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Research Article

What Is the Role of Gastrointestinal Symptoms in Covid-19?

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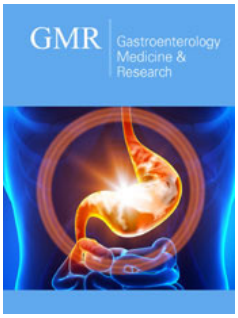

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Abstract

Objective: To describe the role of Gastrointestinal (GI) symptoms as a diagnosis and/or prognosis in COVID-19.

Method: Narrative literature review performed in March 2020 following the PRISMA method.

Results: A total of 285 articles were found in Pubmed and Scielo databases, of which 260 were excluded, 25 analyzed in full and nine included in the review. Gastrointestinal symptoms are very prevalent, present in 58.91% of surveyed patients. The most prevalent symptom was nausea, present in 34.41% of patients with gastrointestinal symptoms, followed by vomiting (22.20%) and diarrhea (15.69%).

Conclusion: Considering the scarcity of information produced so far, was reached the conclusion that the role of gastrointestinal symptoms as a diagnosis/prognosis in COVID-19 cannot be established.
Keywords: COVID-19; Sars-Cov-2; Gastrointestinal symptoms; Diarrhea; Nausea; Vomiting; Anorexia; Abdominal pain

Abbreviations: WHO: World Health Organization; SARSL: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; ACE2: Angiotensin 2 Converting Enzyme; TMPRSS2: Transmembrane Protein Serine; GI: Gastrointestinal; COPD: Chronic Obstructive Pulmonary Disease; SAH: Systemic Arterial Hypertension; GERD: Gastroesophageal Reflux Disease; ICU: Intense Care Unit

Introduction

The coronavirus 19 (COVID-19) disease pandemic was officially declared on January 30, 2020 by the World Health Organization (WHO), after attracting worldwide attention with its rapid advance from the Wuhan province (China) to several countries [1]. Just over a year later, on March 31, 2021, according to the World Health Organization's Coronavirus Panel, the total number of reported deaths was 2,787,593 worldwide. In Brazil, on the same date, there were 312,206 deaths and 12,534,688 confirmed cases [2]. The agent of this disease is the severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2), a single-stranded enveloped RNA virus of the family Coronaviridae, beta-coronavirus lineage [3]. This is the third coronavirus to lead an outbreak in human populations. The other two were the severe acute respiratory syndrome (SARS) coronavirus in 2003 and the Middle East Respiratory Syndrome (MERS) coronavirus in 2012 [3]. Although they belong to the same family, Sars-CoV-2 shares only 74.5% of the genetic material with SARS CoV [4]. As for the structure of Sars-CoV-2, the virus genome is surrounded by membrane proteins (M), peak protein (S) and envelope protein (E). These three proteins together with the nucleocapsid (N) protein are called structural proteins. In addition to these, the virus has sixteen non-structural proteins. The peak protein (S), also called spike, has two subunits: S1 and S2. The S1 subunit is responsible for binding to the receptor on the host cell, and the S2 subunit fuses the viral cell membranes with the host cell membranes [5].

The life cycle of the virus begins when it enters human cells, when the spike protein (S-spike) on the viral surface binds to the Angiotensin 2 Converting Enzyme (ACE2) receptor present in lung cells and intestinal mucosa. This entry is also related to furin and

the Transmembrane Protein Serine (TMPRSS2) on the surface of the virus. Angiotesin 2 converting enzyme receptors decrease the action of the renin angiotensin aldosterone system by metabolizing angiotensin 2, which has effects on the cardiovascular, renal and respiratory systems. Thus, by blocking these receptors, Sars-CoV-2 causes pulmonary failure and respiratory distress syndrome in some patients. The rapid replication of the virus in cells triggers an enormous inflammatory response, called a "cytokine storm" [6]. The transmission of Sars-CoV-2 is through fomites and droplets of infected patients (both symptomatic and asymptomatic), aerosols, direct contact and contaminated surfaces. However, Zhang et al. [4] found the presence of Sars-CoV-2 in an anal swab, indicating the possibility of fecal-oral transmission. The high transmissibility of the virus can be attributed to the unique virological characteristics of Sars-CoV- 2 that differ from other coronaviruses. In addition, asymptomatic cases are the most responsible for infections and the virus can remain on inanimate surfaces. These factors explain the rapid spread of the virus around the world and the high rates of confirmed cases [7]. The wide dissemination of Sars-CoV resulted in several mutations in the initial strain, which initiated a series of new studies to elucidate how these changes would affect transmissibility, infectivity, clinical status and other aspects. To date, the D614G mutation in viral protein S is the most prevalent in the world. Although this mutation is not associated with a more severe clinical picture or higher mortality, it has been shown to be more transmissible between hosts and has a higher viral load. Korber and Volz et al. have shown that the mentioned mutation increases viral replication in the respiratory tract, as well as the susceptibility to neutralization (Figure 1-3).

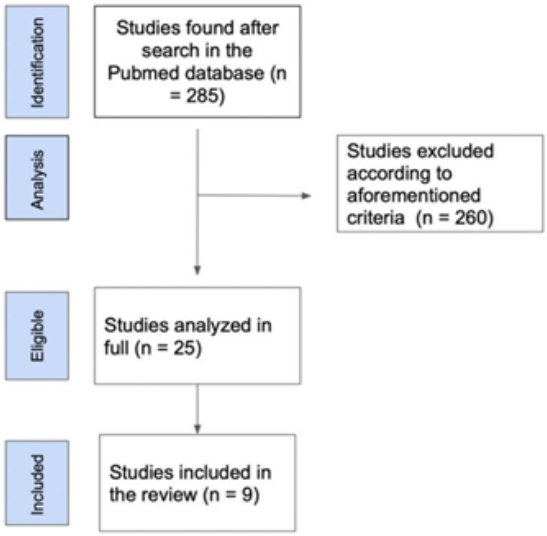

Figure 1:

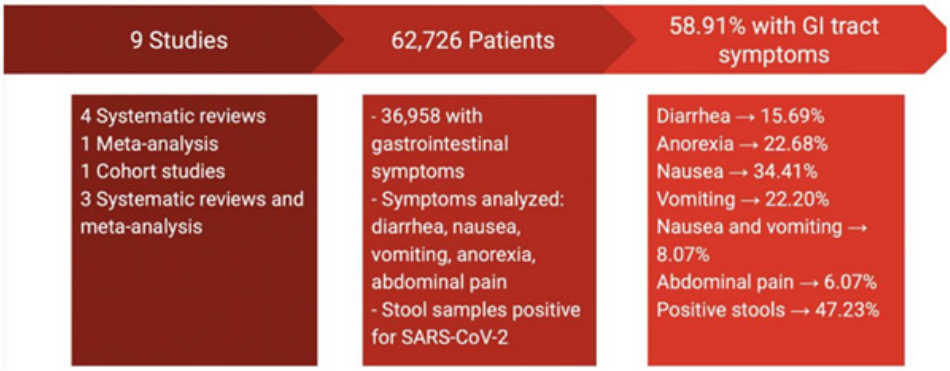

Figure 2: Nine studies were included in the review. Of these, four are systematic reviews, one is meta-analysis, one is a cohort study and three are systematic reviews and meta-analysis. In total, 62,726 patients were studied, of which 36,958 had gastrointestinal symptoms and the following were analyzed: diarrhea, nausea, vomiting, anorexia, abdominal pain and positive stool sample for Sars-Cov-2. Of all patients, 58.91% had GI tract symptoms, of which: diarrhea 15.69%; anorexia 22.68%; nausea 34.41%, vomiting 22.20%, nausea and vomiting 8.07%; abdominal pain 6.07% and positive stool sample 47.32%.

According to Jutzeler et al. [8], the most common symptoms of the disease among patients of all age groups are fever, cough, fatigue, diarrhea, sore throat, expectoration and headache. Lovato et al. [9] also have observed fever, dry cough, dyspnea and fatigue as the main symptoms, and the most serious disease can also include viral pneumonia, severe acute respiratory syndrome and even death. Other symptoms that may also be present are sore throat, nasal congestion and runny nose. Finally, they emphasize that anosmia

as a recurrent symptom is also very important; if appearing before symptoms such as cough and fever, it could be an indication of the disease. According to Almeida et al. [10], the manifestations of Sars-CoV-2 in the Gastrointestinal (GI) tract are frequent. However, more studies are needed to draw better conclusions about its prevalence, which is still very varied. The bibliographical review by Almeida et al. [10] included the analysis of 14 studies; nine retrospective, four meta-analyses and one systematic review. The review indicates that the most frequent gastrointestinal symptoms are diarrhea (present in 8.14%-33.7% of studies), nausea/vomiting (1.53%-26.4%), anorexia (12.1%-40.0%) and abdominal pain (0%-14.5%). Furthermore, laboratory alterations were detected, especially in liver enzymes (AST, ALT and bilirubin, for example), which may be related to worsening of the disease and liver involvement in several patients.

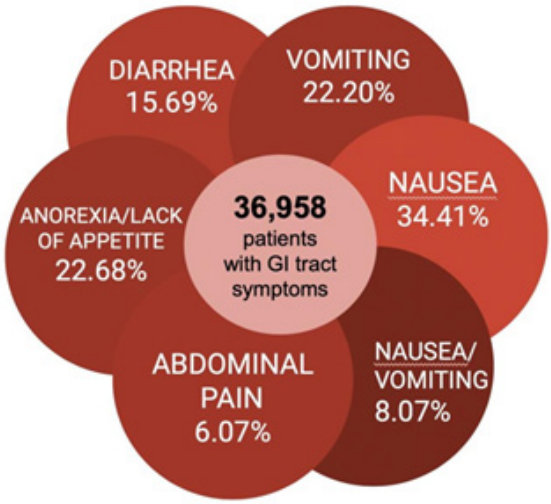

Figure 3: 36,958 patients analyzed had gastrointestinal symptoms, of which: diarrhea 15.69%; anorexia 22.68%; nausea 34.41%, vomiting 22.20%, nausea and vomiting 8.07%; abdominal pain 6.07% and positive stool sample 47.32%.

In four out of the nine studies reviewed, the analysis of patients' stools was performed in search for traces of the virus. The studies concluded that viral RNA can be found in the stool during Sars-CoV-2 infection. Some studies stated that this result remained positive even after negative samples from the respiratory tract, although without concluding if the presence of viral RNA in these samples would be a sign of infecting virus or just viral residues. Confirming the presence of viral RNA in feces raises important questions about the possibility of fecal-oral transmission of Sars-CoV-2. Both the reviewed studies and a study by Almeida et al. [10] reiterate the importance of conducting new studies and analyzes on the possibility of fecal-oral contamination. Cipriano et al. [11], in one of the retrospective studies analyzed, concluded that the anal swab may be as important as the nasopharyngeal swab in virus detection, even in asymptomatic patients. In addition, physicians should consider that the potential for fecal-oral transmission may remain even after viral disappearance from the respiratory tract. The symptom of diarrhea has also been found in MERS-CoV disease, according to a meta-analysis by Rokkas [12]. In addition, SARS-CoV RNA was detected in the stool of patients with SARS. Therefore, diarrhea and the fecal RNA detection in patients with COVID-19 are understandable, as the three agents share a large percentage of genetic material. A meta-analysis study showed a greater presence of gastrointestinal symptoms in patients with severe conditions, suggesting the use of these symptoms as a prognosis for the disease. Regarding different patterns of the disease, the literature review by Sultan S et al. [13] indicates that these may not be as prevalent. Two out of the 43 articles included in the analysis on diarrhea presented patients with diarrhea and absence of respiratory symptoms, and only one article presented patients with diarrhea as an initial symptom preceding other symptoms of COVID-19.

Zafirian et al. [14] reports that intestinal cells widely express the ACE2 receptor, a mediator responsible for the entry of the virus into respiratory cells, which would justify the detection of genetic material of the virus in patients' feces. The author also shows that this detection in feces lasted longer than in samples from the respiratory tract. In addition, patients with diarrhea had a higher frequency of viral RNA detection in feces. According to Almeida et al. [10], Sars-CoV-2 infection decreases and blocks the expression of these ACE2 receptors in brush border cells of intestinal mucosa. Therefore, the ACE2 receptor associated with the amino acid transporter A0T-1 no longer absorbs tryptophan and therefore, no longer stimulates the mTOR pathway, resulting in lower production of antimicrobial peptides. This could result in an alteration of the intestinal microbial population and inflammation. The presence of gastrointestinal symptoms in COVID-19 is clearly a hot issue. In consonance with this idea, we propose to research the role of these symptoms in the disease. Could diarrhea, nausea, vomiting, and anorexia be isolated symptoms in COVID-19 and be used as a diagnosis? Will there be any relationship between the presence of gastrointestinal symptoms and the prognosis of the patient infected with Sars-CoV-2?

Methodology

We conducted and reported this horizontal systematic review with four independent collaborators following the PRISMA method.

A literature search was performed in the Pubmed Central and Scielo databases to identify eligible articles addressing COVID-19 and the gastrointestinal tract. Keywords used were "COVID-19 and gastrointestinal tract", "COVID-19 and diarrhea", "COVID-19, gastrointestinal tract and prognosis", "COVID-19, severity, gastrointestinal", "COVID-19 and fecal transmission". Inclusion criteria were articles in English, Portuguese or Spanish addressing adult patients, COVID- 19, gastrointestinal symptoms, diarrhea. Exclusion criteria were articles addressing only pediatric patients or case reports.

Results and Discussion

Sampling

Six out of nine articles evidenced the origin of patients involved in the studies. Among them, Ren Mao and Shahnaz Sultan analyzed patients from China and the United States (USA). Zhang et al. [15] analyzed patients from China, USA, Italy, France, Singapore and Somalia. Kariyawasam et al. [16] analyzed patients from China, USA, Italy, France, Japan and Singapore. Raseen Tariq was the study with more sources described, namely China, USA, Australia, Netherlands, Italy, Spain, Japan, North Korea, South Korea and Taiwan (Table 1&2). Finally, Cheung's article analyzed patients from China, South Korea, the United Kingdom and the USA. As for age group, the article by Kariyawasam et al. [16] obtained an average age of 53 years, Rong Chen of 59 years, Cheung an average of 45.1 years and Almeida et al. [10] an average of 56.91 years and a final average of 53.5 years. In the analysis of articles, the presence of comorbidities such as: Chronic Obstructive Pulmonary Disease (COPD); obesity; diabetes; Systemic Arterial Hypertension (SAH); Gastroesophageal Reflux Disease (GERD); and smoking were considered important aspects of the study and were analyzed in three articles [10,17]. Almeida et al. [10] described the presence of 232 people with diabetes, 481 with Systemic Arterial Hypertension (SAH) and 121 with COPD among the 2,286 patients analyzed. Rong Cheng described that of the 1113 patients studied, 59 had COPD, 150 had diabetes and 368 had hypertension. Raseen Tariq described 80 patients with GERD out of 140 patients included in the analysis [18-23].

Table 1: Sampling.

1st Author	Year of Work	Type of Work	Total Patients	Origin of Patients	Age Group	Male	Fem	Comorb Idities
Zhang et al. [15]	2020	Systematic Review	12,737	China, USA, Italy, France, Singapore, Somalia.	NA	NA	NA	NA
Kariyawa sam et al. [16]	2021	Systematic Review	9,872	China, USA, Italy, France, Japan, Singapore	Average age 53 years old	NA	NA	NA
Raseen Tariq [17]	2019-2020	Systematic Review and Meta-analysis	12,767	China, USA, Australia, Netherlands, Italy, Spain, Japan, North Korea, South Korea, Taiwan	NA	5,312	7455(58.4) %	80
Galanopoulos ulos [18]	2020	Systematic Review	2,032	NA	NA	NA	NA	NA
Ren Mao [19]	2020	Systematic Review and Meta-analysis	6,686	China, USA	NA	NA	NA	NA
Rong Chen [20]	2020	Retrospective Cohort Study	1,113	NA	59 years	550	563	577
Cheung [21]	2020	Systematic Review and Meta-analysis	4,243	China, South Korea, United Kingdom, USA, Singapore, Vietnam	45,1	2,278	1,965	NA
Almeida et al. [10]	2020	Systematic review	2,286	NA	56,91 (eight studies)	1,117	1,169	834
Shahnaz Sultan [22]	2020	Meta-analysis	10,890	China, USA, Japan, Australia, Germany, Singapore, New Zealand, Netherlands, Italy	NA	NA	NA	NA

Of the six articles that cited the origin of patients, there was no great variation between countries, which reduces the relationship of symptoms with the origin of the strains involved and the disease course itself. The most cited countries were China (in all seven articles) and the USA (also in seven articles). Other countries mentioned were Italy, France, Japan, Singapore, Australia, Netherlands, Spain, North Korea, South Korea, Taiwan and the United Kingdom. Another issue that raised questions about the articles was the lack of detail and differentiation of comorbidities, given the belief that this is a risk factor for a worse course of the disease, including a higher risk of intubation and death, according to Benjamin Gallo et al. [23]. As this fact was not addressed in the articles, it is impossible to draw conclusions on such a relationship from this work.

Table 2: Gastrointestinal tract symptoms.

1st Author	Total Number of Patients	Number of Patients with GI Tract Symptom msn (%)	Diarrhea n (%)	Nausea n (%)	Vomiting n (%)	Nausea and Vomiting n (%)	Anorexia/ Lack of Appetite n (%)	Abdominal pain n (%)	Positive Stools for Sars-CoV- 2
Zhang etal. [15]	12,737	2526(19.38%)	1,441/2,524 (57.09%)	960/2,114 (45%)	786/2,429 (32%)	NA	1,013/1,657 (61%)	442/2,134 (20%)	112/245 (45%)
Kariyaw asam et al. [16]	9,872	933(9.45%)	450/868 (51%)	298/867 (34%)	262/867 (30%)	NA	572/762 (75%)	97/765 (12.4%)	NA
Raseen Tariq [17]	12,767	12,767	1,773/12,688 (13,97%)	NA	NA	988/9,696 (10.18%)	744/3,201 (23.24%)	418/5,896 (7.08%)	NA
Galanopoulos [18]	2,132	1,951	320/1940 (16,49%)	388/1,777 (21.83%)	110/1,773 (6.20%)	NA	271/639 (42.41%)	34/840 (4.04%)	NA
Ren Mao [19]	6,686	6,064 (90.6%)	546 (9%)	NA	NA	364(6%)	1,273 (21%)	182(3%)	54%
Rong Chen [20]	1,113	359(33.3%)	208 (57.93%)	NA	NA	71 (19.8%)	NA	38 (10.6%)	NA
Cheung [21]	4,243	734 (17.2%)	328 (44.6%)	NA	NA	254 (34.6%)	216 (29.42%)	51(6.94%	2,036/4,243 (48.1%)
Almeida et al. [10]	2,286	734(32.10%)	399 (54.35%)	156/448 (34.82%)	90/551 (16.33%)	75/134 (55.97%)	247/448 (55.13%)	74/563 (13.14%)	34/132 (25.75%)
Shahnaz Sultan [22]	10,890	10,890	822/10,6 76 (7.7%)	NA		464/5,95 5 (7.8%)	NA	145/4,03 1 (3.6%)	
TOTAL	62,726	36,958 (58.91%)	5,741/36 ,587 (15.69%)	1,802/5, 236 (34.41%)	1,248/5,6 20 (22.20%)	1,852/22, 942 (8.07%)	3,063/13,5 05 (22.68%)	1,299/21, 386 (6.07%)	2,182/4,6 20 (47.23%)

Symptoms of the Gastrointestinal Tract

Regarding the presence of symptoms in the gastrointestinal tract in patients with COVID, eight articles evaluated their incidence [15-21], totaling 36,958 patients with gastrointestinal symptoms, and an article Shahnaz Sultan [22] analyzed the presence of diarrhea, nausea, and vomiting. All cited articles evaluated the presence of diarrhea as one of the manifestations, totaling 5,741 out of 36,679 patients (15.69%). Four articles analyzed the presence of nausea [10,15,16,18], totaling 1,802 patients with the symptom, out of 5,236 analyzed (34.41%). As for the presence of vomiting, this analysis was made in four articles [10,15,16,18], with a total of 1,248 out of 5,620 patients analyzed with the symptom (22.20%). Six articles analyzed the presence of nausea and vomiting as a single manifestation [10,17,19,20-22], totaling 1,852 patients out of 22,942 analyzed (8.07%). Seven articles analyzed the presence of anorexia/lack of appetite [10,15-19,21], totaling 3,063 patients out of 13,505 (22.68%). The nine articles cited [10,15-22] evaluated the presence of abdominal pain, concluding a total of 1,299 patients with the manifestation out of 21,386 analyzed (6.07%). As for the presence of Sars-CoV-2 in feces, the study by Zhang et al. [15] evaluated it as positive in 112 out of 245 analyzed, totaling 45%. Ren Mao's article evaluated the presence in 54%, and the study by Almeida et al. [10] in 25.75%. Cheung's article concluded a total of 2,036 positive samples for the virus in the stool. At baseline, we expected to find conclusive data on the incidence of gastrointestinal symptoms in Sars-CoV-2 infection. Based on all analyzed patients, the most prevalent symptom was nausea, present in 34.41% of patients with gastrointestinal symptoms, followed by vomiting (22.20%) and diarrhea (15.69%). These data are compared with what was found by Almeida et al. in 2020, in which the most prevalent symptoms were anorexia (12.1%-40.0%), diarrhea (8.14%-33.7%) and nausea/ vomiting (1.53%-26.4%). We expected to find higher percentages of the incidence of these symptoms, considering the affinity of Sars- CoV-2 with the gastrointestinal tract. Statistics taken from the revised literature also brought very varied data. Considering anorexia/lack of appetite, Ren Mao et al. described the symptom in 21% of patients, while Kariyawasam et al. described the symptom in 75% of patients. The same also happened when analyzing the statistics about:

A. Diarrhea, where Shahnaz Sultan et al. [22] and Ren Mao et al. [19] described the symptom in 7.7% and 9% of patients, respectively, while Zhang et al. [15] and Rong Chen et al. [20] described the symptom in 57.09% and 57.93 %, respectively

B. Vomiting was described in 6.20% of patients by Galanopoulos et al. and in 32% of patients by Zhang et al. [15]

C. The nausea symptom was the most uniform, in which the lowest incidence was 21.83% described by Galanopoulos and the highest was 45%, described by Zhang et al. [15], Ren Mao et al. [18], Cheung et al. [21] and Almeida et al. [10] described analyzes of the presence of the Sars-CoV-2 virus in stool samples from contaminated patients. As data in the literature are still very varied and inconclusive, further studies are needed to establish more accurate and reliable statistics on the gastrointestinal involvement of Sars-CoV-2 infection.

Diarrhea symptom analysis

The moment when patients with diarrhea presented the symptom was analyzed in three articles [10,17,20]. In the article by Raseen Tariq, 8.10% of patients manifested diarrhea as the first

symptom, and 10.20% manifested it after hospital admission. In Rong Chen's article, diarrhea was analyzed in conjunction with other gastrointestinal symptoms, and 107 out of 359 patients with gastrointestinal symptoms presented diarrhea as the first manifestation of COVID-19, while the other 70.19% presented it only after hospital admission. Finally, the article by Almeida et al. [10] showed that 18 patients out of 95 had diarrhea as a symptom after admission to the hospital.

We expected to find more data on the details of diarrhea, but this was described in only three out of nine articles included in this work, evidencing a lack of research on the topic. Given the discrepancy in data on the moments of onset of diarrhea that was the initial symptom respectively in 8.10%, 29.80% and 14.70% of cases, it is not possible to conclude whether diarrhea should be considered an alarm symptom about a possible Sars-Cov-2 infection. Matthew Meyers [24] and Xiaodong Yang [25] published case reports in 2020, in which patients had watery diarrhea for three days as an initial and isolated symptom, with subsequent onset of fever, lack of appetite, cough and dyspnea. Both patients had type 2 Diabetes Mellitus and previous cardiovascular diseases. No article showed the presence of diarrhea as the only symptom. We also did not find enough data to conclude about the relationship between the presence of diarrhea and the outcome of the patient with COVID-19. In July 2020, Xiao-Shan Wei et al. published a retrospective study of 84 patients analyzing the association between diarrhea and prolongation of symptoms and viral load by the coronavirus. In this work, it was concluded that the duration of fever and dyspnea was significantly longer in patients with diarrhea, as well as the time for the swab test to become negative, indicating a prolongation of the viral load.

Conclusion

Given the above work, data in the literature are insufficient to conclude about the role of gastrointestinal symptoms in COVID-19. It was shown these are symptoms with significant prevalence, as 58.91% of patients surveyed had some symptom between diarrhea, nausea, vomiting, anorexia and abdominal pain. However, only 8,346 (11.89%) of the 70,202 patients in the survey were analyzed regarding the moment of onset of gastrointestinal symptoms. In the same sense, none of the nine studies analyzed described the outcome of patients with gastrointestinal symptoms (death, intubation, ICU stay, discharge) so there was no possibility of comparing with patients who did not present such symptoms. We highlight the low attention given to this matter by the academy.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, et al. (2020) The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 7(1): 11.
2. Brazil: WHO Coronavirus Disease (COVID-19).
3. Harrison AG, Lin T, Wang P (2020) Mechanisms of SARS-CoV-2 transmission and pathogenesis. Trends Immunol 41(12): 1100-1115.
4. Zhang W, Du RH, Li B, Zheng XS, Yang XL, et al. (2020) Molecular and serological investigation of 2019-nCoV infected patients: Implication of multiple shedding routes. Emerg Microbes Infect 9(1): 386-389.
5. Wang MY, Zhao R, Gao LJ, Gao XF, Wang DP, et al. (2020) SARS-CoV-2: Structure, biology, and structure-based therapeutics development. Front Cell Infect Microbiol 10: 587269.
6. Hu B, Guo H, Zhou P, Shi ZL (2020) Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19(3): 141-154.
7. Mishra SK, Tripathi T (2020) One year update on the COVID-19 pandemic: Where are we now? Acta Trop 214: 105778.
8. Jutzeler CR, Bourguignon L, Weis CV, Tong B, Wong C, et al. (2020) Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 37: 101825.
9. Lovato A, De Filippis C (2020) Clinical presentation of COVID-19: A systematic review focusing on upper airway symptoms. Ear Nose Throat J 99(9): 569-576.
10. De Almeida JFM, Chehter EZ (2020) COVID-19 and the gastrointestinal tract: What do we already know? Einstein (Sao Paulo) 18: eRW5909.
11. Cipriano M, Ruberti E, Giacalone A (2020) Gastrointestinal infection could be new focus for coronavirus diagnosis. Cureus 12(3): e7422.
12. Rokkas T (2020) Gastrointestinal involvement in COVID-19: A systematic review and meta-analysis. Ann Gastroenterol 33(4): 355-365.
13. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, et al. (2020) AGA institute rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. Gastroenterology 159(1): 320-334.e27.
14. Zarifian A, Zamiri BM, Arekhi S, Rafiee M, Gholamalizadeh H, et al. (2021) Gastrointestinal and hepatic abnormalities in patients with confirmed COVID- 19: A systematic review and meta-analysis. J Med Virol 93(1): 336-350.
15. Zhang J, Garrett S, Sun J (2021) Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19. Genes Dis 8(4): 385-400.
16. Kariyawasam JC, Jayarajah U, Riza R, Abeysuriya V, Seneviratne SL (2021) Gastrointestinal manifestations in COVID-19. Trans R Soc Trop Med Hyg 115(12): 1362-1388.
17. Tariq R, Saha S, Furqan F, Hassett L, Pardi D, et al. (2020) Prevalence and mortality of COVID-19 patients with gastrointestinal symptoms: A systematic review and meta-analysis. Mayo Clin Proc 95(8): 1632-1648.
18. Galanopoulos M, Gkeros F, Doukatas A, Karianakis G, Pontas C, et al. (2020) COVID-19 pandemic: Pathophysiology and manifestations from the gastrointestinal tract. World J Gastroenterol 26(31): 4579-4588.
19. Mao R, Qiu Y, He JS, Tan JY, Li XH, et al. (2020) Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol 5(7): 667-678.
20. Chen R, Yu YL, Li W, Liu Y, Lu JX, et al. (2020) Gastrointestinal symptoms associated with unfavorable prognosis of COVID-19 patients: A retrospective study. Front Med 7: 608259.
21. Cheung KS, Hung IFN, Chan PPY, Lung KC, Tso E, et al. (2020) Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: Systematic review and meta-analysis. Gastroenterology 159(1): 81-95.
22. Sultan S, Altayar O, Siddique SM, Davitkov P, Feuerstein JD, et al. (2020) AGA institute rapid review of the gastrointestinal and liver manifestations of COVID-19, Meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. Gastroenterology 159(1): 320-334.e27.

23. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, et al. (2021) Predictors of COVID-19 severity: A literature review. Rev Med Virol 31(1): 1-10.

24. Meyers MH (2020) A case of COVID-19 infection: Chief symptom, diarrhea. Am Fam Physician 101(10): 580.

25. Yang X, Zhao J, Yan Q, Zhang S, Wang Y, Li Y (2020) A case of COVID-19 patient with the diarrhea as initial symptom and literature review. Clin Res Hepatol Gastroenterol 44(5): e109-e112.