

Association of Gastrointestinal Symptoms with Severity of COVID-19 in a University Hospital of Bangladesh

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Abstract

Background: The World has experienced a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since March 11, 2020. At least 216 countries, areas or territories had affected cases of more than seven hundred million confirmed cases of COVID-19, including more than six million deaths. Most patients with COVID-19 present with typical respiratory symptoms and signs. But the number of COVID-19 patients experiencing gastrointestinal symptoms i.e. anorexia, nausea, vomiting, diarrhea and dysgeusia are significant and cannot be overlooked. In some cases, digestive symptoms may occur in the absence of any respiratory symptoms.

Method: This cross-sectional study was carried out in the COVID-19 outpatient and inpatient department of BSMMU involving at least 79 consecutive patients who were RT-PCR positive for coronavirus 2 (SARS-CoV-2). Gastrointestinal symptoms including anorexia, nausea, vomiting, altered taste, diarrhea, hematemesis or melena recorded precisely by face to face interview. Patients were classified as severe and non-severe COVID-19 according to Interim Guidance, 27th May, 2020 on the Management of COVID-19 from WHO. For the convenience of analysis, patients were divided into severe (severe & critical) & non-severe (mild & moderate) groups on the basis of presence of hypoxaemia (SpO₂ < 90%) on the basis of WHO case definition. Presence of gastrointestinal symptoms and their associations with severity of COVID-19 were analyzed statistically.

Result: Among 79 patients, 39 participants were in severe COVID group and 40 were in non-severe COVID group. Baseline characteristics were evenly distributed. Among GI symptoms anorexia (70.88%) and diarrhea (62.02%) were more prevalent and melena (2.53%) was least prevalent. Dysgeusia was present in 36.70% patients. There is no significant association between severities of diarrhea with severity of COVID-19. Three or more GI symptoms are present in both groups.

Conclusion: Gastrointestinal symptoms were commonly found in COVID-19 patients. Anorexia and diarrhea were more prevalent in this study. But this study did not exhibit any association between GI symptoms and severity of disease. Larger multi-centered study is warranted to explore this association.

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Introduction

The world has experienced more than six million deaths from more than seven hundred million confirmed cases between 2020 to 2022 due to COVID-19 pandemic.¹

Although lung is considered to be the primary organ of involvement by COVID-19 infection & most patients presented with typical respiratory symptoms & signs,² there are evidences that SARS-CoV-2 illness also presented with non-respiratory symptoms, most notably digestive symptoms. The gastrointestinal tract is believed to be affected because of a direct viral invasion mediated by the binding of the virus to the angiotensin-converting enzyme-2 (ACE-2) receptor, thereby causing cytotoxic damage.^{3,4}

Gastrointestinal (GI) symptoms, including diarrhea, anorexia, nausea, vomiting, abdominal pain and dysgeusia (distortion of the sense of taste) have been reported in patients with COVID-19.³ The prevalence of these general GI symptoms have been reported to vary between 3% and 79% in patients with confirmed COVID-19.⁵⁻⁸

According to a review published in March 2020 by Tian et al, anorexia was the most commonly reported GI symptom in adults, occurring in 39.9% to 50% of confirmed cases. The next most common symptom was diarrhea, reported for 2% to 49.5% of patients.⁵ The prevalence of nausea and vomiting ranged between 1% and 29.4% in COVID-19 positive adults.⁵ Abdominal pain has been less reported in the literature, with prevalence ranging between 2.2% and 6% of patients with confirmed COVID-19.³ There was no statistically significant difference in severity of COVID-19 between patients with and without GI symptoms, but the proportion of severe disease in patients with GI symptoms was higher than in patients without GI symptoms.⁹

Available data indicates that diarrhea was associated with severe COVID-19. The chance of having a severe COVID-19 infection with diarrhea was 1.71 times higher than those for the non-severely ill patient groups.¹⁰

On the other hand, according to pooled analysis, abdominal pain was significantly associated with increased COVID-19 severity but diarrhea was not associated with disease severity.¹¹

Diarrhea could be a reliable indicator of the onset of severe COVID-19.¹² Diarrhea had emerged as an early symptom of COVID-19 because of its prevalence in otherwise asymptomatic COVID-19 patients. Reports suggest that diarrhea presents between 1 and 8 days after infection onset, with a mean onset of 3.3 days.³ Awareness of the time course of GI symptoms is crucial because these symptoms may be one of the first signs of COVID-19 infection.¹⁰ The first confirmed COVID-19 patient in the United States initially presented to the hospital because of nausea and vomiting and not because of fever or dyspnea.¹³ The presence of early GI symptoms may provide early clues suggesting COVID-19 infection and precipitate follow-up testing and precautions.³

Objective

This study was conducted with an aim to find out the possible association between the GI symptoms and the severity of COVID 19, and to explore the scenario in Bangladeshi population on the background of the different conflicting reports of the association of GI symptoms and severity in different parts of world.

Methods

This cross-sectional analytic study was carried out in Bangabandhu Sheikh Mujib Medical University (BSMMU), a tertiary care hospital of Bangladesh, during the period of July 2020

to September, 2020. Consecutive 79 COVID-19 positive patients from the inpatient department and triage of the fever clinic of BSMMU were included in the study. Informed consent was obtained from each patient. The study protocol along with the ethical clearance was approved by the Institutional Review Board, BSMMU.

The principal author was directly involved in the COVID-19 response team of BSMMU COVID-19 unit & direct interviews in preformed questionnaire were carried out maintaining proper infection control protocol.

Based on clinical and laboratory parameters, COVID-19 patients were categorized as mild, moderate, severe and critical in accordance with Interim Guidance, 27th May, 2020 on the Management of COVID-19 from WHO. For the convenience of analysis, patients were divided into severe (severe & critical) & non-severe (mild & moderate) groups on the basis of presence of hypoxemia ($SpO_2 < 90\%$).¹⁴

Presence of loss of taste, loss of appetite, nausea, vomiting, diarrhea, abdominal pain, melena and other GI symptoms were documented. In case of loss of taste and diarrhea, mean duration of these two symptoms and mean duration between exposure to COVID-19 patient and the onset of the symptoms were documented. As the whole nation was on strict lockdown condition at that

time, and the COVID-19 cases were just starting to spread in the community, point of exposure was relatively definite at that time. Comorbidities were also documented on the basis of history and laboratory investigations.

Diarrhea was divided into mild, moderate and severe according to frequency, volume, presence or absence of dehydration. Frequency 0 to 1 time was considered mild, 2 to 5 times moderate and 5 or more severe.¹⁵

Results

This cross-sectional study was carried out in BSMMU from July 2020 to September 2020. Total 79 RT-PCR confirmed COVID-19 patients were enrolled in this cross sectional study. Among them 39 patients were in severe COVID-19 group and 40 patients were in non-severe COVID-19 group.

Table I showed the baseline characteristics of severe & non-severe COVID were evenly distributed. The mean age of participants of severe COVID-19 group was 58.5 ± 11.6 years and non-severe COVID-19 was 54.3 ± 11.4 years. Most of the patients belonged to 61-70 years' age group (43.6% & 30.0%) in both the groups. (Figure 1) Among the participants most of them were male in both groups (66.7% & 75.0%). (Figure 2) Most of the patients had comorbidities either single or multiple; among them DM and HTN were more prevalent.

Table I: Distribution of the study patients according to demographic characteristics (n=79)

Variables	Severe COVID-19 (n=39) n (%)	Non-severe COVID-19 (n=40) n (%)	p-value
Age (years)			
30-40	4(10.3%)	5(12.5%)	
41-50	6(15.4%)	10(25.0%)	
51-60	9(23.1%)	12(30.0%)	
61-70	17(43.6%)	12(30.0%)	
71-80	3(7.7%)	1(2.5%)	
Mean±SD	58.5±11.6	54.3±11.4	0.101
Sex			
Male	26(66.7%)	30(75.0%)	
Female	13(33.3%)	10(25.0%)	0.415
Comorbidities			
DM	22(56.4%)	22(55.0%)	0.900
HTN	21(53.8%)	20(50.0%)	0.732
IHD	12(30.8%)	7(17.5%)	0.168
Asthma	8(20.5%)	4(10.0%)	0.193
CKD	7(17.9%)	4(10.0%)	0.308
COPD	0(0.0%)	3(7.5%)	0.081

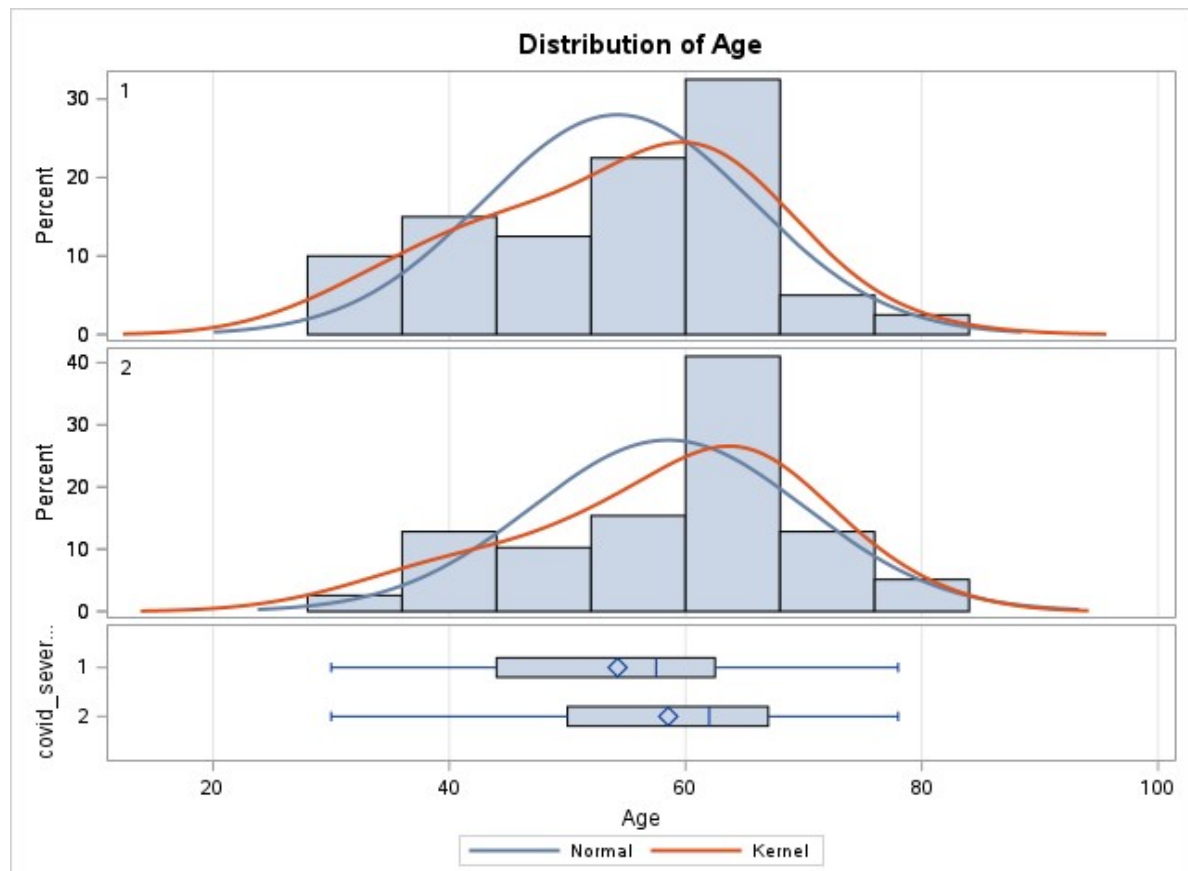


Figure 1. Distribution of the study patients according to age group among severe & non-severe COVID-19 patients.

In this study, anorexia, diarrhea, nausea, dysgeusia, vomiting, abdominal pain, melena were observed. Among the 79 COVID-19 patients, most suffered from anorexia (70.88%). Diarrhea was present among 62.02% patients. These were followed by nausea (41.77%), loss of taste (36.70%), vomiting (32.90%) & abdominal pain (7.59%). Melena was present only in 2.53% cases. (Table II)

Table II: Distribution of the study patients according to GI symptoms (n=79)

GI symptoms	Total (n=79) n (%)	Severe COVID (n=39) n (%)	Non-severe COVID (n=40) n (%)	p-value
Anorexia	56 (70.88%)	28(71.8%)	28(70.0%)	0.861
Diarrhea	49 (62.02%)	26(66.7%)	23(57.5%)	0.401
Nausea	33 (41.77%)	19(48.7%)	14(35.0%)	0.216
Dysgeusia/loss of taste	29 (36.70%)	13(33.3%)	16(40.0%)	0.539
Vomiting	26 (32.90%)	12(30.8%)	14(35.0%)	0.689
Abdominal pain	6 (7.59%)	2(5.1%)	4(10.0%)	0.414
Melena	2 (2.53%)	1(2.6%)	1(2.5%)	0.986

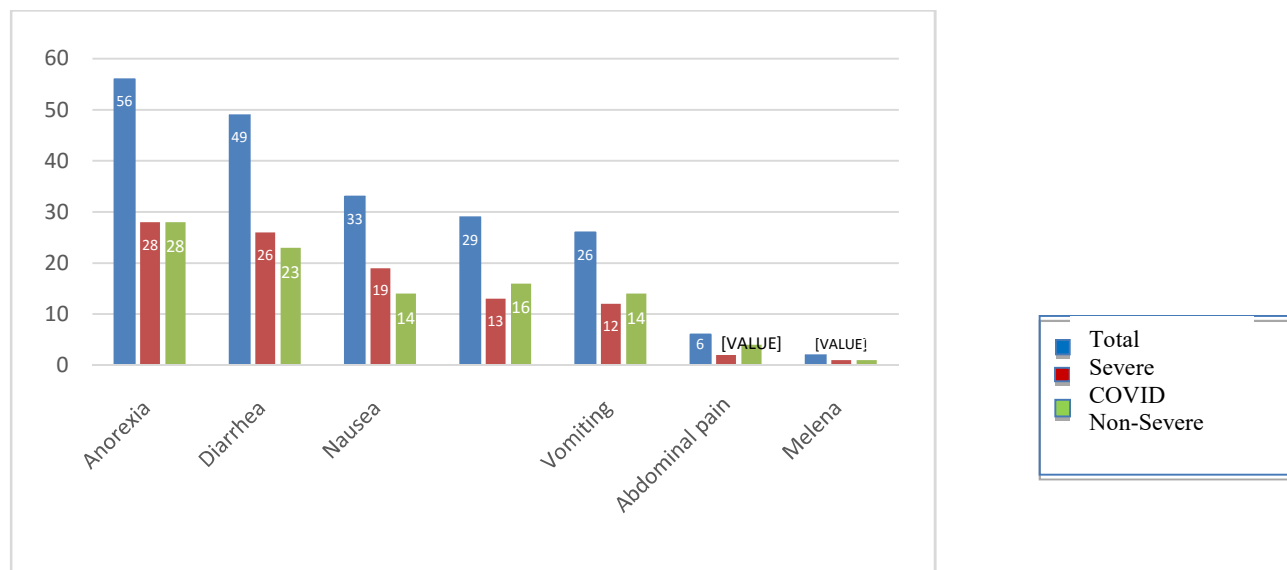


Figure 3. Distribution of the study patients according to GI symptoms among severe & non-severe COVID-19 patients

In severe COVID group 57.7% patients developed mild diarrhea and 19.2% developed severe diarrhea whereas 73.9% patients developed mild diarrhea and 8.7% patients developed severe diarrhea in non-severe COVID group.

In most of the patients, diarrhea resolved within 3 days in both the groups. Mean duration of diarrhea in severe COVID-19 group was 2.96 ± 2.07 days and in non-severe COVID-19 group was 2.70 ± 1.66 days. Mean duration of exposure from onset of diarrhea was 7.69 ± 3.99 days in severe COVID-19 group whereas 7.48 ± 3.73 days was in non-severe COVID-19 group.

There were no statistically significant differences between severe and non-severe COVID patients in respect to severity of diarrhea, duration of diarrhea & mean duration of exposure to the onset of diarrhea. (Table III)

Table III: Association of diarrhea & it's severity with COVID severity (n=49)

Associations	Severe COVID (n=26) n (%)	Non-severe COVID (n=23) n (%)	p-value
Severity of Diarrhea			
Mild	15(57.7%)	17(73.9%)	0.442
Moderate	6(23.1%)	4(17.4%)	
Severe	5(19.2%)	2(8.7%)	
Duration of Diarrhea			
0-3 days	13(50.0%)	14(60.9%)	0.720
3-5 days	12(46.2%)	8(34.8%)	
>5 days	1(3.8%)	1(4.3%)	
Mean duration of diarrhea	2.96±2.07 days	2.70±1.66 days	0.625
Mean duration of exposure to onset of diarrhea	7.69±3.99 days	7.48±3.73 days	0.848

Table IV tried to see the effects of the factors associated with presence of diarrhea among COVID-19 patients. Different age groups, male or female sex, presence of comorbidities were compared between the COVID-19 patients with or without diarrhea. There was no differences between the two sets of patients.

In contrast, there was a statistically significant difference in the number of GI symptoms- one, two, three, or more- between COVID-19 patients with and without diarrhea.

Table IV: Factors Associated with presence of diarrhea (n=79)

Parameters	Diarrhea (n=49) n (%)	No diarrhea (n=30) n (%)	p-value
Age group (years)			
30-40	7(14.3%)	2(6.7%)	0.841
41-50	9(18.4%)	7(23.3%)	
51-60	13(26.5%)	8(26.7%)	
61-70	18(36.7%)	11(36.7%)	
71-80	2(4.1%)	2(6.7%)	
Sex			
Male	35(71.4%)	21(70.0%)	0.892
Female	14(28.6%)	9(30.0%)	
Comorbidity			
Single	15(30.6%)	6(20.0%)	0.559
Multiple	26(53.1%)	19(63.3%)	
No comorbidity	8(16.3%)	5(16.7%)	
GI symptoms			
One	0(0.0%)	9(30.0%)	<0.001
Two	16(32.7%)	13(43.3%)	
Three or more	33(67.3%)	8(26.7%)	

The mean duration of dysgeusia or loss of taste was 5.8 days, with 5.9 for severe COVID-19 and 5.7 for non-severe COVID-19 where there was no significant statistical difference.

However, mean duration from exposure to COVID-19 patient and onset of dysgeusia was 3.8 days. For severe COVID it was 3.8 days. For severe case, it was 4.7 days and for non-severe case, it was 2.9 days which is statistically significant. (Table -V)

Table V: Loss of taste/dysgeusia

Dysgeusia	Total	Severe COVID	Non severe covid	P value
Mean duration of dysgeusia	5.8 days	5.9 days	5.7 days	0.7
Mean duration of exposure to dysgeusia	3.8 days	4.7 days	2.9 days	0.01

While seeking an association between severity of diarrhea and comorbidities, it was found that, among the patients with single comorbidity, 34.4%, 20.0% & 28.6% patients had mild, moderate & severe diarrhea respectively. On the other hand, 56.3%, 50.0%, 42.9% patients had mild, moderate & severe diarrhea respectively among the patients who had multiple comorbidities. In either case there were no statistically significant differences. (Table VI)

Table VI: Association of number of comorbidities with diarrhea severity (n=79)

Comorbidity	Diarrhea severity			p-value
	Mild (n=32)	Moderate (n=10)	Severe (n=7)	
Single	11(34.4%)	2(20.0%)	2(28.6%)	0.481
Multiple	18(56.3%)	5(50.0%)	3(42.9%)	
No comorbidity	3(9.4%)	3(30.0%)	2(28.6%)	
Total	32(100.0%)	10(100.0%)	7(100.0%)	

Discussion

Gastrointestinal symptoms are common in COVID-19 patients and sometimes appear earlier, at the beginning of respiratory symptoms. This study was conducted to identify common GI symptoms in COVID-19 patients and their impact on disease severity.

In this study mean age of both groups, severe COVID and non- severe COVID was 58.5 ± 11.6 years and 54.3 ± 11.4 years. Umbreen Aslam et al.,¹⁶ showed that mean age was 37 ± 15 years in mild diseased group and 41 ± 18 years in severe disease activity group. In this current study, most of the hospitalized patients were elderly, which may make the scenario

different from other studies. Most of the participants of this study were male in both groups. A study conducted by Liu K et al.,¹⁷ revealed majority of the patients were female. This difference may explain different socioeconomic conditions and geographical variations in different countries.

Study population was mostly never smokers and ex-smokers in the current study, with statistical similarity between severe and non-severe COVID-19 patients. While evaluating 1019 COVID-19 patients from 552 hospitals in China, smoking status was found to be similar with the current study. Most of them were never-smoker and there was no difference

between severe and non-severe groups.¹⁸ On the other hand, according to a meta-analysis by AskinGulsen et al., that included 16 articles and 11,322 patients, significant relationship was found between smoking and severity of COVID-19.¹⁹

The majority of COVID-19-associated GI symptoms were mild and self-limiting and included anorexia, diarrhoea, nausea, vomiting and abdominal pain/discomfort. A minority of patients present with an acute abdomen with etiologies such as acute pancreatitis, acute appendicitis, intestinal obstruction, bowel ischemia, haemoperitoneum or abdominal compartment syndrome.²⁰

Anorexia, diarrhea, nausea, dysgeusia, vomiting, abdominal pain, melena were the GI symptoms observed in this study. Among them anorexia (70.88%) and diarrhea (62.02%) were more prevalent. Nausea was observed in 41.77%, dysgeusia/loss of taste in 36.70%, vomiting in 32.90%, and abdominal pain in 7.59% patients' melena was observed only in 2.53% patients. Subsequent cohorts have consistently reported digestive symptoms among COVID-19 patients. A study of 1141 confirmed COVID-19 cases observed 183 (16%) patients presented with gastrointestinal symptoms. These symptoms included diarrhea (68, 37%), vomiting (119, 65%), nausea (134, 73%), loss of appetite (180, 98%) and abdominal pain (45, 25%).²¹

The diarrhea symptom was included in all the studied cohorts of COVID-19 patients although with a quite variable percentage from 2.0% to 55.0%.³ In the first case of COVID-19 in the United States, the patient presented with a two-day history of vomiting and nausea upon admission and diarrhea symptoms by the second day of hospitalization.¹³

Current study showed that most of the participants who developed diarrhea; was in

mild form. Mean duration of exposure to onset of diarrhea showed no statistical significant difference between the severe and non-severe groups. Considering twenty-six papers including 7860 patients with COVID-19 a meta-analysis showed mean duration of diarrhoea was 4.2 (3.6–4.9) days (range 1–16 days), whereas mean bowel movement count was 4.6 (3.8–5.3) and maximum was 20 per day. Diarrhea started on an average 5.1 (3.8–6.5) days after disease onset but was the first manifestation in 4.3% patients.²²

Dysgeusia was observed in 36.70% cases. In severe COVID-19 group, 33.3% developed dysgeusia and 40.0% of patients in non-severe COVID group without any statistically significant difference. The mean duration of exposure to development of dysgeusia was more in severe COVID-19 group comparing to non-severe COVID-19 group with a statistically significant difference. New loss of taste was not included as common symptoms of COVID-19 until March 2020 when the pandemic started in Western countries. It was interesting to know the prevalence of such symptoms and how they were related to disease severity and prognosis at that time. The pooled estimate for taste loss prevalence in COVID-19-positive patients following meta-analysis for the overall cohort was 36.90% (95% CI: 33.27–40.69%).²³

In our study, 71.8% of patients developed anorexia and 66.7% developed diarrhea in the severe COVID-19 group, whereas 70.0% of patients developed anorexia and 57.5% of patients developed diarrhea in the non-severe COVID-19 group. A study conducted by Elena Lak et al.,²⁴ showed 43% of hospitalized COVID -19 patients had at least one GI symptom. They found nausea was more prevalent GI symptom. In a study conducted by Redd et al.,²⁵ 61.3% of patients developed GI symptoms in COVID-19 patients. 34.8% of the patients experienced anorexia, while 33.7% experienced diarrhea. A study conducted by

Guan et al.,¹⁹ reported that 78.6% of patients developed anorexia in COVID-19 patients. During the original outbreak in Wuhan, diarrhea was reported in only 3% of cases.²⁶ This number increased to 10% in a subsequent study from Wuhan and 25% in a study from Singapore.²⁷

Similar to the current study, most of the studies revealed no association between GI symptoms and severity of COVID-19. This study showed that most of the participants who developed diarrhea were mild in severity.¹⁶ The mean duration of exposure to the onset of diarrhea showed no statistically significant difference between the two groups.

Both healthcare professionals and the general public should take into account the non-pulmonary effects and symptoms of the illness. Given that as many as 2% of cases present GI symptoms and no pulmonary symptoms²⁷, many mild cases may be missed because such patients do not associate their symptoms with COVID-19. Patients presenting without respiratory symptoms are still capable of spreading the infection, as demonstrated by the contribution of asymptomatic and pre-symptomatic transmission to COVID-19 spread.^{28,29}

Limitation

The hospital course and outcome of the patient are not mentioned in this study. Presence of SARS-CoV-2 viral load in the in the GI tract is not investigated.

Conclusions

Gastrointestinal symptoms are commonly found in COVID-19 patients. Anorexia and diarrhea were more prevalent in this study. But this study did not exhibit any association between GI symptoms and severity of COVID 19. Further large scale and multi-centered study is warranted to explore this association.

References

1. World Health Organization. COVID-19 weekly epidemiological update, edition 134, 16 March 2022.
2. Zhao N, Zhou ZL, Wu L, Zhang XD, Han SB, Bao HJ, Shu Y, Shu XG. An update on the status of COVID-19: a comprehensive review. *European Review for Medical & Pharmacological Sciences*. 2020 Apr 15; 24(8).
3. Groff A, Kavanaugh M, Ramgobin D, McClafferty B, Aggarwal CS, Golamari R, Jain R. Gastrointestinal manifestations of COVID-19: a review of what we know. *Ochsner Journal*. 2021 Jun 20; 21(2):177-80.
4. Wang MK, Yue HY, Cai J, Zhai YJ, Peng JH, Hui JF, Hou DY, Li WP, Yang JS. COVID-19 and the digestive system: A comprehensive review. *World journal of clinical cases*. 2021 Jun 6; 9(16):3796.
5. Tian Y, Rong L, Nian W, He Y. gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Alimentary pharmacology & therapeutics*. 2020 May; 51(9):843-51.
6. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020 Jul; 75(7):1730-41.
7. Fang D, Ma J, Guan J, Wang M, Song Y, Tian D, Li P. Manifestations of digestive system of hospitalized patients with coronavirus disease 2019 in Wuhan, China: a single-center descriptive study. *Chinese Journal of Digestion*. 2020:151-6.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Yu T. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in

- Wuhan, China: a descriptive study. *The Lancet*. 2020 Feb 15; 395(10223):507-13.
9. Liu J, Cui M, Yang T, Yao P. Correlation between gastrointestinal symptoms and disease severity in patients with COVID-19: A systematic review and meta-analysis. *BMJ Open Gastroenterology*. 2020; 7(1).
 10. Dhakal S, Charoen P, Pan-ngum W, Luvira V, Sivakorn C, Hanboonkunupakarn B, et al. Severity of COVID-19 in patients with diarrhoea: A systematic review and meta-analysis. *Tropical Medicine and Infectious Disease*. 2023; 8(2):84.
 11. Henry BM, de Oliveira MH, Benoit J, Lippi G. Gastrointestinal symptoms associated with severity of coronavirus disease 2019 (covid-19): A pooled analysis. *Internal and Emergency Medicine*. 2020; 15(5):857–9.
 12. Aumpan N, Nunanan P, Vilaichone R. Gastrointestinal manifestation as clinical predictor of severe covid-19: A retrospective experience and literature review of covid-19 in Association of Southeast Asian Nations (asean). *JGH Open*. 2020; 4(6):1096–101. doi:10.1002/jgh3.12394
 13. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*. 2020; 382(10):929–36. doi:10.1056/nejmoa2001191 Clinical management of COVID-19 n.d., World Health Organization, World Health Organization, viewed 17 July 2020, <https://www.who.int/publications/i/item/clinical-management-of-covid-19>
 14. Diarrhoeal disease. n.d., World Health Organization, World Health Organization, viewed 17 July 2020, <https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease>
 15. Aslam U, Bashir MK, Zafar N, Ali N, Siddique S, Basheer N. Comparison of Gastrointestinal Symptoms and Disease Severity in COVID-19 Patients. *Pakistan Journal of Medical & Health Sciences*. 2022 Jun 8; 16(05):303-8.
 16. Liu K, Chen Y, Lin R, Han K. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. *Journal of Infection*. 2020 Jun 1; 80(6):e14-8.
 17. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. *American Journal of Respiratory and Critical Care Medicine*. 2020; 201(11):1380–8.
 18. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 2020; 382(18):1708–20.
 19. van Doorn AS, Meijer B, Frampton CM, Barclay ML, de Boer NK: Systematic review with meta-analysis: SARS-CoV-2 stool testing and the potential for faecal-oral transmission. *Aliment Pharmacol Ther*. 2020; 52:1276-88.
 20. Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19) *ClinGastroenterolHepatol*. 2020; 18(7):1636–1637.
 21. Maslennikov R, Poluektova E, Ivashkin V, Svistunov A. Diarrhoea in adults with coronavirus disease—beyond incidence and mortality: A systematic review and meta-analysis. *Infectious Diseases*. 2021; 53(5):348–60.
 22. Hannum ME, Koch RJ, Ramirez VA, Marks SS, Toskala AK, Herriman RD, et al. Taste loss as a distinct symptom of

- covid-19: A systematic review and meta-analysis. *Chemical Senses*. 2022; 47.
23. Lak E, Sheikholeslami S, Ghorbi M, Shafei M, Yosefi H. Association between gastrointestinal symptoms and disease severity in patients with COVID-19 in Tehran City, Iran. *Gastroenterology Review/Przegląd Gastroenterologiczny*. 2022;17(1):52-8.
 24. Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, Shen L, Chan WW. Prevalence and characteristics of gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection in the United States: a multicenter cohort study. *Gastroenterology*. 2020 Aug 1; 159(2):765-7.
 25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The lancet*. 2020 Feb 15; 395(10223):497-506.
 26. Cheung KS, Hung IF, Chan PP, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TW, Tam AR, Yip CC. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. *Gastroenterology*. 2020 Jul 1; 159(1):81-95.
 27. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al.: Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Med*. 2020, 17:e1003346.
 28. Cevik M, Kuppalli K, Kindrachuk J, Peiris M: Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*. 2020, 371:m3862.