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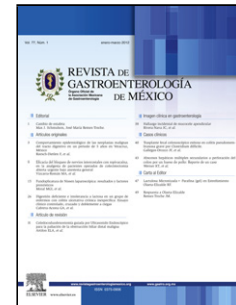
Beware: Gastrointestinal symptoms can be a manifestation of COVID-19

Max Schmulson MD, RFF Dr Fernanda Dávalos Jaime Berumen

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Background

The coronavirus disease-2019 (COVID-19) pandemic, the clinical name of the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection,[1] has been confirmed in 1,237,420 cases worldwide with 67259 deaths.[2] and the disease has hit Mexico over the last three weeks. As of today, April 5th-2020, 2143 cases have been confirmed in our country, 94 reported deaths, and 5209 patients are currently under observation as suspicious cases.[3] Although this viral infection is mainly manifested with fever, dry cough and shortness of breath,[4] we as clinicians and gastroenterologists need to learn from the experience in other countries such as China and be aware that gastrointestinal manifestations, despite infrequent, can be present in the course of the clinical scenario of this infection.[4] Therefore, our aim was to review the recent publications on COVID-19 to learn about the gastrointestinal manifestations of this infectious disease.

Methods

A search was conducted in Medline using the words COVID-19 AND Gastrointestinal symptoms: AND with specific symptoms including Diarrhea; Nausea; Vomiting; Abdominal Pain; Belching; Anorexia. Afterwards, we combined the descriptor COVID-19 AND China; South Korea; Italy; Europe; North America; United States. The review was conducted by two reviewers (MS and MFD). Only full papers published in English were selected. In addition, the search was complemented with other references cited in our identified papers. Reported prevalence of gastrointestinal symptoms in patients with COVID-19, were summarized. We extracted the country from which the cases were diagnosed; the number of patients that were analyzed; the age in median and range and in the papers that did not report median and from which we could not calculate this central tendency measure, the mean is reported; sex percentages; and the number and percentage of total gastrointestinal symptoms if they were reported, as well as the number and percentage of patients reporting the above mentioned individual symptoms. We also review GI symptoms as atypical presentations of COVID-19, relationship to patient prognosis, and with epidemiological factors such as exposure to the Huanan seafood market, if

these were reported. Considering that the majority of the studies were published between December 2019 and April 2-2020, we organized the Table results in alphabetical order of the Surname of the first author.

Results

A total of 15 papers that analyzed the clinical experience with the COVID-19 infection that also reported the presence of gastrointestinal symptoms, were identified.[5-19] Thirteen papers were from China,[5-13, 15-17, 19] one from Singapore,[18] and one from the World Health Organization European Region.[14] (Table 1) These papers analyzed a total of 2800 patients. Of them 210 (7.5%) reported diarrhea, 125 (4.5%) nausea, 124 (4.4%) anorexia, 15 (0.5%) abdominal pain, 9 (0.3%) belching and reflux, and 7 (0.25%) patients from one study reported a combination of different symptoms (i.e. diarrhea, vomiting, nausea). It is important to mention that a total of 37 (1.3%) patients reported vomiting, but in two of the papers nausea and vomiting were grouped together (56 patients).[6, 8] The sex distribution of the patients with COVID-19 that presented GI symptoms, seems to be equally distributed as half of the patients were women and half men and no differences in GI symptoms according to sex were reported.

Some details of these studies deserve to be commented, especially in relation to the characteristics of the GI symptoms and their presence as atypical manifestations, epidemiological associations, their moment of onset and relationship to COVID-19 prognosis. For example, in a retrospective case-series of 138 hospitalized patients in Wuhan-China by Wang D et al, although fever was the most common symptom (98.6%), followed by fatigue (69.6%) and dry cough (59.4%), gastrointestinal symptoms were less common, including diarrhea that was present in 10.1% of the cases, and in a much lower frequency, nausea, vomiting and abdominal pain.[15] In the first report of COVID-19 from the WHO European Region, a low frequency of gastrointestinal symptoms was also found.[14] In contrast, among 140 cases also from Wuhan, Zhang J-J et al, reported a higher frequency (39.6%) of gastrointestinal symptoms. In their series, nausea was the most common symptom while the frequency of diarrhea was very similar (12.9%).[19] Another

study from the province of Zhuhai in China, GI symptoms were present in 11.6% of the cases, with diarrhea (24.2%) and anorexia (17.9%), being the most common ones.[11] **(Table)**

In addition, GI symptoms as atypical manifestations of COVID-19 should be considered. For example, the report of Pan L that 7% of their patients presented only with digestive symptoms,[13] and Huang C et al and Liu K et al, in which 2% and 25% did not present fever, attest to this regard.[9, 12] As for the moment of onset of GI symptoms, in the case-series from Zhuhai, province of Guandong in China, among the 61.1% of their 95 patients with GI symptoms, in 19% these symptoms were present on admission, while in the remaining 81%, the symptoms developed during the hospital stay.[11] In the 651 cases from the province of Zhejiang in China, the onset of the GI symptoms was not reported, however, the median duration of diarrhea was four days, ranging from one to nine days. And in the majority of the cases, was self-limited.[10]

In terms of epidemiological factors related to the presence of GI symptoms, Chen N et al, reported that 49% of their 99 patients had a history of exposure to the Huanan seafood market, from where the first cases of COVID-19 appeared to raise.[6] However, they did not report if this epidemiological factor was related or not with the presence of gastrointestinal symptoms or any other clinical manifestation. In the series by Huang C et al, 66% of the patients also had direct exposure to Huanan seafood market. Notwithstanding, neither was this factor analyzed in relation to the prevalence of symptoms. They only compared the symptoms according to hospitalization in the ICU or not, without finding any difference in the prevalence of diarrhea.[9] In the previously mentioned Zhejiang study, the history of presence in Wuhan or contact with other patients with COVID-19, was not different among patients with or without GI symptoms, however family clustering was significantly higher among patients with those symptoms.[10]

In relation to the patients prognosis according to the presence or not of GI symptoms, Wang D et al compared the frequency of gastrointestinal symptoms between patients hospitalized in the intensive care unit (ICU) or not, without finding any difference, except for abdominal pain that was more common in the first ones (8.3% vs 0, p=0.02).[15] In agreement with this finding, among the first 18 hospitalized patients with transcriptase–polymerase chain reaction (RT-PCR)-

confirmed SARS-CoV-2 in Singapore, three patients reported diarrhea, and none of them required supplemental oxygen.[18] Also, Lin L et al, did not find any difference in clinical outcomes such as hospital stay, discharge or mortality among those with or without GI symptoms in a series of patients from the province of Zhuhai-China.[11] The above two case-series possibly suggest a milder outcome in patients without digestive symptoms such as abdominal pain and diarrhea.[15, 19] In contrast, other studies have reported different outcomes. Pan L et al found that 48.5% presented to the hospital with digestive symptoms as their main complaint. These patients had a significantly longer time from onset to admission than those without digestive symptoms (9.0 vs. 7.3 days), and seven patients only reported digestive symptoms without respiratory ones.[13] Also, digestive symptoms became more evident as the severity of the disease, increased; and those without GI symptoms were twice as likely to be cured and discharged than those with GI symptoms (60% vs. 34.3%).[13] Jin X et al, in Zhejiang, reported that almost 23% of patients with GI symptoms, had a severe or critical type of illness, and the presence of acute respiratory distress syndrome as well as the need for mechanical ventilation, were significantly more frequent among those with GI symptoms compared to those without them.[10] In another case-series from Wuhan-China, among 52 critically ill patients with SARS-CoV-2 pneumonia, two cases reported diarrhea, one among survivors and one in the non-survivor group.[17] Furthermore, in the largest study, so far published, among 1099 hospitalized patients at 552 sites in China, diarrhea was the only GI symptom described, with a low 3.8% prevalence.[8] Their primary endpoint was admission to an intensive care unit (ICU), the use of mechanical ventilation, or death. They did not report whether diarrhea was different according to these endpoints. However, the Authors recognized that in 291 patients there was recall bias which could have affected their results.[8]

Discussion

We have summarized all papers that have reported gastrointestinal symptoms among patients with COVID-19 disease, up till April 2, 2020. The majority of the studies (87%) came from China, [5-13, 15-17, 19] with one from Singapore[18] and only one small series from Europe.[14] The frequency of GI symptom varied widely from 3.0 to 39.6% in the reviewed studies, with diarrhea

being the most frequently reported. However, because the majority of the studies are retrospective, recall bias may have been a factor for this low prevalence. In addition, because the pulmonary-related symptoms are the most important ones in terms of survival of these patients, the majority of the analyses and patient charts, may have been biased towards collecting information regarding the respiratory manifestations and not of other systems such as the GI symptoms. Notwithstanding, the fact that in some cases, GI symptoms were the only ones or the first clinical manifestation even before fever and respiratory symptoms, healthcare providers need to be alert when consulting these patients in current times under this pandemic.[13, 17] In addition, the reports in the literature from gastrointestinal symptoms is mainly from hospitalized patients, and information regarding milder outpatients, is lacking.[8] Also, to the best of our knowledge, there are no published reports about the presence of GI symptoms in patients with COVID-19 in Mexico, only the personal experience of those of us that have already diagnosed some cases with this pandemic, whom presented GI manifestations. Therefore, we need to be aware of this possibility.

The underlying explanation for gastrointestinal symptoms among patients infected with SARS-CoV-2 that developed COVID-19 disease, needs to be address. It has been reported that the angiotensin-converting enzyme 2 (ACE2) is the main host cell receptor of the novel 2019 coronavirus SARS-CoV-2, and plays a crucial role in the docking and entry of the virus into the cell.[20] These receptors have been identified in type II alveolar cells of the lung, the stratified epithelial cells of the esophagus, the enterocytes from ileum and colon and cholangiocytes, as well as myocardial cells, kidney proximal tubule cells, and bladder urothelial cells.[20-22] More recently, it has been demonstrated that ACE2 is expressed on the mucosa of the oral cavity and was highly enriched in the epithelial cells of the tongue.[23] Thus, the oral cavity and digestive tract may be a rout of infection and the expression of the ACE2 in the digestive tract may explain why digestive symptoms may occur in patients with COVID-19. Furthermore, SARS-Cov-2 viral nucleic acids have not only been found in respiratory samples but also in saliva and stools.[18, 24] For example, Zhang JC reported that the nucleic acid detection of COVID- 19 in fecal specimens

was equally accurate than pharyngeal swab specimens, and patients with a positive stool test did not experience gastrointestinal symptoms.[25] In fact, in the Singapore series, the virus was detected in stools of four out of eight patients that were tested, regardless of the presence of diarrhea.[18] In addition, in another study, the presence of viral RNA in the feces was not related to the presence or severity of GI symptoms.[11] Also, a positive stool test was not related to the severity of the lung infection.[25] Of more importance is the fact that a group from China found that in more than 20% of the patients infected with SARS-Cov-2 that had a negative conversion of the viral RNA in the respiratory tract, the viral RNA was still present in the stools.[26] These evidences support a fecal-oral transmission of the SARS-CoV-2, which deserves further investigations.[24]

Another important issue to highlight is the recent finding reported by Lin et al, of the presence of herpetic-type erosions and ulcers localized in the esophagus as source of GI bleeding in one of their patients, with detection of SARS-Co-V-2 RNA in these erosions.[11] The viral RNA was also detected in biopsies of the esophagus, stomach, duodenum and rectum in two other patients without endoscopic lesions, suggesting that the virus can be docked in the digestive tract.[11]

Despite all of the digestive findings in relation to coronavirus, as of today, there are no guidelines for the diagnostic approach in the presence GI symptoms under the COVID-19 pandemic, nor for their treatment. Currently there are only preventive measures that should be considered in endoscopy units[27, 28] which are beyond the scope of the current review but that can be summarized as delaying elective procedures for eight weeks, the implementation of a pre-procedural triage, and regarding the use of personal protective equipment (PPE) in case there is a time sensitive endoscopic procedure that needs to be performed.[29] Neither have there been found differences in inflammatory markers such as C reactive protein and procalcitonin among patients with COVID-19 with or without GI symptoms.[10] The most important issue still remains to be for physicians and care givers to be alert on the possibility that patients may be having this infection. However, the possibility of fecal-oral transmission may have implications for preventive measures. On the one hand, aerosols can be generated from the toilet flushing with the possibility

of fomite transmission.[30] On the other hand, GI symptoms have been related to family clustering as it was previously described.[10] Therefore, toilet isolation measures should be implemented in households with positive cases of possible contacts of COVID-19. In addition, the fact that patients with infection with SARS-CoV-2 may atypically present with GI symptoms even before fever or respiratory symptoms, suggest that in cases in which other GI infections have been ruled-out, testing for this virus may be recommended. Also, healthcare providers may consider preventive actions to not contract the infection from these patients in the clinic. However, the latter ones are only suggestions based on the current available studies herein reviewed, but there are no published guidelines on these situations and newer studies may shed light on this matter.

Conclusions

We have reviewed 15 papers reporting gastrointestinal symptoms among patients with COVID-19, published until April 2-2020. The frequency of these symptoms varies from 3.0 to 39.6% of the patients, with diarrhea being the most common one. GI symptoms may be present even before fever or respiratory symptoms however, no conclusions can be drawn regarding their association with illness prognosis. Furthermore, these studies are based on hospitalized patients, therefore the presence of GI symptoms among milder out-patients is unknown. The most important issue to consider is that clinicians and gastroenterologists need to be aware and alert of the GI manifestations in patients with COVID-19, especially during the current pandemic. Also, the possibility of fecal-oral transmission, may have preventive implications in terms of household infection transmission and in the clinic.

Ethic Responsibilities:

A).- This is a Brief Review of the Literature therefore patients were not studied, and no informed consent was collected. The introductory mathematical projection model of the COVID-19 patients

that my emerge in Mexico, has been calculated by the Authors based on the daily public report of

COVID-19 cases by the Health Secretariat of the Mexican Government.

B).- Because this is a Review of the Literature, no Ethics Committee authorization, was required.

C).- Also, no specific cases are discussed, therefore, no patient identification is possible.

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Figure Caption

Table 1. Summary of papers reporting gastrointestinal symptoms among patients with COVID-19.

Authors	Place	Patients n	Age median (range)	Sex F/M (%)	Dia-rrhea n (%)	Nausea n (%)	Vomi-ting n (%)	Abdo-minal Pain n (%)	Anor-ex-ia n (%)	Belching /Reflux n (%)	Othe rs /Mix ed
Chang D et al.[5]	Beijing-China	13	34* (34-48)	23/77	1 (7.7)	--	--	--	--	--	--
Chen N et al.[6]	Wuhan-China	99	55.5** (21-82)	32/68	2 (2)	1 (1)	Included in Nausea	--	--	--	--
Chen Q et al.[7]	Anhui-China	9	50 (14-56)	45/55	2 (22.2)	--	--	--	--	--	--
Guan W et al.[8]	30 Regions-China	1099	47 (35-58)	42/58	42 (3.8)	55 (5.3)	Incl. in Nausea	--	--	--	--

42table| Huang C et al.[9]	Wuhan-China	41/38″	49 (41-58)	27/73	1 (3)	--	--	--	--	--	--
Jin X et al.[10]	Zhejiang-China	651	46.1	49/51	53 (8.1)	10 (1.5)	11 (1.7)	--	--	--	7 (1.1)
Lin L et al.[11]	Zhuhai-China	95	45.3 ±18.3***	53/47	23 (24.2)	17 (17.9)	4 (4.2)	-- †	17 (17.9)	2 (2.1)	--
Liu K et al.[12]	Hubei-China	137	57 (20-83)	55/45	11 (8)	--	--	--	--	--	--
Pan L et al.[13]	Hubei/Wuhan-China	204	54.9 ± 15.4***	48/52	29 (14.2)	--	8 (3.9)	4 (2.0)	83 (40.7)	--	--
Spiteri G et al.[14]	WHO European Region	38	42 (2-81)	34/66	1 (2.6)	1 (2.6)	--	--	--	--	--

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Wang D et al.[15]	Wuhan-China	138	56.0 (22-92)	46/54	14 (10.1)	14 (10.1)	5 (3.6)	3 (2.2)	--	--	--
Wang Z et al.[16]	Wuhan-China	69	42 (35-62)	54/46	10 (14)	3 (4)	--	--	7 (10)	--	--
Yang X et al.[17]	Wuhan-China	52	59.7 (30-79)	33/67	..	--	2 (4)	--	--	--	--
Young BE et al.[18]	Singa-pore	18	47 (31-73)	50/50	3 (17)	--	--	--	--	--	--
Zhang J-J et al.[19]	Wuhan-China	140	57 (25-87)	49/51	18 (12.9)	24 (17.3)	7 (5)	8 (5.8)	17 (12.2)	7 (5)	--

*Range was not reported only (25th-75th percentile, 34-48 years). Also, 2 patients were children, aged 2 and 15 years; **Age was reported as mean; ***: Age was reported in mean±SD; ″: Only 38 were analyzed for GI symptoms; †: 2 (2.1%) Epigastric discomfort was reported; --: Not Reported