

Gastrointestinal Symptoms in Patients with COVID-19

Mohammed Abbas^{1*}; Rafik ElBeblawy¹; Islam Gadelmoula¹; Suvarna Rekha²; Bettina Sinanova²; Jose Bordon^{1,2}

¹Center of Excellence for Research in Infectious Diseases, Division of Infectious Diseases, University of Louisville School of Medicine, Louisville, KY, USA; ²Washington Health Institute, Washington, D.C., USA

*mka.abbas@louisville.edu

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Abstract

Introduction: Though coronavirus disease 2019 (COVID-19) is predominantly a respiratory illness, a growing number of studies reported gastrointestinal (GI) symptoms among these patients. We examined the incidence of GI symptoms in patients with COVID-19 and GI symptoms as the initial presentation of the disease.

Methods: We examined peer-reviewed studies in English of patients with COVID-19 that reported GI symptoms. We searched PubMed and Google Scholar for articles published up to June 30, 2020, by using the keywords "COVID-19," "Coronavirus," "severe acute respiratory syndrome coronavirus 2," "SARS-CoV-2," "gastrointestinal tract," "gastrointestinal diseases," and "gastrointestinal symptoms and signs." Studies with fewer than 30 patients and also those studies that did not report nausea, vomiting, and diarrhea were excluded.

Results: We reviewed 26 studies that reported GI symptoms among patients with COVID-19. Twenty-three studies were from China, and the three remaining studies were from three different countries: the US, France, and South Korea. The mean age of patients was 47.2 years, and 50.3% were females. Out of a total of 7,212 patients, 672 patients had nausea and/or vomiting (8.7%), and 732 (9.5%) had diarrhea; 6.8% of patients had GI symptoms as the initial presentation of COVID-19.

Conclusion: GI symptoms are not common in COVID-19 patients. However, the recognition of GI symptoms may significantly help in implementing steps to prevent SARS-CoV-2 transmission. Testing for COVID-19 in patients presenting with only GI symptoms may help detect and prevent the spread of COVID-19.

Introduction

COVID-19 has been reported primarily as a respiratory illness, however patients with COVID-19 also have GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain.[1, 2] Interestingly the first case of COVID-19 reported in the US developed vomiting and diarrhea 4-6 days after the onset of the fever and respiratory symptoms.[3] Subsequent stool tests detected SARS CoV-2. The GI tract is the target of the SARS-CoV-2 given that the cell membrane angiotensin-converting enzyme 2 (ACE-2); which is the SARS CoV-2 receptor, is present in the enterocytes of the small and large intestine.

A recent systematic review from studies published until March 30, 2020 reported that 12% of patients with COVID-19 have GI symptoms.[4] There is a growing literature of COVID-19 associated with GI involvement and many questions with pending answers. There is a need for the clinical characterization of the GI symp-

toms of patients with COVID-19. In this regard, it remains to be determined the severity, incidence and types of presentations of the GI symptoms among patients with COVID-19. A characterization of the GI symptoms of patients with COVID-19 will guide physicians to deliver the optimal medical management of these patients.

In an effort to characterize the GI clinical symptoms of patients with COVID-19, we reviewed the English literature to determine the incidence of GI symptoms of patients with COVID-19 and to determine how many patients presented initially with GI symptoms only or the GI symptoms associated with other symptoms.

Methods

Review design

This was a secondary analysis of studies published in English language of peer-reviewed journals on COVID-19 associated with GI symptoms.

Database search strategies

We searched PubMed and Google Scholar for articles up to June 30, 2020. We used the following keywords in our search, ‘COVID-19’, ‘Coronavirus’, ‘SARS-CoV-2’, ‘gastrointestinal tract’, ‘gastrointestinal diseases’, ‘gastrointestinal symptoms and signs’.

Inclusion criteria

Peer review studies on COVID-19 that reported GI symptoms in the English language.

Exclusion criteria

Scientific studies with a patient count below 30 and those studies that did not report nausea, vomiting, and diarrhea.

After reviewing the articles, we included 26 studies for analysis. Institutional review board approval was not required given this study did not involve direct human participant research.

Results

Studies included in the review

A total of 26 studies reported GI symptoms among patients with COVID-19 (Table 1).[5-30] Twenty-one studies were not included according to the exclusion criteria. All included studies were retrospective or case series. Twenty-three studies were from China and the 3 remaining studies were from three different countries: US, France and South Korea. The mean age of patients was 47.2 years and 50.3% were female.

Table 1. Characteristics of COVID-19 positive cases and deaths from COVID-19 in Jefferson County (KY) as of May 6th, 2020.

Study	Characteristics	Nausea and vomiting (%)	Diarrhea (%)
Guan <i>et al.</i> [5] N Engl J Med China, <i>n</i> =1,099	Median age: 47.0 years [IQR 35, 58] Females 49.1%	55 (5)	42 (3.8)
Pan <i>et al.</i> [6] Am J Gastroenterol China, <i>n</i> =204	Mean age: 52.9 years (SD 16) Females 47.5%	4 (2)	35 (17.1)
Zhou <i>et al.</i> [7] N Engl J Med China, <i>n</i> =149	Median age: 56.0 years [IQR 46.0, 67.0] Females 38%	7 (3.7)	9 (4.7)
Lu <i>et al.</i> [8] N Engl J Med China, <i>n</i> =171	Median age: 6.7 years (Range 1–15) Females 39.2%	11 (6.4)	15 (8.8)
Yang <i>et al.</i> [9] J Infect China, <i>n</i> =149	Mean age: 45.1 years (SD 13.35) Females 45.6%	11 (7.4)	2 (1.3)
Zhang <i>et al.</i> [10] Allergy China, <i>n</i> =140	Median age: 57.0 years (Range 25–87) Females 49.3%	31 (22.1)	18 (12.9)
Wang <i>et al.</i> [11] JAMA China, <i>n</i> =138	Median age: 56.0 years [IQR 42, 68] Females 45.7%	19 (13.8)	14 (10.1)

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Abbreviations: IQR, interquartile range; SD, standard deviation.

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Liu <i>et al.</i> [12] Chin Med J (Engl) China, n=137	Median age: 57.0 years (Range 20–83) Females 55.5%	0 (0)	11 (8)
Zhao <i>et al.</i> [13] AJR Am J China, n=101	Median age: 43.0 years (Range 17–75) Females 46.6%	2 (2)	3(3)
Chen <i>et al.</i> [14] Lancet China, n=99	Mean age: 55.5 years (Range 21–82) Females 32.3%	1 (1)	2 (2)
Xu <i>et al.</i> [15] Eur J Nucl Med Mol Imaging China, n=90	Median age: 50 years (Range 18–86) Females 57%	7 (7.8)	5 (5.6)
Shi <i>et al.</i> [16] Lancet Infect Dis China, n=81	Mean age: 49.5 years (Range 25–81) Females 48%	4 (4.9)	3 (3.7)
Wu <i>et al.</i> [17] Clin Infect Dis China, n=80	Median age: 46.1 years (SD 15.42) Females 51.3%	1 (1.3)	1 (1.3)
Chen <i>et al.</i> [18] J Med Virol China, n=42	Median age: 51 years [IQR 42.75, 62] Females 64.3%	7 (16.7)	7 (16.7)
Wei <i>et al.</i> [19] Clin Gastroenterol Hepatol China, n=84	Median age: 37 years (Range 24–74) Females 66.7%	22 (26.2)	26 (31)
Lin <i>et al.</i> [20] Gut China, n=95	Mean age: 45.3 years (SD 18.3) Females 52.6%	21 (22.1)	23 (24.2)
Song <i>et al.</i> [21] Radiology China, n=51	Mean age: 49.0 years (Range 16–76) Females 51%	3 (5.9)	5 (9.8)
Han <i>et al.</i> [22] Am J Gastroenterol China, n=206	Mean age: 62.5 years (Range 27–92) Females 55.8%	24 (11.7)	67 (32.5)
Nobel <i>et al.</i> [23] Gastroenterology USA, n=278	Females 48%	63 (22.7)	56 (20.1)
Luo <i>et al.</i> [24] Clin Gastroenterol Hepatol China, n=1,141	Females 44%	204 (17.9)	69 (6)
Jin <i>et al.</i> [25] Gut China, n=651	Mean age: 46.1 years (SD 14.19) Females 50%	21 (3.2)	53 (8.1)
Park <i>et al.</i> [26] Clin Gastroenterol Hepatol Korea, n=46	Median age: 26 years (Range 18–57) Females 54%	1 (2.2)	7 (15.2)
Lian <i>et al.</i> [27] Influenza Other Respir Viruses China, n=465	Median age: 45 years (Range 5–88) Females 47.7%	22 (4.7)	36 (7.7)

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Abbreviations: IQR, interquartile range; SD, standard deviation.

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Klopfenstein <i>et al.</i> [28] Clin Res Hepatol Gastroenterol France, <i>n</i> =114	Median age: 56 years (SD 18) Females 58%	34 (29.8)	55 (48.2)
Zhang <i>et al.</i> [29] Dig Liver Dis China, <i>n</i> =504	Mean age: 51.2 years (SD 17.2) Females 54.9%	40 (7.9)	62 (12.3)
Zheng <i>et al.</i> [30] J Med Virol China, <i>n</i> =1,320	Median age: 50 years [IQR 40, 57] Females 56.1%	57 (4.3)	107 (8.1)
Total <i>n</i> =7,212	Females 50.3%	672 (8.7)	732 (9.5)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Incidence of GI symptoms among patients with COVID-19

The total patient count from all studies was 7,212. Out of all patients, 672 had nausea or/and vomiting (8.7%) and 732 (9.5%) patients had diarrhea.

Characterization of GI symptoms among patients with COVID-19

The most common GI symptoms were nausea or/and vomiting 8.7 %, and diarrhea 9.5 %. Other symptoms such as anorexia, constipation, and abdominal pain were rarely mentioned and therefore not included in our study.

Percentage of patients initially presenting with GI symptoms only

Our review revealed that 6.8% of patients had GI symptoms as the only or initial presentation of COVID-19 (**Table 2**).

Included studies that reported GI symptoms among patients with COVID-19.

This review included 26 studies of patients with COVID-19 and GI symptoms published up to June 30, 2020. Most of the studies were from China and had a relatively small number of patients. A similar review to ours included 29 studies published until March 30, 2020.[4] Preprint publications were not included in our review. In an effort to maximize the data quality, our review included only peer reviewed articles in English.

Incidence of GI symptoms in COVID-19 patients and its significance.

Our study examined 1,404 patients (19.5%) with GI symptoms from a total of 7,212 patients with documented COVID-19. Furthermore, our study revealed an incidence of 8.7% of nausea/vomiting and 9.5% diarrhea among patients with COVID-19. There has been

a wide variation in the percentages of these symptoms in different studies. Parasa *et al.* reported an incidence of nausea and vomiting of 4.6% and diarrhea 7.4%.[4] The variation of incidence of the nausea, vomiting and diarrhea could be due to many factors such as failure to report these symptoms in the early months of the pandemic by patients and healthcare workers, the novelty of the disease, and lack of awareness of the possible relationship between GI symptoms and the COVID-19. Overall, GI symptoms in COVID-19 were not common.

Discussion

The presence of GI symptoms among COVID-19 patients can be explained by two mechanisms. First, the GI tract is abundant with ACE-2 receptors to which the virus binds and enters the cell.[31] This is similar to how the virus binds to the respiratory tract where it multiplies and causes symptoms.[10] This mechanism suggests that the virus may cause acute gastritis and/or enteritis, resulting in nausea, vomiting, and diarrhea.[25] The second mechanism is a recent theory, through the ‘Gut-Lung Axis’.[32, 33] Normally, the change in the microbiota and immune regulation of the digestive tract causes an indirect dysregulating effect on the respiratory tract and thus leads to lung infection. However recently, a study suggested that this axis could be bidirectional.[34] This means that lung microbiota may affect the gut microbiota composition, therefore leading to GI symptoms (**Figure 1**).

Another important observation seen in COVID-19 patients is that they can present with GI symptoms initially before the respiratory symptoms (**Table 2**). Therefore, it is important to report and inquire about GI symptoms to help identify infection and control the spread of the disease. Patients with GI symptoms should be isolated and tested for COVID-19 by polymerase chain reaction (PCR) from a respiratory swab. There is also evidence for fecal viral shedding in pa-

Table 2. Number of COVID-19 cases presented initially with gastrointestinal symptoms only.

Study	Characteristics	Gastrointestinal symptoms (%)
Pan <i>et al.</i> [6] Am J Gastroenterol China, n=204	Mean age: 52.9 years (SD 16) Females 47.5%	6 (2.9)
Wang <i>et al.</i> [11] JAMA China, n=138	Median age: 56.0 years [IQR 42, 68] Females 45.7%	14 (10.1)
Liu <i>et al.</i> [12] Chin Med J (Engl) China, n=137	Median age: 57.0 years (Range 20–83) Females 55.5%	11 (8)
Chen <i>et al.</i> [14] Lancet China, n=99	Mean age: 55.5 years (Range 21–82) Females 32.3%	3 (3)
Lin <i>et al.</i> [20] Gut China, n=95	Mean age: 45.3 years (SD 18.3) Females 52.6%	11 (11.6)
Total n=673		45 (6.7)

Abbreviations: IQR, interquartile range; SD, standard deviation.

tients with COVID-19.[18, 22, 35] At this point, the stool testing for SARS CoV-2 may help with the early detection of COVID-19 patients presenting only with GI symptoms.

It is recommended that awareness is raised among healthcare workers and the general public regarding the important relationship between GI symptoms and COVID-19. To help make sure that an individual does not transmit the disease, people with these symptoms are advised to seek medical attention for appropriate evaluation and treatment. PCR testing of patients with just GI symptoms for COVID-19 using respiratory swabs may also help with early detection of the disease and reduce the risk for disease spreading. Although PCR testing of stool samples is not approved yet, it could be used as another option for screening. Even when there are no risk factors, patient-isolation for a few days could be beneficial until the test results are available, or the patient develops upper respiratory symptoms. To have a clearer picture, healthcare personnel need to document GI symptoms for COVID-19 patients whether at presentation or throughout the disease course. Special precautions should be extended

to all individuals dealing with stool from patients with COVID-19.

Our review has some strengths and limitations. Some of the strengths are the inclusions of peer reviewed studies in English and inclusion of publications up to June 30, 2020. In relation to the limitations, most of these studies were predominantly from China and the relatively small number of patients per studies. Therefore, these results cannot be used to represent the worldwide population. In addition, only a handful of studies mentioned the patients that presented initially with GI symptoms only.

In conclusion, GI symptoms are not common in COVID-19 patients and the recognition of these symptoms may significantly help in implementing steps for preventing disease transmission. It is essential to share this knowledge among the community, encourage the reporting and documentation of these symptoms. Testing for COVID-19 in patients presenting with GI symptoms only may help detect and prevent spreading of the disease. More studies are needed to capture targeted data so that more accurate and precise outcomes can be drawn.

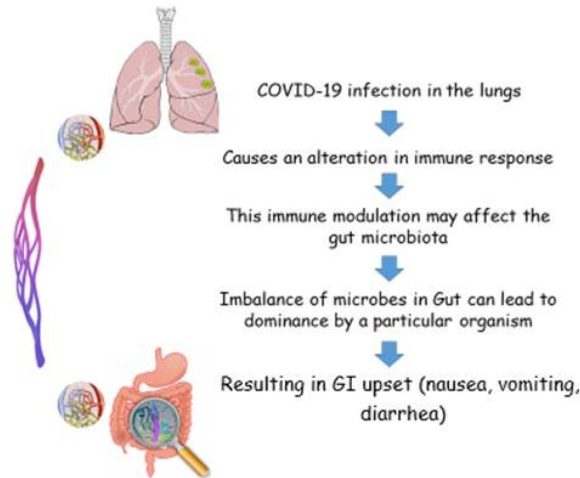


Figure 1. Proposed bidirectional gut-lung axis.

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