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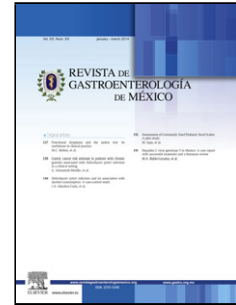
Beware: Gastrointestinal symptoms can be a manifestation of COVID-19

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

Alerta: Los síntomas gastrointestinales podrían ser una manifestación del COVID-19

Short title:

Gastrointestinal symptoms in COVID-19

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Abstract

Introduction: There is an increasing number of reports on the presentation of gastrointestinal symptoms in cases of COVID-19.

Aim: To review the studies reporting gastrointestinal symptoms in COVID-19. **Results**: Fifteen articles (2,800 patients) were identified. Gastrointestinal symptom frequency varied from 3.0% to 40.7% and included diarrhea (7.5%), nausea (4.5%), anorexia (4.4%), vomiting (1.3%), abdominal pain (0.5%), and belching/reflux (0.3%). Those symptoms can be the first manifestation of COVID-19, but whether they reflect a better or worse prognosis, is

controversial. The potential relation of the angiotensin converting enzyme 2 (ACE2) receptor in the digestive tract as an entry route for the virus is discussed.

Conclusion: Gastrointestinal symptoms may be common in COVID-19, appearing as the first manifestation, even before fever and respiratory symptoms. Therefore, clinicians and gastroenterologists must be aware of those atypical cases during the current pandemic, as well as of the fecal-oral route and corresponding preventive measures.

Keywords: COVID-19; Gastrointestinal symptoms; Diarrhea; Prognosis; Fecal-oral transmission

Resumen

Antecedentes: Existe un incremento de reportes sobre casos de COVID-19 que presentan síntomas gastrointestinales (GI). **Objetivo:** Revisión de estudios que reportaron síntomas GI en COVID-19. **Resultados:** Quince artículos (2800 pacientes), fueron identificados. La frecuencia de síntomas GI varió de 3.0% a 40.7%, incluyendo diarrea: 7.5%, náuseas: 4.5%, anorexia: 4.4%, vómito: 1.3%, dolor abdominal: 0.5%, eructos/reflujo: 0.3%. Estos pueden ser la primera manifestación de COVID-19, pero existe controversia sobre si reflejan mejor o peor pronóstico. Se discute la relación potencial del receptor de la enzima convertidora de angiotensina-2 (ACE2) en el tracto digestivo como ruta de entrada del virus. **Conclusión:** Los síntomas GI pueden ser comunes en COVID-19 y ser la primera manifestación incluso antes de fiebre y síntomas respiratorios. Por ello los clínicos y gastroenterólogos debemos estar alerta a estos casos atípicos durante la actual pandemia y sobre la probable transmisión fecal-oral, y considerar medidas preventivas.

Palabras Clave: *COVID-19, Síntomas Gastrointestinales, Diarrea, Pronóstico, Transmisión fecal-oral.*

Introduction

The coronavirus disease-2019 (COVID-19), 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 67,259 deaths.[2] The disease struck Mexico 3 weeks ago, and as of April 5, 2020, there have been 2,143 confirmed cases and 94 reported deaths, with a total of 5,209 patients currently under observation as suspicious cases.[3] Although the main manifestations of this viral infection are fever, dry cough, and shortness of breath,[4] as clinicians and gastroenterologists, we must learn from the experience of other countries, such as China, and be aware that gastrointestinal (GI) manifestations, albeit infrequent, can 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 GI manifestations of this infectious disease.

Methods

A search was conducted utilizing the Medline database, with the words COVID-19 AND Gastrointestinal symptoms: AND with specific symptoms including Diarrhea; Nausea; Vomiting; Abdominal Pain; Belching; Anorexia. We then 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 the papers identified. The reported prevalence of GI symptoms in patients with COVID-19 was summarized. The following information was extracted: the countries of the diagnosed cases; the number of patients analyzed; age in median and range (for the papers that did not report a median, in which that central tendency measure could not be calculated, the mean was reported); and sex percentages. In addition, the number and percentage of total GI symptoms were extracted, if they were reported, as well as the number and percentage of patients reporting the abovementioned individual symptoms. We also reviewed GI symptoms as atypical presentations of COVID-19 and their relation to patient prognosis and to epidemiologic factors, such as

exposure to the Huanan Seafood Market, if reported. Given that the majority of the studies were published between December 2019 and April 2, 2020, the Table results are listed in alphabetical order, by the surnames of the lead authors.

Results

A total of 15 papers were identified that analyzed the clinical experience with the COVID-19 infection and reported the presence of gastrointestinal symptoms.[5-19]   Thirteen papers were from China,[5-13, 15-17, 19] one was from Singapore,[18] and one was from the World Health Organization (WHO) European Region[14] (table 1), and together, they analyzed a total of 2,800 patients. In general, the prevalence of GI symptoms varied widely from 3.0% to 40.7%. Specifically, 210 (7.5%) patients 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). Importantly, 37 (1.3%) patients reported vomiting, but in 2 of the papers, nausea and vomiting were grouped together (56 patients).[6, 8] The sex distribution of the COVID-19 patients that presented with GI symptoms appears to be equally distributed. One-half of the patients were women and one-half were men, with no reported differences in GI symptoms, according to sex.

Certain details of those studies merit comment, especially in relation to the characteristics of the GI symptoms and their presence as atypical manifestations, their epidemiologic associations, time of onset, and relation to COVID-19 prognosis. For example, in a retrospective case series by Wang D et al. that evaluated 138 hospitalized patients in Wuhan, China, fever was the most common symptom (98.6%), followed by fatigue (69.6%) and dry cough (59.4%). Gastrointestinal symptoms were less common, and they included diarrhea in 10.1% of the cases, and nausea, vomiting, and abdominal pain, at a much lower frequency.[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, in another study from Wuhan, with 140 cases, Zhang J-J et al. reported a higher

frequency (39.6%) of gastrointestinal symptoms. In their case series, nausea was the most common symptom, whereas there was a similar frequency of diarrhea (12.9%).[19] Another study from the city of Zhuhai in China, GI symptoms were present in 11.6% of the cases, and the most common were diarrhea (24.2%) and anorexia (17.9)[11](table 1).

There is evidence that GI symptoms should be considered atypical manifestations of COVID-19. For example, Pan L et al. reported that 7% of their patients strictly presented with digestive symptoms,[13] and in the studies by Huang C et al. and Liu K et al, 2% and 25% of their patients, respectively, did not present with fever.[9,12] Regarding the time of onset of GI symptoms, in the case series from the Chinese city of Zhuhai, in the province of Guandong, 61.1% of the 95 patient total presented with GI symptoms. Nineteen percent of them had symptoms upon hospital admission, whereas the remaining 81% developed symptoms during hospital stay.[11] In the 651 cases from the Chinese province of Zhejiang, the onset of GI symptoms was not reported, but the median duration of diarrhea was 4 days, ranging from one to 9 days, and was self-limited in the majority of cases.[10]

In terms of epidemiologic 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, where the first cases of COVID-19 appear to have arisen.[6] However, they did not report whether that epidemiologic factor was related or not to the presence of GI symptoms or any other clinical manifestations. In the case series by Huang C et al., 66% of the patients also had direct exposure to the Huanan Seafood Market, but that factor was not analyzed in relation to the prevalence of symptoms, either. They only compared the symptoms according to hospitalization in the intensive care unit (ICU) or not, finding no difference in the prevalence of diarrhea.[9] In the previously mentioned Zhejiang study, there was no difference in patients with or without GI symptoms, with respect to a history of having been in Wuhan or in contact with other patients

with COVID-19. However, family clustering was significantly higher in the patients with GI symptoms.[10]

In relation to patient prognosis, according to the presence or absence of GI symptoms, Wang D et al. compared the frequency of GI symptoms between patients hospitalized in the ICU and those that were not. They found no difference, except for abdominal pain, which was more common in the patients in the ICU (8.3% vs 0, p=0.02).[15] In agreement with that finding, diarrhea was reported in 3 of the first 18 patients hospitalized with transcriptase–polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 in Singapore, none of whom required supplemental oxygen.[18] Lin L et al. also found no difference in clinical outcomes, such as hospital stay, discharge, or mortality, in patients with or without GI symptoms, in a case series conducted in the Chinese city of Zhuhai.[11] The last 2 case series described above possibly suggest a milder outcome in patients that do not present with 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% arrived at the hospital with digestive symptoms as their main complaint. Those patients had a significantly longer time interval from onset to admission than those with no digestive symptoms (9.0 vs. 7.3 days), and 7 patients presented only with digestive symptoms, not respiratory ones.[13] Digestive symptoms also became more apparent, as the severity of the disease increased. The patients with no GI symptoms were twice as likely to be cured and discharged, than those with GI symptoms (60% vs. 34.3%).[13] In Zhejiang, Jin X et al. reported that almost 23% of the patients with GI symptoms had a severe or critical type of illness. The presence of acute respiratory distress syndrome and the need for mechanical ventilation were significantly more frequent in the patients with GI symptoms, compared with the patients that did not have them.[10] In another case series from Wuhan, China, that included 52 critically ill patients with SARS-CoV-2 pneumonia, 2 cases reported diarrhea, one in the survivor group and one in the non-survivor group.[17] Furthermore, in the largest study published so far, diarrhea was the only GI symptom described in the 1,099 patients hospitalized at 552 sites in China, with a

low prevalence of 3.8%.[8] The primary endpoints of that study were admission to an ICU, the use of mechanical ventilation, or death, and the authors did not report whether diarrhea was different, according to those endpoints. However, they did recognize there was recall bias in 291 patients that could have affected their results.[8]

Discussion

We summarized all papers that reported GI symptoms in patients with COVID-19 disease, up to 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 case series from Europe.[14] The frequency of GI symptoms varied widely from 3.0% to 40.7% in the studies reviewed, and diarrhea was the most frequently reported, followed by anorexia. However, because the majority of the studies were retrospective, recall bias may have been a contributing factor to that low prevalence. In addition, given that pulmonary-related symptoms are the most important in terms of patient survival, most of the analyses and patient charts may have suffered bias in the collection of information regarding the respiratory manifestations and not that of other systems, such as the GI symptoms. Nevertheless, the fact that in some cases, GI symptoms were the only symptoms, or the first clinical manifestation, even before fever and respiratory symptoms, means that healthcare providers must be aware of that phenomenon, when seeing such patients during the current pandemic.[13, 17] Furthermore, reports in the literature on GI symptoms are mainly from hospitalized patients, and information regarding outpatients with milder symptoms, is lacking.[8] 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 presenting with GI manifestations during the present pandemic. Therefore, we must be aware of this possibility.

The underlying explanation for GI symptoms, in patients infected with SARS-CoV-2 that developed COVID-19 disease, needs to be addressed. 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]   Those receptors have been identified in type II alveolar cells of the lung, the stratified epithelial cells of the esophagus, the enterocytes from the ileum and colon, and cholangiocytes, as well as in myocardial cells, kidney proximal tubule cells, and bladder urothelial cells.[20-22] More recently, ACE2 has been shown to be expressed in the mucosa of the oral cavity, and highly enriched in the epithelial cells of the tongue.[23] Thus, the oral cavity and digestive tract may be a route of infection, and ACE2 expression in the digestive tract may explain why digestive symptoms 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 et al. reported that the nucleic acid detection of COVID-19 in fecal specimens was as accurate as pharyngeal swab specimens, and patients with a positive stool test did not experience GI symptoms.[25] In fact, in the Singapore case series, the virus was detected in the stools of 4 out of 8 patients that were tested, regardless of the presence of diarrhea.[18] In another study, the presence of viral RNA in feces was not related to the presence or severity of GI symptoms.[11] In addition, a positive stool test was not related to the severity of the lung infection.[25]   More importantly, a group from China found that viral RNA was still present in the stools of more than 20% of the patients infected with SARS-Cov-2 that had a negative conversion of the viral RNA in the respiratory tract.[26] Such evidence supports a fecal-oral transmission of the SARS-CoV-2, which deserves further study.[24]

Another important issue to highlight is the recent finding reported by Lin et al., of the presence of herpetic-type erosions and ulcers located in the esophagus, as a source of GI bleeding in one of their patients, along with the detection of SARS-Co-V-2 RNA in those erosions.[11] Viral RNA was also detected in biopsies of the esophagus, stomach, duodenum, and rectum in 2 other patients that had no endoscopic lesions, suggesting that the virus can be docked in the digestive tract.[11]

Despite all of the digestive findings associated with the coronavirus, there are currently no guidelines for the diagnostic approach in the presence of GI symptoms related to the COVID-19 pandemic, nor for their treatment. At present, there are only preventive measures that should be considered in endoscopy units.[27, 28] They are beyond the scope of the current review but can be summarized as delaying elective procedures for 8 weeks, implementing a pre-procedural triage, and using personal protective equipment (PPE), if there is a time-sensitive endoscopic procedure that needs to be performed.[29] Likewise, no differences in inflammatory markers, such as C-reactive protein and procalcitonin, have been found in patients with COVID-19, with or without GI symptoms.[10] It is still of the utmost importance that physicians and caregivers be aware of the possibility that patients may be having this infection. However, the possibility of fecal-oral transmission implies there can be preventive measures. On the one hand, toilet flushing can produce aerosols, resulting in fomite transmission.[30] On the other hand, GI symptoms have been related to family clustering, as previously described.[10] Therefore, toilet isolation measures should be implemented in households with positive cases of likely COVID-19 contact. In addition, the fact that patients with SARS-CoV-2 infection may atypically present with GI symptoms, even before fever or respiratory symptoms, suggests that testing for that virus may be recommended, in cases in which other GI infections have been ruled-out. Healthcare providers may also consider preventive actions to not contract the infection from those patients in the clinic. However, the latter suggestions are based only on the current available studies reviewed herein, but there are no published guidelines on these situations and newer studies may shed light on them.

Conclusions

We reviewed 15 papers published up to April 2, 2020 that reported GI symptoms in patients with COVID-19. The frequency of those symptoms varied from 3.0% to 40.7% of the patients, and diarrhea was the most common. GI symptoms may be present, even before fever or

respiratory symptoms, but no conclusions can be drawn, regarding their association with illness

prognosis. Furthermore, the studies analyzed are based on hospitalized patients, therefore the

presence of GI symptoms in outpatients with milder symptoms is unknown. It is vitally important

that clinicians and gastroenterologists be aware of the GI manifestations in patients with COVID-

19, especially during the current pandemic. The possibility of fecal-oral transmission may also

have preventive implications, in terms of infection transmission, both at home and in the clinic.

Acknowledgements

Ethical disclosures

This is a Brief Review of the Literature, and so patients were not studied, and no informed

consent was collected.

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

 No specific cases are discussed in the present review, making patient identification impossible.

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Figure Caption

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

Authors	Location	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 (%)	Others /mixed
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 with 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)	Included with nausea	--	--	--	--
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)	--	--