiratory system. Verbal consent was taken from all the confirmed COVID19 patients after explaining the nature and purpose of the study at the beginning. All the patients were handled by the same doctors to minimize bias. Their age, sex, were noted, and the detailed history, examination, and investigations were taken on specified proforma. The patients of chronic hepatitis B and C, biliary tract disease, hepatocellular carcinoma, metastatic liver disease, obstructive jaundice, use of hepatotoxic drugs, fatty liver, typhoid, less than 18 years of age were excluded.

The liver function test, i.e., serum total bilirubin, alanine aminotransferase (ALT), and aspartate

aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT) were assessed. Activated partial prothrombin time (APTT), prothrombin time (PT), and serum albumin were also noted. Liver test abnormalities were defined as: ALT >40 IU/L, AST >40 IU/L, GGT>49 IU/L, ALP >130 IU/L, and total bilirubin >1.2 mg/dL, serum albumin 3.5-5 mg/dl, PT 10-12sec, APTT 30-33sec.

We categorized the study group into two groups, mild to moderate group and severe to critical group

**Mild Disease:** Patients with fever, cough, sore throat, malaise, headache, muscle pain, and with no shortness of breath, and abnormal radiological (CXR, HRCT) findings.

**Moderate Disease:** Clinical and radiological findings in favor of lower respiratory disease and oxygen saturation (SpO2) over 93% on room air at sea level.

**Severe Disease:** Respiratory rate more than 30 breaths per minute, SpO2 up to 93% on room air at sea level, ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO2/FiO2) below 300, or more than 50% lung infiltrates in HRCT chest.

**Critical Disease:** Evidence of respiratory failure, septic shock, and/or multiple organ failure (MOF)[7].

Each item was read out by researcher to the patient and symptoms marked according to response.

**Data Analysis Procedure**

The statistical package for social sciences (SPSS, version 24.0) was used to enter and analyze the data in the form of tables and graphs, frequencies and percentages were calculated; chi square test was used and the p-value less than 0.05 were considered as significant.

**Results**

A total of 100 confirmed COVID19 patients were included in this study, 67 (67%) were male and 33 (33%) were female. Major symptoms were fever (96%), fatigue (88%), myalgia (86%), cough (80%), headache (55%), anosmia (52%), shortness of breath (35%), diarrhea (19%), and vomiting (10%) as shown in Figure-1.

The 76% of the patients were categorized in the mild to moderate group, and 24% of the patients were in the severe to critical group. Serum total bilirubin level was increased in 12.5% vs 4% of the patients in the mild to moderate group and the severe to critical group, respectively with a p-value of 0.248.

The ALT level between 10-40IU/L in 36% vs 0 % of the patients in the mild to moderate group and the severe to critical group, respectively; 41-100IU/L in 60% vs 54%; and >100IU/L in 2.6% vs 46% with a p-value 0.000 as shown in the Table 1.

The AST level between 10-40IU/L in 51% vs 8.4% in the mild to moderate and the severe to critical group, respectively; 41-100IU/L in 48% vs 50%; >100IU/L in 0% vs 41.6% with a p-value 0.000.

The ALP >130IU/L in 14.4% vs 16.7% of the patients in the mild to moderate and the severe to critical group, respectively with a p-value 0.000.

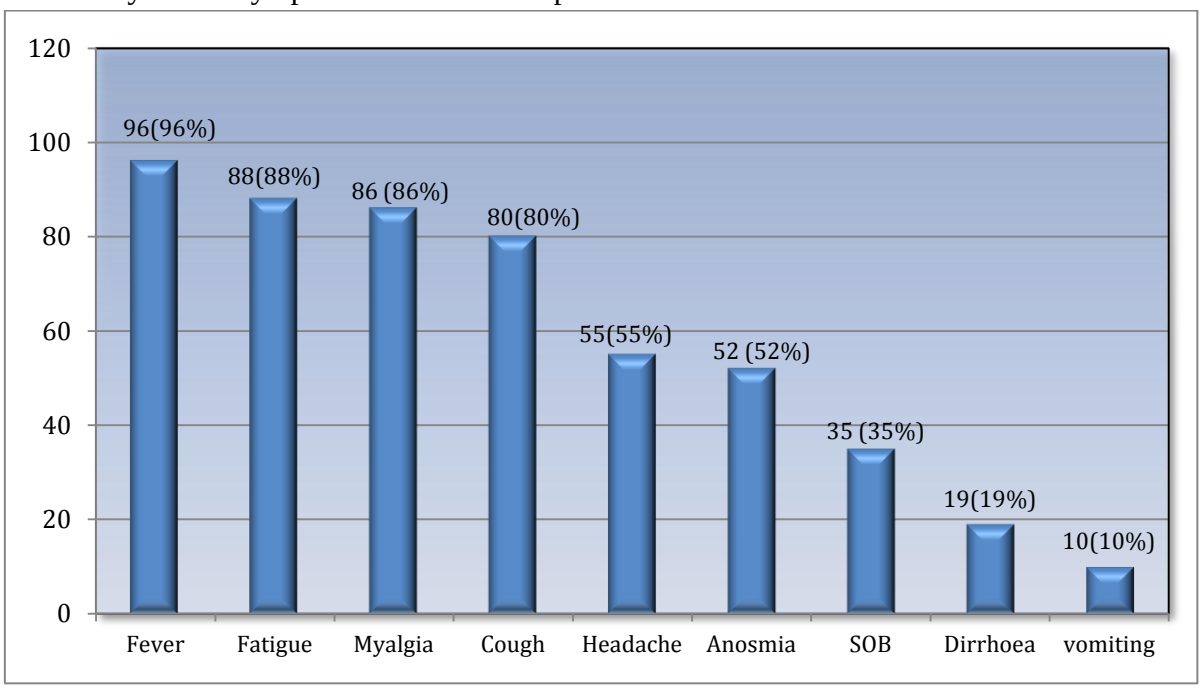
The GGT level between 10-49IU/L in 29% vs 0% of the patients in the mild to moderate and the severe to critical group, respectively; 50-100 IU/L in 44.7% vs 8.3%; > 100IU/L in 26% vs 41.6%; > 200IU/L in 0% vs 51.1% with a p-value 0.000 as shown in Table 1

The serum albumin is mildly low in the severe to critical group with a p-value of 0.005; the PT was raised in the severe to critical group with a p-value of 0.10; and the APTT was raised with a p-value 0.062.

Temperature between 99-100F in 72% vs 18% in the mild to moderate and the severe to critical group, respectively; 41.6% patients had >103F temperature in the severe to critical group with a p-value 0.000.

Low blood pressure was present in the 9% of the patients of the severe to critical group with a p-value 0.000 as shown in the Table 1.

**Figure 1:** Severity of the Symptoms of COVID19 patients




SOB: Shortness of Breath.

**Table 1:** Liver function tests of COVID19 patients, temperature and blood pressure.

| | Mild to Moderate | Severe to Critical | P-value |
|---|---|---|---|
| **Total Bilirubin** | | | |
| 0.5-1.2 mg/dl | 73(96%) | 21(87.5%) | 0.127 |
| >1.2mg/dl | 3(4%) | 3(12.5%) | 0.248 |
| **Total** | **76** | **24** | |
| **Alanine Aminotransferase (ALT)** | | | |
| 10-40 IU/L | 28(36%) | 0 (0%) | 0.000 |
| 41-100 IU/L | 46(60%) | 13(54%) | |
| >100 IU/L | 2(2.6%) | 11(46%) | |
| **Total** | **76** | **24** | |
| **Aspartate Aminotransferase (AST)** | | | |
| 10-40 IU/L | 39(51%) | 2(8.4%) | 0.000 |
| 41-100 IU/L | 37(48%) | 12(50%) | |
| >100 IU/L | 0 (0%) | 10(41.6%) | |
| **Total** | **76** | **24** | |
| **Alkaline Phosphatase (ALP)** | | | |
| 35-130 IU/L | 65(85.6%) | 4(16.7%) | 0.000 |
| >130 IU/L | 11(14.4%) | 20(83.3%) | |
| **Total** | **76** | **24** | |
| **Gamma-Glutamyl Transferase (GGT)** | | | |
| 10-48 IU/L | 22(29%) | 0 (0%) | 0.000 |
| 49-100 IU/L | 34(44.7%) | 2(8.3%) | |
| >100 IU/L | 20(26%) | 10(41.6%) | |
| >200 | 0(0%) | 12(50.1%) | |
| **Total** | **76** | **24** | |
| **Temperature** | | | |
| 99-100F | 72% | 18% | 0.000 |
| >103F | - | 41.6% | |
| **Blood pressure** | | | |
| Low | - | 9% | 0.000 |
| Normal | 76% | 15% | |

**Discussion**

The COVID19 is the disease of respiratory system but it also involves the different vital organ of the body. The hepatic and gastrointestinal abnormalities in the form of abnormal LFTs and digestive symptoms are reported with COVID19. It is reported that liver injury is more common in male patients and in cases with high grade fever[8]. In our study deranged liver functions are also more common in male patients and with moderate to high grade fever.

The studies[9,10] reported 10% to 17% gastrointestinal involvement also in our study major symptoms were diarrhea (19%) and vomiting (10%). Other studies[9,11] showed fever, fatigue, cough, and shortness of breath are main clinical features, while in our study major symptoms were also fever (96%), fatigue (88%), myalgia (86%), and cough (80%).

Data showed that SARS-1 and COVID19 enter in the human cells through the facilitation of Angiotensin Receptor II (ACE-II) which are present on different human cells including the brain, heart, lungs, kidneys, gastrointestinal tract, cholangiocytes, and vessels. The liver involvement is also reported in 60% of cases of SARS -1 with deranged liver function test[12]. In our study, the ALT was raised from base line, similar result was reported in severe acute respiratory syndrome (SARS-1) and in other studies[13,14]. Serum bilirubin level was raised in few cases of the severe to critical group in our study, and also reported in few cases in other studies[15].

In some studies, increased liver enzymes are associated with severity of disease[9,16]. In our study, the 36% of the patients of the mild to moderate group have normal liver enzymes throughout the disease, but there was no patient with normal ALT in the severe to critical group. Abnormity in raised ALT of >100IU/L are documented in 46% of the patients in the severe to critical group as compared with the mild to moderate group with 2.6%. Similarly, raised AST >100IU/L are reported in 41.6% of the patients of the severe to critical group as compared to mild to moderate group with no patient. The value of ALP also raised mildly in 83.3% cases of the severe to critical group and normal in the mild to moderate group. There were no features of obstructive jaundice and/or intrahepatic cholestasis.

Another study[17] showed that elevated levels of liver enzymes increase along with increase of CRP, myohemoglobin, erythrocyte number, and muscle enzymes.

In one study 54% cases were reported with raised GGT indicates biliary injury along with hepatic[6]. In our study GGT is highly increased in 41.6% cases of the severe to critical group while mild to moderate group have only 2.6% cases. The raised GGT >200IU/L in 50.1% cases of the severe to critical group and slowly returned back to normal during recovery phase.

The other studies[18] showed that ACE-II receptors are only 2.6% present on the liver cells, but 59.7% are present on the epithelial cells of the bile duct cells (cholangiocytes), so the direct injury to hepatocytes is less as compare to the bile duct cells which explained markedly elevated GGT as compared to AST and ALT.

Another study reported[19] that there was increased in both activated partial prothrombin time (APTT) and prothrombin time (PT), but in our study APTT and PT are mildly raised in the severe to critical group which indicate that synthetic functions of the liver are mildly affected with COVID19 infection as compared to other liver infections.

The liver injuries are occurred by two ways one through direct targeted involvement by viruses or bacteria, drugs or toxins which replicate and cause damage, and the second is the indirectly through systemic involvement[8]. In our study, there is no marked increase in ALT, AST, ALP, total bilirubin as normally seen in the acute hepatitis secondary to Hepatitis A and E, or in the cases of acute fulminant hepatic failure (AFHF) so might be indirect involvement is possibility in COVID19.

The study[18] showed that micro vesicular

steatosis, increase in mitotic cells, eosinophils, and balloon-like liver cells were present during biopsies of SARS-1 and MERS cases. The possible cause of hepatic injuries might be due to immune response and inflammation and presence of SARS-COV protein on hepatocytes.

The studies[20,10,13] showed that activation of cytokine storm is responsible for tissue damage of liver during COVID19 infection in severe cases. The cytokine storm is a life threatening condition which occurred in late stages of the disease. The virus enters the cell and start replication after controlling the DNA and lysosome then infected cell rapture and inflammatory process can occur. These cytokines e.g. IL2, IL6, IL12, TNF-alpha, etc., appear to regularize the inflammation. These uncontrolled systemic inflammatory response and cytokine storm cause acute respiratory distress syndrome (ARDS), multi organ failure (MOF), and finally death.

**Conclusions**

The main symptoms of COVID19 are fever, cough, myalgia, and fatigue. The liver enzymes ALT, AST, ALP, GGT, increased with the severity of the disease, but the serum albumin, PT/APTT were mildly deranged. The GGT is the main enzyme, elevation of which is strongly associated with the severity of the disease, and also it is very useful in assessing the recovery phase of the COVID19 patient.

**Recommendations**

1) The liver enzymes should be monitored during COVID19 pandemic because they give important information in the diagnosis and assessment of the severity of the disease.
2) We can differentiate COVID19 infection from other hepatic infection by assessing the liver biomarkers. In acute viral hepatitis all liver enzymes are highly raised (more than thousands), but in COVID19 GGT mainly increase more than 200IU/L as the disease progress to the severe to critical condition.
3) The GGT takes weeks to settle down after recovery from COVID19. So we can assess the undiagnosed patients of COVID19 in the recovery phase by measuring the GGT levels. The biliary injuries are characteristics feature of COVID19 without intrahepatic cholestasis.
4) Clinicians should have high index of suspicion of COVID19 in every patient with the raised GGT without features of intrahepatic cholestasis.
5) Due to high false-negative results, in the RT-PCR negative patients with the severe to critical symptoms, we can make GGT as a criterion of making diagnosis of COVID19.

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