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Research Article

Impact of Gastrointestinal Symptoms on in-Hospital Outcomes and Long-Term Sequelae in Hospitalized COVID-19 Patients: A Prospective Cohort Study

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Abstract

Background: Gastrointestinal (GI) symptoms have become increasingly recognized as a significant aspect of COVID-19. However, the long-term impact of GI symptoms on disease course, outcomes, and post-discharge sequelae remains poorly understood. This study aimed to investigate the disease course, outcomes, and long-term sequelae of hospitalized COVID-19 patients with and without GI symptoms. *Methods:* A prospective cohort study was conducted on 246 hospitalized COVID-19 patients at Dhaka Medical College Hospital. Participants were divided into two groups: 123 with GI symptoms and 123 without. Clinical outcomes during hospitalization and post-discharge follow-up were compared between the two groups. *Results:* Patients with GI symptoms demonstrated better in-hospital outcomes, including lower oxygen requirements and a higher frequency of complete recovery. However, rates of ICU admission, mechanical ventilation, and mortality were similar between both groups. Long-term follow-up revealed comparable rates of post-COVID-19 symptoms in both groups, with persistent symptoms being more common than new symptoms. *Conclusion:* Our study found that patients with GI symptoms had better in-hospital outcomes regarding oxygen requirements and complete recovery. However, long-term post-discharge sequelae were similar in both groups. These findings highlight the importance of ongoing research to better understand the long-term impact of COVID-19, including the potential role of GI symptoms in disease course and outcomes.

Keywords

COVID-19, SARS-CoV-2, Gastrointestinal Symptoms, Outcomes, Post-COVID-19 Syndrome

1. Introduction: CorrespondingAuth: Sushanta Barua

At the end of 2019, a cohort of unidentified viral pneumonia cases was first reported in Wuhan, the capital city of Hubei Province in China. [1] On January 7, 2020, a novel coronavirus was isolated and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV). [2] This pneumonia was called Coronavirus Disease 2019 (COVID-19) by the World Health Organization on February 11, 2020. Very soon, the COVID-19 outbreak has become a pandemic that is threatening global health, undermining the global economy, and destabilizing societies across the world. [3, 4] In Bangladesh, the virus was confirmed to have spread in March 2020. The first three known cases were reported on 8 March 2020 by the country's epidemiology institute, IEDCR & gradually spread over the whole nation.From initial studies it was known that COVID-19 is predominantly a respiratory disease where most patients present with fever, fatigue along with respiratory signs and symptoms, such as dry cough and dyspnea. [5, 6] But many patients also have presented with some extra pulmonary symptoms along with respiratory symptoms and sometimes without any respiratory symptoms, suggested by some studies. [7] However, with the evolution of the pandemic and the accumulation of case data, we are now able to describe the initial clinical presentations of patients with COVID-19; and our experience is revealing that gastrointestinal symptoms are not uncommon. [7] In particular, our initial observations with COVID-19 indicate that many patients present initially with diarrhea, anorexia, nausea, vomiting and abdominal pain not necessarily with respiratory symptoms at first. Viral tropism for the angiotensin-converting enzyme receptor 2 (ACE2 receptor) found in the GI tract has been proposed as a potential mechanism for the virus affecting the GI system. [8] It has also been postulated that fecal-oral transmission is also possible given the presence of viral RNA in stool samples. The clinical importance of gastrointestinal manifestations still remains controversial, with very limited and conflicting studies. Some analysis showed that those who have presented with GI symptoms had a worse outcome; on the other hand, some showed no difference in outcome. [9, 10] As about 10% of COVD-19 patients may present with gastrointestinal manifestations. There has been an increasing interest in whether gastrointestinal symptoms are associated with a worse outcome or not. Therefore, in this study, our aim is to analyze if the presence of gastrointestinal symptoms in COVID-19 patients will be associated with increased mortality and morbidity or not when compared to those who don't have gastrointestinal symptoms.

2. Materials & Methods

2.1. Study Design

Prospective cohort study.

2.2. Study Place

Gastroenterology department, Dhaka Medical College Hospital. Data collected from COVID-19 dedicated Dhaka Medical College Hospital (DMCH-2), Dhaka, Bangladesh.

2.3. Study Period

This study has been conducted from August 2020 to July 2021.

2.4. Study Population

Consecutive adult (>18 years) SARS COV-2 RT PCR positive symptomatic and hospitalized patients who will fulfill inclusion & exclusion criteria attending in DMCH-2 during the study period and give informed written consent.

2.5. Inclusion Criteria

Adult patients (aged 18 years and above) of both sex who are SARS COV-2 RT PCR test positive, symptomatic, hospitalized and willing to give written informed consent have been included in the study.

2.6. Exclusion Criteria

1. Patients with pre-existing known diseases who usually manifest as chronic diarrhea, abdominal pain, & anorexia, e.g. chronic pancreatitis, Intestinal tuberculosis, CKD, advanced malignancy.
2. Pregnant women.

2.7. Outcomes

1. Requirement of Oxygen in terms of duration (days) and amount (liter/min).
2. Requirement of HDU/ICU or mechanical ventilation during the period of acute illness.
3. Recovery from acute illness (complete or partial).
4. Long term consequences following complete or partial recovery.
5. Death from any cause during the period of illness.

2.8. Study Procedure

Consecutive symptomatic & hospitalized patients have been selected from COVID-19 dedicated Dhaka Medical College Hospital (DMCH-2). Patients who are tested positive

for SARS COV-2 RT PCR have been recruited for assessment of inclusion and exclusion criteria. After meeting the exclusion and inclusion criteria, patients will be enrolled for data collection.

2.9. Stratification of Study Cohort

In this study, the study cohort was stratified into two groups based on the presence of GI symptoms: COVID-19 with GI symptoms with or without other symptoms and COVID-19 with symptoms other than GI.

2.10. Data Analysis

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-Square test with Yates correction was used to analyze the categorical variables, shown with cross tabulation. Student t-test was used for continuous variables. P values <0.05 were considered as statistically significant.

3. Result

It was observed that approximately 86% of patients were aged 31 to 70 years, with a similar age distribution in both groups. The mean age was 50.9 ± 14.3 years in the GI symptoms group and 52.5 ± 13.3 years in the without GI symptoms group. Male and female representation was nearly equal (128/118) in both groups. Most patients (80%) in both groups had a BMI of 18.5 to 29. The mean BMI was 25.6 ± 4.0 in the GI symptoms group and 25.4 ± 3.8 in the without GI symptoms group. These subtle differences were not statistically significant.

Comparison of Groups:

Regarding smoking status, comorbidities, and symptom onset to hospitalization duration, there were no statistically significant differences between the two groups. Table 2 presents the frequency distribution of gastrointestinal symptoms in the GI symptoms group. The most common complaints were anorexia (78%), followed by diarrhea (50.4%), vomiting, nausea, and abdominal pain. Table 3 shows the frequency distribution of symptoms other than gastrointestinal in both groups. The most common general symptom was fever (81.7%), followed by fatigue (23.6%) and myalgia (22.8%) in both groups. There were no statistically significant differences between the GI and without GI symptoms groups. Among respiratory symptoms, the most common were cough (67.5%) and dyspnea (67.5%), followed by chest pain (11.4%). Significant differences were not observed between the two groups, except for dyspnea, which was less frequent in the GI symptoms group (61% vs. 74%).

Neurological Symptoms and Other Factors:

Neurological symptoms such as headache (16.3% vs. 5.7%) and anosmia (13.0% vs. 5.7%) were more frequent in the GI symptoms group compared to the without GI symptoms group. No statistically significant differences were observed for other infrequent symptoms. Table 4 compares outcomes at the hospital between the two groups. The number of cases requiring oxygen was lower in those with GI symptoms than without (60.2% vs. 73.2%; RR 0.82, 95% CI, 0.69-0.98; p=0.030). Complete recovery from acute illness was more common in the GI symptoms group (76.4%) than in the without GI symptoms group (61%), but the time taken for complete recovery was similar in both groups. There were no significant differences in the requirement of mechanical ventilation or death rate between the two groups.

Follow-up:

Figure 1 shows that persistent symptoms prevailed throughout the six-month follow-up in both groups. New symptoms were distributed similarly in both groups and increased slightly over time. Re-infection, re-admission, and death were more observed in the without GI symptoms group, although these differences were not statistically significant.

Table 1. Demographics and clinical characteristics of the study patients (n=246).

Variable	Total (n=246)		GI group (n=123)		Without GI group (n=123)		p-value
	n	(%)	n	(%)	n	(%)	
Age (years)							
≤30	22	(8.9)	12	(9.8)	10	(8.1)	
31-50	98	(39.8)	50	(40.7)	48	(39.0)	
51-70	113	(45.9)	55	(44.7)	58	(47.2)	
71-90	13	(5.3)	6	(4.9)	7	(5.7)	

Variable	Total (n=246)		GI group (n=123)		Without GI group (n=123)		p-value
	n	(%)	n	(%)	n	(%)	
Mean ±SD	51.7	±13.8	50.9	±14.3	52.5	±13.3	[a]0.345[ns]
Sex							
Male	128	(52.0)	62	(50.4)	66	(53.7)	[b]0.610[ns]
Female	118	(48.0)	61	(49.6)	57	(46.3)	
BMI (kg/m^2)							
<18.5	4	(1.6)	1	(0.8)	3	(2.4)	
18.5-24.9	107	(43.5)	54	(43.9)	53	(43.1)	
25.0-29.9	91	(37.0)	44	(35.8)	47	(38.2)	
30.0-34.9	44	(17.9)	24	(19.5)	20	(16.3)	
Mean ±SD	25.5	±3.9	25.6	±4.0	25.4	±3.8	[a]0.784[ns]
Smoking status							
Smoker	24	(9.8)	10	(8.1)	14	(11.4)	
Ex-smoker	23	(9.3)	10	(8.1)	13	(10.6)	[b]0.521[ns]
Non-smoker	199	(80.9)	103	(83.7)	96	(78.0)	
Co-morbidities							
DM	108	(43.9)	52	(42.3)	56	(45.5)	0.607[ns]
HTN	97	(39.4)	48	(39.0)	49	(39.8)	0.896[ns]
IHD	21	(8.5)	11	(8.9)	10	(8.1)	0.820[ns]
Bronchial asthma	29	(11.8)	14	(11.4)	15	(12.2)	0.843[ns]
COPD	3	(1.2)	0	(0.0)	3	(2.4)	0.123[ns]
CLD	2	(0.8)	2	(1.6)	0	(0.0)	0.249[ns]
Symptom onset to hospitalization (days)	16	±4.75	8.5	±4.8	7.5	±4.75	[b]0.131[ns]

ns= not significant, [a]P value reached from unpaired t-test . [b]P value reached from chi square test

Table 2. Frequency of Gastrointestinal symptoms of the study patients at admission (n=123).

Gastrointestinal symptoms	Number of patients	Percentage
Anorexia	96	78.0
Nausea	38	30.9
Vomiting	42	34.1
Diarrhea	62	50.4
Abdominal pain	30	24.4
Constipation	7	5.7
Oral ulcer	4	3.3

***Table 3.*** *Symptoms prevalence other than gastrointestinal symptoms among study patients at admission (n = 246).*

Variable	Total (n=246)		With GI symptoms (n=123)		Without GI symptoms (n=123)		p-value
	n	(%)	n	(%)	n	(%)	
General symptoms							
Fever	201	(81.7)	105	(85.4)	96	(78.0)	0.138^{ns}
Fatigue	58	(23.6)	30	(24.4)	28	(22.8)	0.764^{ns}
Myalgia	56	(22.8)	30	(24.4)	26	(21.1)	0.543^{ns}
Sore throat	17	(6.9)	8	(6.5)	9	(7.3)	0.802^{ns}
Weakness	6	(2.4)	2	(1.6)	4	(3.3)	0.342^{ns}
Others	7	(2.8)	1	(0.8)	6	(4.9)	0.060^{ns}
Respiratory symptoms							
Cough	166	(67.5)	79	(64.2)	87	(70.7)	0.276^{ns}
Dyspnea	166	(67.5)	75	(61.0)	91	(74.0)	0.029^{s}
Chest pain	28	(11.4)	13	(10.6)	15	(12.2)	0.688^{ns}
Cold	15	(6.1)	4	(3.3)	11	(8.9)	0.062^{ns}
Hemoptysis	5	(2.0)	1	(0.8)	4	(3.3)	0.185^{ns}
Neurological symptoms							
Headache	27	(11.0)	20	(16.3)	7	(5.7)	0.008^{s}
Anosmia	23	(9.3)	16	(13.0)	7	(5.7)	0.049^{s}
Vertigo	7	(2.8)	4	(3.3)	3	(2.4)	0.500^{ns}
Delirium	4	(1.6)	3	(2.4)	1	(0.8)	0.311^{ns}
Insomnia	3	(1.2)	2	(1.6)	1	(0.8)	0.500^{ns}
Sleep disturbance	3	(1.2)	2	(1.6)	1	(0.8)	0.500^{ns}
Unconsciousness	2	(0.8)	1	(0.8)	1	(0.8)	0.751^{ns}
Convulsion	2	(0.8)	1	(0.8)	1	(0.8)	0.751^{ns}
Other symptoms							
Restlessness	3	(1.2)	0	(0.0)	3	(2.4)	0.123^{ns}
Leg swelling	3	(1.2)	1	(0.8)	2	(1.6)	0.500^{ns}
Conjunctivitis	1	(0.4)	1	(0.8)	0	(0.0)	0.500^{ns}
Leg pain during walk	1	(0.4)	0	(0.0)	1	(0.8)	0.500^{ns}

s= significant, ns= not significant, P value reached from chi square test

Table 4. Outcomes of the study patients at hospital (n=246).

Outcomes	With GI Symptoms (n=123)		Without GI Symptoms (n=123)		RR (95% CI)	p-value
	n	(%)	n	(%)		
Requirement of oxygen (O2)						
Low flow O2 (≤15 L/min)	69	(56.1)	81	(65.9)	1.04 (0.94-1.14)	[a]0.460[ns]
High flow O2 (>15 L/min)	5	(6.8)	9	(10)	0.68 (0.24-1.93)	[a]0.460[ns]
Number of patient required O2	74	(60.2)	90	(73.2)	0.82 (0.69-0.98)	[a]0.030[s]
O2 requirement in days	14.3	±11.3	16.0	±13.3		[b]0.388[ns]
Requirement of mechanical ventilation						
Days	6.3	±4.8	6.8	±6.4		[b]0.871[ns]
Number	7	(5.7)	6.8	(10.6)	0.54 (0.22-1.30)	[a]0.162[ns]
Recovery						
Complete recovery from acute Illness	94	(76.4)	75	(61.0)	1.25 (1.06-1.49)	[a]0.009[s]
Partial recovery from acuteIllness	24	(19.5)	36	(29.3)	0.67 (0.42-1.05)	[a]0.075[ns]
Days required for complete Recovery	24.2	±12.9	20.9	±10.8		[b]0.078[ns]
Death	4	(3.3)	10	(8.1)	0.38 (0.10-1.37)	[a]0.097[ns]

s= significant, ns= not significant, [a]P value reached from chi square test, [b]P value reached from unpaired t-test
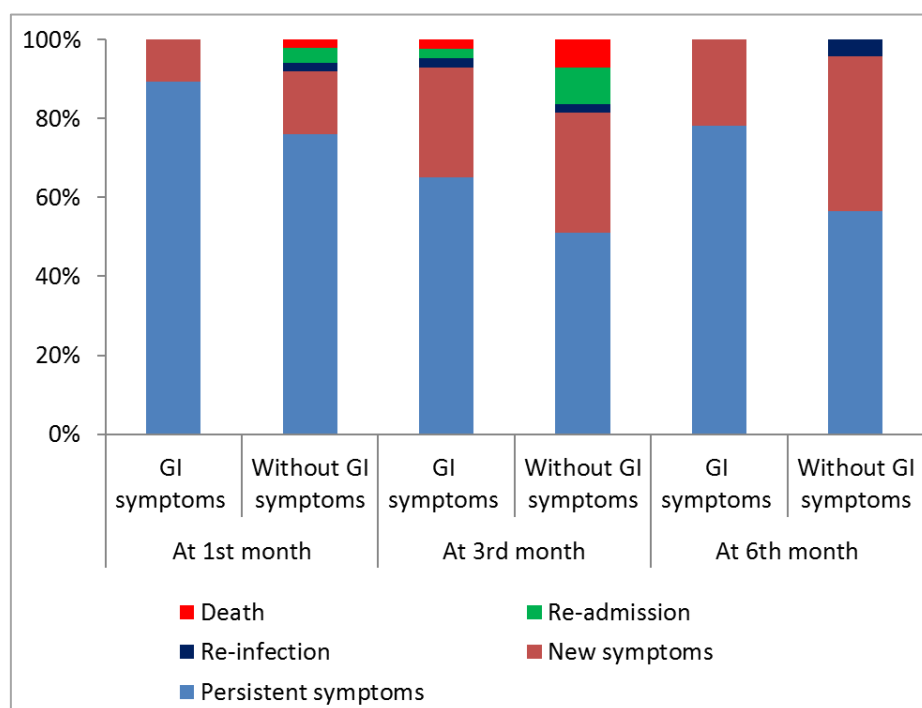
Figure 1. Follow up at different intervals after discharge among partially recovered individuals.

Component bar diagram showing consequences at different intervals in follow up after discharge among partially recovered individuals.

4. Discussion

This was a prospective cohort study mainly to search for any difference in clinical outcome at hospital and within 6 months after discharge from hospital between patients who had GI symptoms and who had not. The study was conducted upon 246 confirmed COVID-19 (SARS CoV-2 RT PCR positive) patients hospitalized in a tertiary care hospital Bangladesh among them 123 patients had GI symptoms and 123 had symptoms other than GI. Demographics, characteristics of patients are almost same in both groups. Among the 123 GI symptoms patient anorexia (78%) was most common symptoms followed by Diarrhea (50.4%), vomiting (34.1%), nausea (30.9%), abdominal pain (24.4%), constipation (5.7%) and oral ulcer (3.3%). Similar symptom frequency i.e. 79% & 98% with anorexia, 34% & 37% with diarrhea was found by (Pan, Mu, & Yang, 2020) and (Luo, Jiang, & Zhang, 2020) respectively. [10, 11] Among non GI symptoms fever (81.7%), cough (67.5%), dyspnea (67.5%), fatigue (23.6%) and myalgia (22.8%) no significant differences in symptoms between two groups. Similar symptoms and frequency was found by various other studies (COVID-19 CDC, 2021). In our study, no statistically significant differences in laboratory parameters, chest x-ray and CT scan of chest findings were observed. Similar findings were observed by (Reed, Zhou, Onukogu, & Ghanta, 2020) and (P, I, & S, 2020). [12, 4] But a large cohort (Laszkowka, Faye, & Kim, 2021) found that patients with GI symptoms had lower inflammatory markers including CRP, D-dimer and LDH. [13] This discrepancy may be due to the smaller sample size of our study, as we also noticed a lower trend of inflammatory markers in patients with GI symptoms but they are not statistically significant.Regarding hospital outcomes, we observed that oxygen was required by fewer patients who had GI symptoms than those who hadn't GI symptoms (60.2% vs 73.2%; RR 0.82, 95% CI, 0.69-0.98; p=0.030). On the contrary, (Siddiqui, Abro, & Bhatti, 2021) observed that more patients with GI symptoms required oxygen at discharge (29.5% vs 13.7% p=0.001). [14] We observed that complete recovery from acute illness was higher in the GI symptoms group than without GI symptoms group (76.4% vs 61%; RR 1.25, 95% CI, 1.06-1.49; p=0.009). But no difference in complete recovery time from symptom onset (24.2±12.9 vs 20.9±10.8 days, p=0.075) in between two groups. On the contrary, (Laszkowka, Faye, & Kim, 2021) found a longer median disease course from symptom onset in GI symptom group (13.8 vs 10.8 days, p=0.048). BMI and disease severity affect these outcomes. [13] In our study we also observed that there was no significant difference between with and without GI symptoms patients group in terms of requirement of mechanical ventilation (5.7% vs 10.6%; RR 0.54, 95% CI 0.22-1.30; p=0.162). Similar findings were observed by (P, I, & S, 2020). They didn't find any difference between the two groups (29% vs 26.7%). On contrary (Laszkowka, Faye, & Kim, 2021) (HR 0.66, 95% CI, 0.55-

0.79.) and (Nabil, Fallouh, Katrina, & Chichi, 2021) (OR 0.75, 95% CI, 0.44-1.29) showed that patients with GI symptoms had lower requirement of ICU or mechanical ventilation. [15] Regarding ICU days we didn't find any difference between two groups (6.3±4.8 vs 6.8±6.4) as like (Pan, Mu, & Yang, 2020). [10] We observed that there were no significant difference in death rate between with and without GI symptoms patients group (4.1% vs 11.4%; RR, 0.36; 95% CI, 0.13-0.96; p=0.097). Similar finding was observed by, (P, I, & S, 2020) 41.9% vs 37.8% p=0.68, and a meta-analysis of 3 study by (Fahad, Kevin, & Julie, 2020) OR 0.91, 95% CI, 0.49-1.68. On contrary (Laszkowka, Faye, & Kim, 2021) HR, 0.71; 95% CI, 0.59-0.87 and (Hajifathalian, Krisko, & Mehta, 2020) 8.5% vs 16.5% p=0.006 found lower death rate in GI symptoms patient group. [16, 13, 17] We didn't find any significant difference in symptom onset to hospital admission (8.5±4.8 vs 7.5±4.7 days, p=0.132). Similar findings observed by (Chao, Meiping, Li, & Xiaomin Chen, 2020) but (Laszkowka, Faye, & Kim, 2021) observed longer time from symptom onset to hospitalization (7.4 vs 5.4 days, p=0.01) and longer disease course in GI symptoms group. [18, 13]

We followed up the patients after discharge from hospital to look for any new or persistent symptoms or complications like death, re-infection & re-admission at the end of 1st, 3rd and 6th month. At the end of 1st month, we observed that symptoms frequency and complications rate was not much different between two groups (40.9% vs 47.2% p=0.346). Persistent symptoms were prevailing over new symptoms throughout my follow up. The most common symptoms at the end of 1st month were fatigue (24.6%), exertional dyspnea (22.9%) and cough (22%) in both groups but overall respiratory (19.1% vs 31.1%, p=0.039) and cardiac (0.9% vs 6.1%, p=0.025) symptoms were less frequently observed in GI symptoms group than without GI symptoms group. Almost similar rates of symptoms & complications were seen at 3rd month (38.4% vs 43.4%, p=0.457) at the end of 3rd month of follow up. Exertional dyspnea (22.6%), fatigue (21.6%) and cough (15.1%) overall were the most common persisting symptoms and there were no significant differences in symptoms between two groups. Follow up at the end of 6th month of discharge from hospital some patients still experience some symptoms (29.6% vs 24%, p=0.362) in GI and without GI symptoms group. Exertional dyspnea (15.9%) and cough (11%) remain as the most persisting symptoms and multiple new symptoms have appeared with decreasing frequency in both groups. The new symptoms were not proven to be caused by COVID-19. There were no significant differences in symptoms between two groups. A questionnaire based study by (Kayasslan, Eser, & Kalem, 2021) on 1007 hospitalized patients after discharge found that 47.5% had persistent symptoms at least after 3 months. [19] Fatigue/easy fatigability, myalgia, and loss of weight were the most frequent persistent symptoms (overall 29.3%), and followed by respiratory symptoms (25.4%). A cohort study to see 6-month consequences of COVID-19 in patients

discharged from hospital by (Huang, Huang, Wang, & Li, 2021) found that fatigue or muscle weakness, sleep difficulties and anxiety or depression were more frequent symptoms. [8] In a clinical review by (Crook, Raza, & Edison, 2021) of 218 articles regarding long COVID found similar type and rate of complications. [20] Another review by (Carod-Artal, 2021) found that 10-65% of survivors with mild / moderate COVID-19 have symptoms of post-COVID-19 syndrome for 12 weeks or more and chronic fatigue was described as the most frequent persisting symptom by various studies. [21] The possible explanation for this post COVID-19 syndrome is long term tissue damage by binding with ACE2 receptors present in different organ systems and unresolved inflammation.

In this study we didn't find any statistically significant difference in terms of readmission (0.8% vs 4.9%, p=0.311) and reinfection (0.8% vs 2.4%, p=0.060) between two group possibly because very low number of cases (1/6 & 1/3) with readmission and reinfection respectively.

5. Conclusion

In conclusion, our study found that patients with GI symptoms had better in-hospital outcomes regarding oxygen requirements and complete recovery. However, long-term post-discharge sequelae were similar in both groups. These findings highlight the importance of ongoing research to better understand the long-term impact of COVID-19, including the potential role of GI symptoms in disease course and outcomes.

Abbreviations

DMCH　　Dhaka Medical College Hospital

Acknowledgments

Data Availability Statement

The datasets used in this study can be obtained from the corresponding author upon reasonable request.

An ethical clearance was taken from Dhaka Medical College & Informed consent was obtained, with participants having the freedom to withdraw at any point.

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Conflicts of Interest

The authors declare no conflict of interest.

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