

## Hepatic and Gastrointestinal Tract Manifestation with its Relation in Severe Covid 19 patients

<sup>1</sup>Dr. Mohammad Asadur Rahman, Medical Officer, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>2</sup>Dr. Mahedi Hasan, Consultant, Central Police Hospital, Dhaka, Bangladesh.

<sup>3</sup>Dr. ABM Safiullah, Assistant Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>4</sup>Dr. MD. Zahidur Rahman, Assistant Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>5</sup>Dr. Mohammad Shoaib Chowdhury, Assistant Professor, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>6</sup>Dr. Dewan Saifuddin Ahmed, Professor and Chairman, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

**Corresponding Author:** Dr. Mohammad Asadur Rahman, Medical Officer, Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Email: dr.asad74@gmail.com.

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### Abstract

**Background:** The COVID-19 pandemic, caused by SARS-CoV-2, has demonstrated a wide range of clinical manifestations beyond respiratory symptoms. While gastrointestinal (GI) and hepatic involvement has been reported in previous coronavirus outbreaks like SARS and MERS, their prevalence and significance in COVID-19 remain unclear.

**Objective:** This study aimed to investigate the frequency and characteristics of GI and hepatic manifestations in COVID-19 patients, and to explore their potential association with disease severity.

**Methods:** We conducted an observational study on 206 COVID-19 positive patients with mild to moderate symptoms, aged 20-50 years, at a single center in Bangladesh. Socio-demographic data, clinical symptoms, and laboratory findings were collected and analyzed.

**Results:** GI symptoms were prevalent among the study population, with diarrhea (65.5%), nausea (57.3%), anorexia (53.4%), and vomiting (45.6%) being the most common. Disease severity was classified as severe in 52.9% of patients, moderate in 22.8%, and mild in 24.3%. Liver function abnormalities were observed, including raised SGOT (62.1%), SGPT (51.5%), serum bilirubin (31.1%), and prolonged prothrombin time (22.8%). Notably, 81.1% of patients had raised serum albumin levels. Anorexia, nausea, diarrhea, and GI bleeding were significantly more frequent in severe COVID-19 cases ( $p < 0.05$ ). Elevated SGPT and SGOT were significantly associated with severe disease, while raised bilirubin, ALP, and prolonged PT were more common in mild to moderate cases ( $p < 0.05$ ).

**Conclusions:** This study highlights the high prevalence of GI and hepatic manifestations in COVID-19 patients. The association between certain GI symptoms, liver function abnormalities, and disease severity underscores the importance of monitoring these parameters in COVID-19 management. Further research is needed to elucidate the mechanisms underlying these manifestations and their prognostic implications.

**Keywords:** COVID-19, SARS-CoV-2, gastrointestinal symptoms, liver function, disease severity

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### I. Introduction

The COVID-19 pandemic is a crisis of a completely different magnitude and it is challenge of life threading of whole world including Bangladesh. Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide.<sup>1</sup> The coronavirus pandemic has infected; there have been 311,311,213 confirmed cases of COVID-19, including 5,514,590 deaths, reported to WHO. The outbreak spread from the Chinese city of Wuhan to more than 180 countries and territories—affecting every continent except Antarctica.<sup>2</sup> Gastrointestinal and liver symptoms have reportedly been the initial presentation of coronavirus disease-2019 (COVID-19) in a large group of patients.<sup>3</sup> In the SARS epidemic, 16% to 73% of patients had diarrhea during the period of the disease usually in the first week of sickness. In the initial MERS outbreak in 2012, a quarter of patients presented gastrointestinal symptoms such as diarrhea or abdominal pain. Besides, patients with SARS

and MERS have showed different degrees of liver injury.<sup>4</sup> Due to the phylogenetic similarities between COVID-19 and previous SARS-like coronaviruses, it is not unlikely that this novel coronavirus infection present with gastrointestinal symptoms in some patients.<sup>5</sup> Despite being frequently overlooked, involvement of the gastrointestinal (GI) tract and the hepatic system is now being increasingly reported.<sup>6</sup> Indeed, the first case of COVID-19 in the United States presented with nausea and vomiting in addition to systemic and respiratory symptoms, and later developed abdominal discomfort and diarrhea.<sup>7</sup> In this article, we will observed the GI and hepatic manifestations and the related pathophysiology (however limited) in patients with COVID-19 infection. Lastly, we will discuss the effect of COVID-19 in patients with underlying chronic GI diseases.

## II. Methodology

It was an observational study including consecutive samples that received the diagnosis of COVID-19, which was performed in the Department of COVID-19 isolation unit, BSMMU. COVID-19-positive patients with mild to moderate symptoms between 20 and 50 years of age. Data were collected from patients who attended the COVID-19 isolation unit. The severity of the COVID cases was assessed based on the WHO interim guidance. Data were collected only from non-critical COVID-19 patients, as critical patients required immediate intensive care admission, making them unable to respond to the questions. Using a case record form that had undergone testing, experienced clinicians evaluated and collected socio-demographic and clinical data. Verbal consent was taken from all participants. Demographic and clinical data were collected by a structured questionnaire and analysis was done with the help of SPSS (Statistical Package for Social Science) version 23. Continuous scale data were presented as mean standard deviation and categorical data were presented as number percentages. The summarized data were presented in the table and chart.

## III. Results

Out of 206 patient's majority 135(65.5%) had diarrhea, 118(57.3%) had nausea, 110(53.4%) had anorexia, and 94(45.6%) had vomiting (Table-1). More than half (52.9%) patients had severe COVID-19 disease, 50(24.3%) had mild and 47(22.8%) had moderate (Table-2). Raised serum bilirubin was 64(31.1%), more than half (51.5%) had raised SGPT, majority 128(62.1%) had patients had raised SGOT, 47(22.8%) had raised PT, 46(22.3%) had raised PT and majority 167(81.1%) had raised serum albumin (Table-3). Anorexia, nausea, diarrhea and GI bleeding were significantly higher in patients who had severe COVID-19 disease ( $p < 0.05$ ) (Table-4). Raised S. bilirubin, ALP and PT were significantly higher in mild to moderate COVID-19 disease. However, raised SGPT, SGOT were significantly higher in severe COVID-19 disease ( $p < 0.05$ ). Serum albumin was not statistically significant ( $p > 0.05$ ) compared with severity of COVID-19 (Table-5).

**Table 1: Distribution of the study patients by risk factors**

Risk factors	Number	Percentage
Anorexia	110	53.4
Nausea	118	57.3
Vomiting	94	45.6
Diarrhea	135	65.5
Abdominal pain	24	11.7
GI Bleeding	08	3.9

**Table 2: Severity of COVID-19 patients**

Severity of COVID-19	Number	Percentage
Mild	50	24.3
Moderate	47	22.8
Severe	109	52.9
Total	206	100.0

**Table 3: Investigations of the study patients risk factors**

	Number	Percentage
<b>S. Bilirubin</b>		
Normal	142	68.9
Raised	64	31.1

<b>SGPT</b>		
Raised	106	51.5
Normal	100	48.5
<b>SGOT</b>		
Raised	128	62.1
Normal	78	37.9
<b>ALP</b>		
Normal	159	77.2
Raised	47	22.8
<b>PT</b>		
Normal	160	77.7
Raised	46	22.3
<b>S. Albumin</b>		
Raised	167	81.1
Normal	39	18.9

**Table 4: Association of risk factors and severity of COVID-19 patients**

Risk factors	Severity of COVID-19		Total	p value
	Mild to moderate	Severe		
Anorexia	28	82	110	<0.001
Nausea	32	86	118	<0.001
Vomiting	47	47	94	0.48
Diarrhea	42	93	135	<0.001
Abdominal pain	08	16	24	0.15
GI Bleeding	00	08	08	0.007

**Table 5: Association of investigations and severity of COVID-19 patients**

Investigations	Severity of COVID-19		Total	p value
	Mild to moderate n=97	Severe n=109		
<b>S. Bilirubin</b>				
Normal	54	88	142	
Raised	43	21	64	<0.001
<b>SGPT</b>				
Raised	40	66	106	
Normal	57	43	100	0.006
<b>SGOT</b>				
Raised	40	88	128	
Normal	57	21	78	<0.001
<b>ALP</b>				
Normal	66	93	159	
Raised	31	16	47	0.003
<b>PT</b>				
Normal	66	94	160	

Raised	31	15	46	0.002
<b>S. Albumin</b>				
Raised	74	93	167	
Normal	23	16	39	0.09

#### IV. Discussion

In this study showed that the majority 135(65.5%) had diarrhea, 118(57.3%) had nausea, 110(53.4%) had anorexia, and 94(45.6%) had vomiting. The frequency of gastrointestinal symptoms such as diarrhea and vomiting, nausea/vomiting, and abdominal pain was 13%, 10%, and 9%, respectively, in the meta-analysis<sup>8</sup>, which is considered lower than that of SARS and MERS. Cha et al.<sup>9</sup> reported the most common GI presentation in patients with COVID-19 is diarrhea (3.8%-34%), followed by nausea and/or vomiting (3.9%-10.1%) and abdominal pain (1.1%-2.2%).<sup>10-11</sup> Other common GI symptoms reported in patients with COVID-19 are anorexia, anosmia, and dysgeusia<sup>12</sup>. Cheung et al.<sup>13</sup> in their meta-analysis of 60 studies involving 4243 COVID-19 patients from six countries found GI symptoms in 17.6% of the patients with anorexia (26.8%), diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain/discomfort (9.2%). Most notably, the latest and most comprehensive meta-analysis to date was produced by Borges and colleagues<sup>14</sup>, involving 59254 patients from 11 countries.

The results of the meta-analysis showed that 9% of all included patients displayed GI symptoms. These findings are not unexpected, as previous studies of SARS (2002-2003), which was caused by SARS-CoV, also revealed concurrent GI manifestations, similar to the current pandemic. Garland et al.<sup>15</sup> also suggested a lower percentage of patients with GI symptoms (3%). However, mounting evidence reports as many as 30%-50% may have diarrheal symptoms, 1%-29% reported abdominal pain, and 1%-29% reported nausea and vomiting, and a case report of hemorrhagic enterocolitis Zarifian et al.<sup>3</sup> reported this meta-analysis showed that the three most prevalent gastrointestinal symptoms among patients with confirmed COVID-19 were anorexia (10.2%, 95% CI = 6.2%-16.4%), diarrhea (8.4%, 95% CI = 6.2%-11.2%), and nausea (5.7%, 95% CI = 3.7%-8.6%), respectively.

In current study showed that more than half (52.9%) patients had severe COVID-19 disease, 50(24.3%) had mild and 47(22.8%) had moderate. In some cases, oxygen is required within a week of onset, and in more severe cases, the patient is admitted to the intensive care unit after 10 days<sup>16</sup>. According to the data of 44,672 patients in China, 81% had mild disease (no or mild pneumonia), 14% had severe disease (dyspnea, hypoxemia, and pneumonia image occupying > 50% of lung area within 24-48 h), and 5% had the most severe disease (respiratory failure, shock, and multiple organ failure)<sup>17</sup>.

Present study observed that raised serum bilirubin was 64(31.1%), more than half (51.5%) had raised SGPT, majority 128(62.1%) had patients had raised SGOT, 47(22.8%) had raised PT, 46(22.3%) had raised PT and majority 167(81.1%) had raised serum albumin. Cha et al.<sup>9</sup> reported the elevation of liver chemistries, including aspartate transferase, alanine transferase, and total bilirubin, has been reported since early observational studies. First is direct assault of SARS-CoV-2 on hepatocytes, leading to abnormal liver enzyme levels. Although this hypothesis is the most direct explanation, hepatocytes have not been shown to express high-level ACE2, making the liver an unlikely target for infection.<sup>18</sup> Yao et al.<sup>19</sup> did not provide evidence of SARS-CoV-2 infection of hepatocytes, suggesting this as an unlikely cause of liver injury. The second proposal suggests drug hepatotoxicity as the cause of abnormal liver function tests. This is possible, as acetaminophen is commonly used to control fever, which is a common presentation in COVID-19 infections. The use of acetaminophen within recommended dose, however, is unlikely to cause liver injuries as seen in the reported case series. It is also possible that systemic inflammatory response syndrome and multiorgan dysfunction contributed to the development of a cytokine storm and subsequently liver impairment, which may explain the higher prevalence of abnormal liver chemistries in patients with severe COVID-19 infection. Lastly, the occurrence of SARS can lead to hypoxic injury, which then leads to liver dysfunction<sup>20</sup>. Garland et al.<sup>15</sup> observed in addition to diarrhea, COVID-19 can cause liver damage. Studies have shown mild to moderate elevation of aminotransferase, bilirubin, and gamma-glutamyl transferase (GGT). Aspartate aminotransferase (AST) and GGT are more likely to be elevated, compared to Alanine aminotransferase (ALT) and bilirubin. The pattern of liver injury can be hepatocyte, cholestatic or mixed type. Meta analysis of 12 studies of 1267 patients found abnormal liver studies in 19% of patients (9-32; range 1-53; I<sup>2</sup>=96%). Zarifian et al.<sup>3</sup> reported common liver function abnormalities were mild decrease in albumin level (39.8%, 95% CI = 15.3%-70.8%), and mild increase in AST (22.8%, 95% CI = 18.1%-28.4%), ALT (20.6%, 95% CI = 16.7%-25.1%). Moreover, 18.0% (95% CI = 3.0%-60.8%) showed elevated prothrombin time. Total bilirubin and ALP levels were slightly elevated in 7.8% (95% CI = 5.0%-12.0%) and 4.6% (95% CI = 2.6%-7.9%), respectively.

Present study observed that the anorexia, nausea, diarrhea and GI bleeding were significantly higher in patients who had severe COVID-19 disease ( $p < 0.05$ ). Cha et al.<sup>9</sup> reported the studies looking at the association between severity of COVID-19 in patients with concurrent GI symptoms has yielded mixed results. A meta-analysis by Cheung et al.<sup>13</sup> suggested GI symptoms are more common in severe disease (17.1%). A case series study focusing on GI manifestations, conducted by Pan et al.<sup>21</sup>, found that most cases of diarrhea are mild and nondehydrating, typically up to three times daily. Both adult and pediatric populations can present with GI symptoms, although vomiting may be more prominent in the pediatric population<sup>22</sup>. Interestingly, few COVID-19 case studies and case series have been reporting cases with GI symptoms preceding respiratory symptoms, with some patients only presenting with digestive symptoms in the absence of respiratory symptoms.<sup>23-24</sup> Garland et al.<sup>15</sup> reported the most common digestive symptom is diarrhea, occurring in both mild and severe COVID-19 disease. Zarifian et al.<sup>3</sup> observed although anorexia was the most common gastrointestinal finding in both subgroups, its prevalence was two times higher in severe patients compared with not severe ones (31.4% vs 14.9%). Besides, the prevalence of diarrhea, vomiting, and abdominal pain were also markedly higher in patients with severe disease, while abdominal distension was more frequent in not severe cases.

In this study showed that raised S. bilirubin, ALP and PT were significantly higher in mild to moderate COVID-19 disease. However, raised SGPT, SGOT were significantly higher in severe COVID-19 disease ( $p < 0.05$ ). Serum albumin was not statistically significant ( $p > 0.05$ ) compared with severity of COVID-19. Cha et al.<sup>9</sup> reported abnormal liver enzymes are associated with higher risk of severe disease; daily check of liver function test may not be warranted. Most patients only have mild elevation of liver enzymes' levels, which resolves as the patient improves clinically.<sup>25-26</sup> The most common cause of death in COVID-19 infection is respiratory failure and sepsis. To date, only 1 case of COVID-19 has been reported with presentation of acute liver failure<sup>27</sup>. As there are no effective hepatoprotective treatments currently, it is important for clinicians to not be distracted by minimally elevated liver enzymes' level and to instead focus on general management and supportive care.<sup>25</sup> Garland et al.<sup>15</sup> reported the extent of lab abnormality is associated with severity of disease and worse outcomes. Studies have observed significant differences in AST, ALT, bilirubin, and GGT values between those with severe and non-severe disease.<sup>16, 28</sup> In a study of 1099 patients in China, 18.2% with non-severe disease had abnormal liver tests compared to 39.4% with severe disease.<sup>29</sup> Of note, underlying liver disease was uncommon and only observed in 2.3% of the study population. A smaller study reported 25% of non-severe cases had abnormal AST compared to 62% of intensive care (ICU) patients.<sup>16</sup> Few reports have documented liver failure, often associated with multiorgan failure.<sup>28</sup> Given liver dysfunction, it has been recommended baseline liver tests are collected at hospital admission.

## V. Conclusion:

In this study suggested common risk factors were found diarrhea, nausea, anorexia, and vomiting. Raised serum bilirubin, raised SGPT, SGOT, and raised serum albumin were significant relation with severe COVID-19 disease. Anorexia, nausea, diarrhea and GI bleeding were significantly higher in patients who had severe COVID-19 disease.

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