Bowel symptoms associated with coronavirus disease 19 in hospitalized patients with moderate to severe illness

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Abstract

Bowel symptoms, such as diarrhea, have higher prevalence during coronavirus disease 2019 (COVID-19). The correlation between the severity of these symptoms and their prognosis has not been defined yet. Furthermore, higher prevalence of gastrointestinal symptoms after recovery from COVID-19 has been reported. This study aimed to analyze the correlation of potential factors with the severity of diarrhea during COVID-19 and to assess the progression of post-COVID-19 bowel symptoms. This prospective longitudinal cohort included 109 patients with moderate to severe COVID-19 symptoms who were hospitalized from May to July 2021. Patients were interviewed to assess the presence and intensity of bowel symptoms during COVID-19 and 3–6 months after hospital discharge using the Gastrointestinal Symptom Rating Scale questionnaire. Demographic and clinical data were obtained and their correlations with the intensity of bowel symptoms were examined. The presence of severe diarrhea was correlated with the need for ventilatory support and the use of anticoagulants but not with the use of antibiotics. In addition, bowel symptoms, such as loose stools and incomplete evacuation but not diarrhea, constipation, or abdominal pain, persisted for at least 3–6 months after hospital discharge. These results suggest that the severity of diarrhea during COVID-19 may be associated with worsening of the disease and that only loose stools and incomplete evacuation are present after COVID-19. The chronicity of these bowel symptoms should be evaluated to improve the treatment of patients with COVID-19.

Keywords: Diarrhea; COVID-19; Constipation, Surveys and Questionnaires.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) pandemic, which was declared by the World Health Organization on March 11, 2020. SARS-CoV-2 primarily affects the respiratory system. However, gastrointestinal manifestations, such as nausea, vomiting, and diarrhea, are also common extrapulmonary symptoms of COVID-19.[1,2] During COVID-19, 15%–50.5% of patients develop intestinal manifestations such as diarrhea.[3,4,5,6,7]

Owing to the high prevalence of gastrointestinal symptoms, associations between these symptoms and a more severe clinical course of the disease have been investigated. Patients with severe COVID-19 reportedly have a higher risk of developing gastrointestinal symptoms,[5] and the presence of diarrhea is correlated with

the severity of respiratory symptoms,[6] indicating that diarrhea may be a risk factor for disease severity. In another study, however, there was no association between gastrointestinal symptoms and the clinical course of the disease.[8] In contrast, some studies showed that the presence of diarrhea appears to be associated with improved prognosis or a more indolent form of COVID-19.[2,3,9]

Furthermore, one of the hallmarks of COVID-19 is the persistence of post-infection gastrointestinal symptoms, as seen in 41% of post-COVID-19 patients.[10] These cases may be related to psychological changes along with intestinal microbiota disorders or persistent intestinal inflammation.[11,12,13] Therefore, the post-COVID-19 gastrointestinal effects after recovery require further investigation.

Since there is still no consensus in this regard and given the numerous ways in which gastrointestinal symptoms have been recorded in previous studies, it is necessary to evaluate these patients for a longer period using a standardized evaluation method. Among the existing tools used in the diagnosis of digestive diseases, the Gastrointestinal Symptom Rating Scale (GSRS),[14] which has been translated into Portuguese,[15] is considered the most appropriate instrument for assessing intestinal function. One of the main advantages of using GSRS is that the questions are always asked about the previous week, which is easy to understand and requires less time to complete.

Therefore, the present study aimed to analyze the correlation of potential factors with the severity of diarrhea in a prospective cohort of hospitalized patients with moderate to severe COVID-19 and to evaluate the progression of bowel symptoms using the GSRS questionnaire.

2. Methods

2.1 Study design

This prospective longitudinal cohort study was conducted at the ████████████████████ ████████████████████, where hospitalized patients were evaluated, recruited, and interviewed. This study was conducted in compliance with the principles of the Declaration of Helsinki. The study's protocol was revised and approved by the local ethics committee (opinion 4.510.094). Written informed consent was obtained.

2.2 Patients

The study population comprised 109 patients, including men and women, hospitalized from May to July 2021 with a diagnosis of COVID-19 confirmed by polymerase chain reaction in the ward of a ████ ████████████.

Individuals under 18 years and over 70 years of age and those with pathologies, such as obstructive pulmonary disease, peptic ulcer, gastric obstruction, and digestive tract neoplasia were excluded from the study population. We also excluded pregnant women and patients with incomplete medical records, chronic infectious diseases that may alter the functioning of the digestive tract, or cognitive impairment that make it difficult to collaborate with the study.

2.3 Data collection

The participants were interviewed using a validated questionnaire (GSRS)[15] to assess gastrointestinal symptoms. In the present study, bowel symptoms, such as flatulence, constipation, diarrhea, loose stools, urgency to defecate, feeling of not completely emptying the bowels when defecating, and abdominal pain, were measured on a scale of 1 to 7. On this scale, the patient scores each of the aforementioned symptoms using the following responses: 1) no discomfort/not once, 2) minimal discomfort/rarely, 3) mild discomfort/very few times, 4) moderate discomfort/few times, 5) moderately severe discomfort/sometimes, 6) strong discomfort/often, and 7) very strong discomfort/very often. In the present study, moderate to severe scores in the frequency range of rarely to very often were considered severe symptoms.[14]

Time-zero of this cohort study was recorded as the time of first application of the questionnaire (May to July 2021), during the period of hospital stay when the presence of symptoms before and during the infection was evaluated. A third application of the questionnaire was performed 3 to 6 months after hospital discharge.

Additionally, demographic and clinical data were obtained from the electronic medical records of the patients. The application of the questionnaire and collection of data from electronic medical records were performed by health professionals.

2.4 Statistical analysis

The results were analysed using the unpaired Student's *t*-test Wilcoxon test, and Kruskal–Wallis one-way analysis of variance test were performed as appropriate (Graph Pad Prism Software, San Diego, CA, USA). The results were considered statistically significant for p values < 0.05.

3. Results

3.1 Study patients

The average age of the patients interviewed in the present study was 50.4 years, with a majority of male patients; 57.8% of the participants were male and 42.2% were female (Table 1). More than 70% of the patients were previously diagnosed with chronic diseases, and systemic arterial hypertension was present in 37.6% of them. Regarding the need for ventilatory support, 60% of the patients used a nasal catheter or high-flow support, while 7% used mechanical ventilation and were admitted to the intensive care unit. In addition, approximately 62% of the respondents had a hospital stay of ≥ 8 days.

Table 1. Demographic and clinical characteristics of the study population

Potential covariants		Total
		n = 109
Sex	Men	63 (57.8%)
	Women	46 (42.2%)
Age		50.4 (13.7%)
Early gastric symptoms (nausea, vomiting, diarrhea)		56 (51.4%)

Bowel symptoms associated with coronavirus disease 19 in hospitalized patients with moderate to severe illness

Intensive therapy	8 (7.3%)
Ventilatory support	73 (67.0%)
Hospitalization time >8 days	68 (62.4%)
Chronic diseases	
Chronic diseases	80 (73.4%)
Diabetics	32 (29.4%)
Hypertensive	41 (37.6%)
Obesity	25 (22.9%)
Immunosuppressed (neoplasms, tx, autoimmune)	6 (5.5%)
Chronic respiratory diseases)	4 (3.7%)
Gastrointestinal diseases	8 (7.3%)
Medications used during hospitalization	
Antibiotics	101 (92.7%)
Anti-parasitic	48 (44%)
Anticoagulant	61 (56%)
Corticosteroid	54 (49.5%)
Continuous use medications	54 (49.5%)

Most patients were symptomatic and approximately half of them reported early gastrointestinal complaints, such as nausea, vomiting, and diarrhea (which was the most prevalent initial gastric symptom) (Fig. 1). Finally, among the medications used during hospitalization, antibiotics were the most prevalent, being prescribed to 92.7% of hospitalized patients.
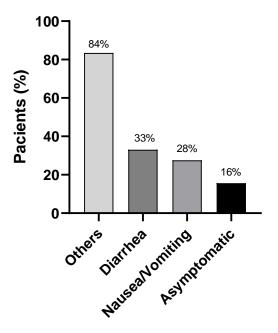

Figure 1. Initial symptoms in patients hospitalized with SARS-CoV-2 virus infection in 2021. Initial symptoms or their absence as reported by the study population. Other symptoms: fever (59%), cough (60.5%),

adynamia (71%), ageusia (36%), dysphagia (34%), coryza (27.5%), odynophagia (41%), dyspnea (60%), anosmia (33%), and headache (15.5%). SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

3.2 Prevalence of the use of ventilatory support in patients with severe diarrhea

The use of ventilatory support was greater in the group of patients with severe diarrhea during SARS-CoV-2 infection than in the group of patients without severe diarrhea (Table 2). In addition, more than 75% of the patients with severe diarrhea required anticoagulant use. In contrast, the need for antibiotic use was similar between patients with intense and non-intense diarrhea during the infection.

Table 2. Correlation of Potential factors with the severity of diarrhea in patients with COVID-19

Potential covariates	Total	Intense diarrhea	Without intense diarrhea	p-value
	n=109	n=17	n= 92	
Male	63 (57.8%)	13 (76.5%)	50 (54.3%)	0.07
Age, years	50.4	46.6	51.3	0.20
Early gastric symptoms (nausea, vomiting, diarrhea)	56 (51.4%)	11 (64.7%)	45 (48.9%)	0.35
Intensive therapy	8 (7.3%)	1 (5.8%)	7 (7.6%)	0.64
Ventilatory support	73 (67.0%)	16 (94.1%)	57 (61.9%)	0.01*
Chronic diseases	80 (73.4%)	12 (70.6%)	68 (73.9%)	0.49
Length of hospital stay >8 days	68 (62.4%)	9 (52.9%)	59 (64.1%)	0.27
Antibiotics use	101 (92.7%)	16 (94.1%)	85 (92.4%)	0.64
Anticoagulant use	61 (56%)	13 (76.5%)	48 (52.2%)	0.05*
Corticosteroid use	78 (71.5%)	7 (41.2%)	47 (51.1%)	0.31
Continuous use medications	54 (49.5%)	10 (58.8%)	44 (47.8%)	0.29

Age values: cell content represents mean (SEM) or frequency (%); Student's t test. Other covariates: cell content represents sample value or frequency (%.); Chi-square (Fischer's exact) test. Intensity of Diarrhea according to GSRS: Gastrointestinal Symptom Rating Scale. *$p<0.05$.

3.3 Analysis of the GSRS questionnaire

Regarding the data obtained through the GSRS questionnaire, it was observed that there was an increase in the incidence of diarrhea during the period of infection, but this symptom did not persist after the interviewees recovered. However, bowel movement did not return to the frequency reported before the infection (Fig. 2A). In contrast, complaints of passage of loose stools increased during the period of infection and persisted even after the patient recovered (Fig. 2B); however, abdominal pain remained a symptom of minimal discomfort that rarely occurred throughout the course of the disease and after recovery (Fig. 2C).

Bowel symptoms associated with coronavirus disease 19 in hospitalized patients with moderate to severe illness
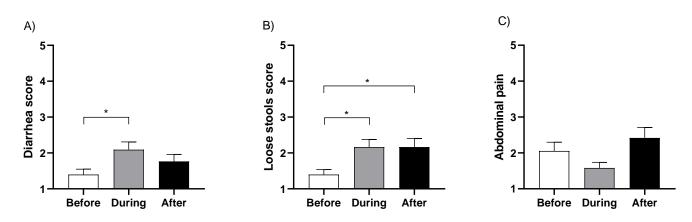

Figure 2. Intestinal symptoms over the course of COVID-19. Symptoms of diarrhea (A), loose stools (B), and abdominal pain (C) were investigated using the Gastrointestinal Rating Scale (GSRS) before, during, and after COVID-19. N = 55 per group. The values correspond to mean ± SEM of the rating scale. One-way ANOVA, Kruskal–Wallis test, *p < 0.05 *vs.* before. COVID-19, coronavirus disease 19; ANOVA, analysis of variance.

Constipation and flatulence scores did not show any changes during the study period. Indeed, among the patients interviewed (Fig. 3A and C), an increase in the feeling of incomplete bowel emptying was observed after the period of infection compared with that before and during the infection (Fig. 3B).
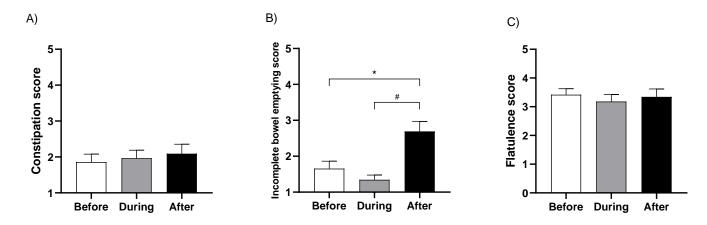

Figure 3. Evolution of the intensity and frequency of intestinal symptoms before, during, and after SARS-CoV-2 virus infection. Symptoms of constipation (A), incomplete bowel emptying (B), and flatulence (C) were investigated using the Gastrointestinal Rating Scale (GSRS). N = 55 per group. The values correspond to the mean ± SEM of the rating scale. One-way ANOVA, Kruskal–Wallis test, *p < 0.05 *vs.* before or #p < 0.05 *vs.* during. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ANOVA, analysis of variance.

4. Discussion

A growing body of evidence has demonstrated the relevance of digestive manifestations in patients with COVID-19. In particular, the frequency and intensity of intestinal symptoms indicate the susceptibility of the intestines to SARS-CoV-2 infection. Therefore, the present study aimed to analyze the correlation of potential factors with the severity of diarrhea during COVID-19 and to evaluate the progression of bowel

Bowel symptoms associated with coronavirus disease 19 in hospitalized patients with moderate to severe illness

symptoms after COVID-19 in a prospective cohort of patients with moderate to severe COVID-19 hospitalized in a Brazilian university hospital. The novelty and main findings of the present study were as follows: 1) the need for ventilatory support and use of anticoagulants, but not antibiotics, are related to severe diarrhea during COVID-19 and 2) bowel symptoms persisted after COVID-19, especially passage of soft stools and incomplete evacuation.

Overall, the hospitalized patients who participated in the study were mostly men and people with chronic diseases. In fact, evidence of sex differences in COVID-19 have shown that male patients seem to experience more severe outcomes than female patients, as observed in 37 of 38 countries evaluated[16] and in Brazil.[17] This greater severity has been attributed to a delay in viral clearance in men compared with that in women.[18,19] In fact, pre-existing chronic diseases, such as diabetes, hypertension, obesity, and coronary artery/cardiovascular disease, have been correlated with an increased risk of COVID-19 severity in different countries[20,21] as well as in Brazil.[17] The prevalence of ventilatory support use observed among patients in the present study is also in line with data previously found during the COVID-19 outbreak in 14 Chinese hospitals[6] and had also been verified during the SARS-CoV outbreak in 2003.[22] Most patients in the present study had a length of hospital stay of ≥8 days. Our data aligns with those of a previous study that observed a median hospital length of stay of 14 days in China and 5 days outside China.[23] Additionally, the use of corticosteroids and antibiotics, followed by the use of anticoagulants, were the most prevalent. Similar findings were observed in a study of patients with COVID-19 admitted to Brazilian hospitals with an antibiotic administration rate of 90%,[24] and in a review of 18 studies, 72% of patients were administered antibiotics.[25] Overall, these results confirm that the study population of COVID-19 in this study was similar to that reported in other studies.

Our analysis showed that diarrhea (33%) was the main gastrointestinal symptom in patients with COVID-19, followed by nausea/vomiting (28%). This result was also seen in a cohort carried out in 2020 involving 299 infected patients, of which 47% reported nausea, vomiting, and/or diarrhea, with diarrhea as the main symptom (39%), followed by nausea (25%) and vomiting (13%).[2] According to another study of 73 patients, the prevalence of diarrhea in the infected patients was up to 35.6%.[26] These findings are not consistent with those found in the past, as documented in Hong Kong during a SARS outbreak in 2003, wherein out of 138 patients, only 22.5% had nausea/vomiting and only 19.6% had diarrhea;[27] this can potentially be explained by the fact that these data are from outbreaks caused by different strains of viruses that evolved throughout the years. Furthermore, another analysis from February to August 2020 in a public hospital in Bandar Abbas, Iran, showed that out of the 507 COVID-19 patients, 47.9% had at least one gastrointestinal symptom.[28] In a cohort study carried out in Italy, diarrhea was also the most frequent intestinal symptom in patients, affecting 27.1% of them,[9] as well as in a Southern US population in which diarrhea was present in 28.3%, nausea and/or vomiting in 23.1% and abdominal pain in 8.8% patients.[7] Therefore, this change in symptom prevalence could indicate a difference in viral tropism stemming from new strain mutations compared with the pandemic that started in 2019 with previous outbreaks.[29]

The results of the present study also showed that potential severity variants, such as the use of ventilatory support and anticoagulants, were correlated to the group of patients with severe diarrhea. In this sense, a study evaluating the enteric implication in hospitalized patients with COVID-19 outside of Wuhan

showed that diarrhea may be a risk factor for the severity of the disease.[6] Thus, severe COVID-19 is associated with changes in the compositional alterations of the gut microbiome, disrupted intestinal barrier integrity, mucosal inflammation impact on the function of the enteric nervous system, and the activation of sensory fibers conveying information to the central nervous system and its contribution to the severity of COVID-19.[30] In agreement with these data, a meta-analysis conducted recently suggested that digestive symptoms are not uncommon and that those with severe COVID-19 have a higher risk of developing gastrointestinal symptoms.[5] However, according to Aghemo et al. (2020),[9] among the admission parameters analyzed, the presence of any gastrointestinal symptoms (such as diarrhea or vomiting) was significantly associated with delayed intensive care unit transfer or death. Contrary to previous evidence, another study found that when comparing the severity of COVID-19 in patients with and without gastrointestinal symptoms, moderate heterogeneity was evident with no statistical difference between the two groups, indicating no significant correlation between gastrointestinal symptoms and disease severity in patients with COVID-19.[31] One possible reason for the apparent discrepancy between the findings of the present study and those of other studies could be the method used to measure the presence of gastrointestinal symptoms in the present study. In the present study, the GSRS was used because it is the most appropriate instrument for assessing intestinal function as it is easier to understand and requires less time to complete.[14]

Regarding the post-COVID-19 period, the normalization of diarrhea symptoms was observed 3–6 months after the end of the disease. The present findings are in accordance with the literature, as demonstrated by Aiyegbusi et al. in 2021[32] that only 6% of individuals who had chronic COVID-19 symptoms (lasting longer than 4 weeks) also reported persistent diarrhea. One possibility is that after the end of COVID-19, there was no persistence or emergence of gastrointestinal symptoms; however, this was not the case. In the present study, despite recovering from diarrhea, passage of loose stools persisted even after the infection had ceased.

Such an occurrence could be associated with an increase in functional diseases of the digestive tract such as irritable bowel syndrome, a functional gastrointestinal disorder characterized by symptoms including abdominal pain associated with a change in stool frequency or consistency.[33] However, this hypothesis does not seem likely because the scores for abdominal pain did not show a notable difference over the course of the disease. In addition, COVID-19 can cause harmful and persistent changes in the gut microbiota, with an increase in the amount of opportunistic pathogens and a decrease in beneficial commensals; these changes are associated with greater disease severity.[34,35] Thus, it is possible that the alterations in the microbiota or even the intestinal absorptive capacity of infected individuals are responsible for altering the consistency of feces. Further studies are needed to directly correlate these findings.

Regarding the sensation of incomplete evacuation, the present study observed for the first time that there was a significant increase in the intensity and frequency of this symptom after the COVID-19 period. We speculate that this finding may be due to an increase in stool consistency or the degree of evacuation difficulty. Regarding constipation, our study demonstrated that there was no increase in this symptom during or after COVID-19. These data are in line with those of other published studies.[36] Therefore, at first, it may seem contradictory that incomplete evacuation is also associated with the presence of soft stools in the same study population; however, the difficulty of elimination in this case is possibly also associated with evacuation

capacity and anorectal motor disorders and not only with the consistency of the stools.[37] In this sense, one can hypothesize the existence of neurogenic bases to explain gastrointestinal dysmotility in COVID-19; however, specific data were unavailable at the time of publication.

A close correlation between affective disorders, such as anxiety, and functional gastrointestinal disorders is well known, especially when the gastrointestinal symptoms are more severe.[11] Therefore, the pathophysiologic and psychosocial mechanisms surrounding anxiety could explain the gastrointestinal repercussions of COVID-19. Nevertheless, determining the chronicity of post-infectious dysmotility is an important topic to consider because the emergence of this condition can directly and permanently affect the patient's quality of life.[38]

The findings of this study should be interpreted in the context of certain limitations. Our study was limited by the small sample size (109), 55 of whom were evaluated during the post-infection period. In addition, data were obtained from only one medical center. Furthermore, there is a lack of evaluation methods for motor disorders, dysmotility, gut microbiota, and anxiety.

5. Conclusion

In summary, our data showed that the presence of severe diarrhea was correlated with the need for ventilatory support and the use of anticoagulants but not with the use of antibiotics, in hospitalized patients with moderate to severe COVID-19. These results suggest that the severity of enteric symptoms may be associated with worsening of the disease. Furthermore, we clearly showed for the first time that bowel symptoms, such as loose stools and incomplete evacuation, persist after hospital discharge and 6 months of recovery. Thus, from these results, one can understand the importance of evaluating the chronicity of these enteric alterations after COVID-19 and of studying the underlying pathophysiological mechanisms as this will aid in the development of novel intervention strategies that can reduce or prevent severe outcomes of COVID-19.

6. Acknowledgments

7. Author Contribution

Conceptualization: SMP, MHLPS.

Methodology: SMP, LGMS, DSLLF, RRCS, ICB, DVA, SSM, MHLPS.

Project administration: SMP, MHLPS.

Visualization: SMP, LGMS, DSLLF, MÂNS, MHLPS.

Writing-original draft: SMP, DSLLF, ICB, DVA, SSM, MHLPS.

Writing-review and editing: SMP, MÂNS, MHLPS.

Approval of final manuscript: all authors.

8. Conflict of Interest

The authors have no conflicts of interest to declare.

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