



REVIEW ARTICLE

Gastrointestinal manifestations of COVID-19: An updated systematic review

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ARTICLE HISTORY

Received: 13 May 2022

Revised: 28 July 2022

Accepted: 28 July 2022

Published: 30 September 2022

ABSTRACT

Lack of knowledge about the type and prevalence of gastrointestinal symptoms as a clinical manifestation is one of the reasons for delayed diagnosis and treatment of COVID-19 patients. This review study aimed to systematically review the type and prevalence of gastrointestinal symptoms in COVID-19 patients. To study the gastrointestinal manifestations of COVID-19, we used the O6- PRISMA registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-Analysis Facility (SyRF) database. PubMed, Embase, Web of Science, Google Scholar, and Scopus databases were searched for publications on the gastrointestinal manifestations of COVID-19 with no publication time frame. Articles were found using the following terms and search strategy: ["COVID-19, Coronavirus, 2019-nCoV, Clinical Symptoms-Gastrointestinal or gastric or intestinal manifestations"]. Out of 27652 papers, 35 papers on a total of 6730 COVID-19 patients up to 2022 met the inclusion criteria. Remarkably, most articles (28 papers, 77.8%) were from China (77.8%). The most common gastrointestinal manifestations were nausea or vomiting (13.1%), diarrhea (11.05%), anorexia (8.7%), and abdominal pain (2.4%), respectively. The findings of the present review revealed that contrary to what was initially assumed in the COVID-19 outbreak, this infection does not manifest only as respiratory symptoms but also as gastrointestinal symptoms. Therefore, clinicians and gastroenterologists must be alert to these unusual cases and fecal-oral transmission during the COVID-19 pandemic and implement preventive strategies.

Keywords: Coronavirus; gastrointestinal; symptoms; vomiting; diarrhea.

INTRODUCTION

In December 2019, a sudden increase occurred in the referrals of patients with clinical signs of SARS-like pneumonia (SARS-COV) due to an unknown new strain from the coronavirus family in Wuhan, China. The newly discovered strains were found to be progressing rapidly and later identified as SARS-COV-2. As of July 22, 2020, 14971036 people have been definitively infected and 618017 people have died as a result (Galanopoulos *et al.*, 2020). SARS-COV-2 is an enveloped virus that contains single-stranded RNA and belongs to the genus *Beta-coronaviruses*. SARS-COV-2, like SARS-COV, attacks the body by binding to the angiotensin-converting enzyme 2 (ACE2). Reports of SARS-COV-2 virus infection indicate that the virus is found not only in the respiratory tract but also in the gastrointestinal tract (esophageal epithelial cells, ileal and colon enterocytes) and the liver (Sukumaran & Sathianarayanan, 2021).

COVID-19 patients often presented with fever and respiratory symptoms such as dyspnea, coughs, and bilateral pulmonary infiltration. However, the occurrence of gastrointestinal symptoms (e.g., diarrhea, nausea or vomiting, anorexia, and abdominal pain) and the identification of the RNA virus in feces, as well as liver damage have been reported by several studies (Cai *et al.*, 2020).

The results of recent investigations on the occurrence of the gastrointestinal symptoms of COVID-19 patients are varied (Figure 1). In some studies, no evidence of gastrointestinal symptoms was found, while in others, all patients demonstrated gastrointestinal signs and symptoms (Chan *et al.*, 2020). Overall, in these studies, the incidence of gastrointestinal symptoms was reported in 16 to 50% of patients.

Since the presence of GI manifestations is correlated with a risk of clinical deterioration of COVID-19 (Ye *et al.*, 2020), it is necessary to manage and treat GI manifestations in patients. In this regard, metoclopramide, domperidone, or 5-hydroxytryptamine receptor antagonists are used for treating nausea and vomiting (Zhang *et al.*, 2020). On the other hand, although no specific therapy is present for diarrhea caused by SARS-CoV-2, dioctahedral montmorillonite and probiotics may be used for treating diarrhea (Zhang *et al.*, 2020).

Lack of knowledge about the type and prevalence of gastrointestinal symptoms as a clinical manifestation is one of the reasons for the delayed diagnosis and treatment of patients with COVID-19. Therefore, this review study aimed to systematically review the type and prevalence of gastrointestinal symptoms in COVID-19 patients.

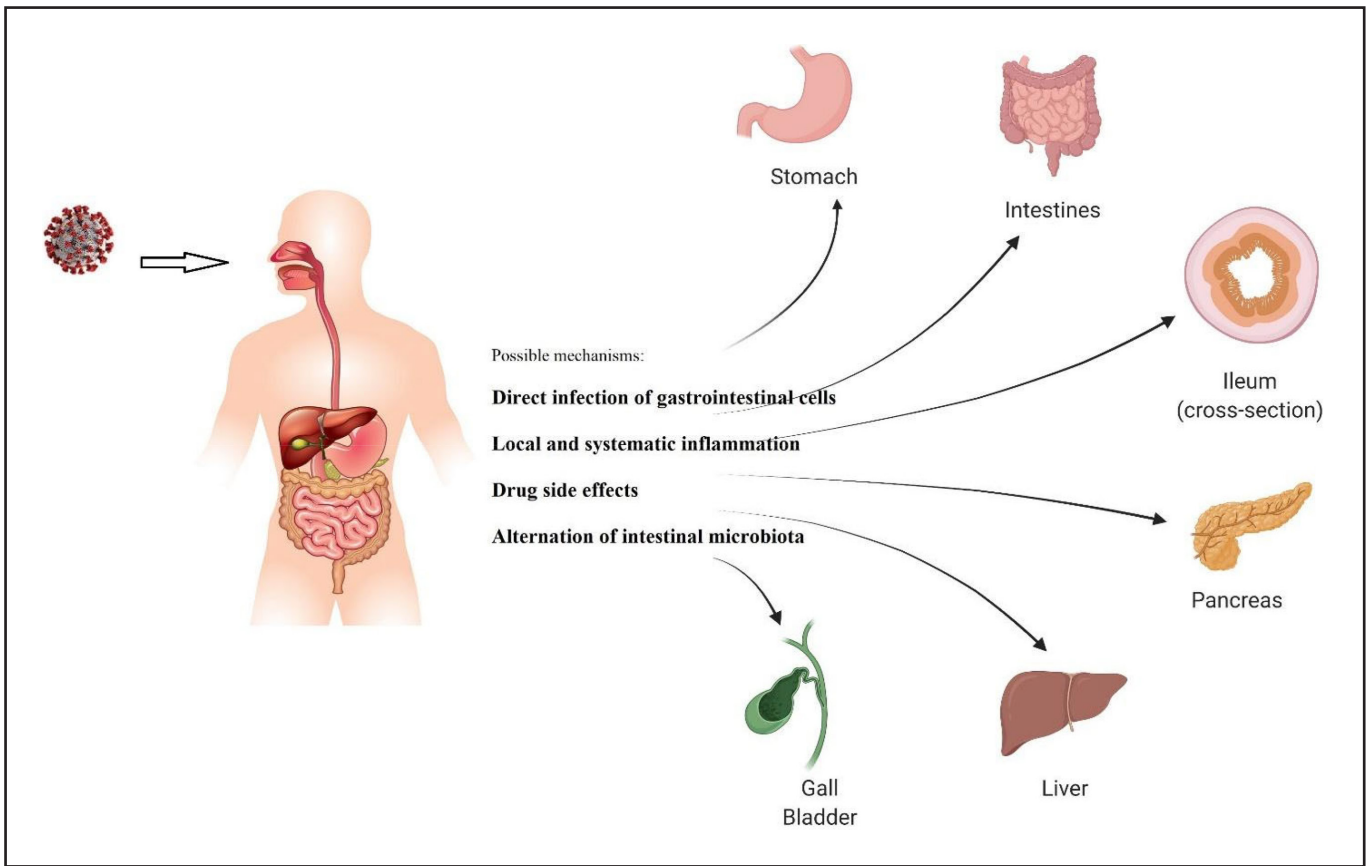


Figure 1. Effect of COVID-19 disease on different parts of gastrointestinal system.

MATERIALS AND METHODS

RESULTS

Search strategy

To examine the gastrointestinal manifestations of COVID-19, we used the O6- PRISMA registered in the CAMARADES-NC3Rs Preclinical Systematic Review and Meta-Analysis Facility (SyRF) database. PubMed, Embase, Web of Science, Google Scholar, and Scopus databases were used to conduct a systematic literature search about the gastrointestinal manifestations of COVID-19 with no publication time frame. Articles were found using the following search terms: ["COVID-19, Coronavirus, 2019-nCoV, Clinical Symptoms-Gastrointestinal or gastric or intestinal manifestations"].

Study selection

Initially, the selected publications were imported into the EndNote X9 software, and the duplicates were omitted. The titles and abstracts of the articles were screened, and the appropriate articles were considered for further analysis. In the next step, the eligible articles with appropriate inclusion criteria were selected.

Inclusion and exclusion criteria

Clinical articles evaluating the gastrointestinal manifestations of COVID-19 were included in this study. Publications with insufficient results, articles without a full text, papers with mismatches between methods and results, and misinterpretation of results were excluded from this review.

Data extraction

The data extracted from the selected articles were author, country, mean age, the number of patients, diarrhea, nausea or vomiting, decreased appetite or anorexia, and abdominal pain.

The complete PRISMA flow chart is depicted in Figure 2. Out of 27652 papers, 35 papers with publication dates up to 2022 met the inclusion criteria for this systematic review. Most articles (28 papers, 77.8%) were from China, in which 6730 patients with COVID-19 were studied. The point to consider in the current review study was that in various studies, the initial clinical symptoms of most patients with COVID-19 were reported as gastrointestinal

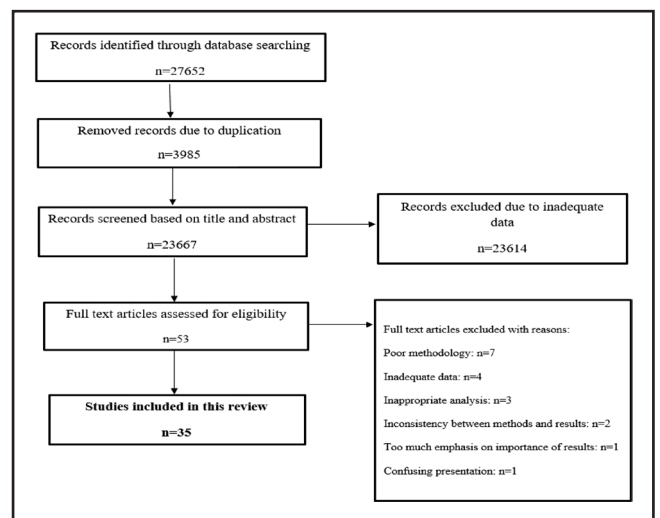


Figure 2. PRISMA flow chart of the present study.

manifestations, i.e., without fever or respiratory symptoms (Table 1). However, in general, the incidence of gastrointestinal manifestations in the studies varied (Table 2). The most common gastrointestinal manifestations were nausea or vomiting (13.1%), diarrhea (11.05%), anorexia (8.7%), and abdominal pain (2.4%), respectively.

DISCUSSION

COVID-19 is an infection with respiratory symptoms (dry cough and dyspnea) of a new known coronavirus that is thought to have emerged and mutated as a virus transmitted between humans

Table 1. The initial manifestation of COVID-19 is purely with gastrointestinal symptoms

Author Name	Sample size	No. primary gastrointestinal symptoms (%)	No. Diarrhea	No. Nausea or vomiting	No. Decreased appetite or anorexia	No. Abdominal pain
Han et al. (2020)	206	23.3	23	7	46.0	2
Luo et al. (2020)	1141	16.03	68	179	18	45
An et al. (2021)	9	100	1	1	6.0	1
Wang et al. (2020)	138	10.1	14	14	–	–

Table 2. Frequency of gastrointestinal manifestations in patients with COVID-19

Author	Country	Mean Age	Number of patients	Diarrhea	Nausea or vomiting	Decreased appetite or anorexia	Abdominal pain
Chang et al. (2020)	Beijing/China	34-48	13	7.69	–	–	–
Chen et al. (2020)	Wuhan/ China	55.5	99	2.02	2.02	–	–
Cheung et al. (2020)	Hong Kong	58.5	59	22.03	1.69	–	11.86
Fang et al. (2020)	Wuhan/ China	57.0	201	21.89	45.27	–	5.97
Gou et al. (2020)	Wuhan/ China	36.6	174	12.06	9.77	–	–
Guan et al. (2020)	Wuhan/ China	47.0	1099	3.73	5	–	–
Han et al. (2020)	Wuhan/ China	63.0	206	32.52	11.65	49.51	4.36
Hu et al. (2020)	Nanjing/ China	25-59	24	8.33	–	–	–
Huang et al. (2020)	Wuhan/ China	41-58	41	2.43	–	–	–
Jin et al. (2020)	Zhijiang/ China	45.6	651	8.14	2.61	–	–
Kong et al. (2020)	South Korea	20-73	28	7.14	–	–	–
Liu et al. (2020)	Hubei/ China	57.0	137	8.02	–	–	–
Luo et al. (2020)	Wuhan/ China	58.3	1141	5.65	22.17	15.77	3.94
Mo et al. (2020)	Wuhan/ China	54.0	155	4.51	3.87	–	1.93
Montazeri et al. (2021)	Iran	56.19	611	9.3	20.4	–	4.9
Ng et al. (2020)	Hong Kong	37-65	18	11.11	–	–	–
Nobel et al. (2020)	New York/USA	>18	278	20.14	22.66	–	–
Pan et al. (2020)	Hubei/ China	52.9	204	17.15	1.94	39.70	0.98
An et al. (2021)	Wuhan/ China	35.8	9	1.11	2.22	6.66	–
Qian et al. (2020)	Wuhan/ China	50.0	91	23.07	18.68	25.27	–
Redd et al. (2020)	Massachusetts/USA	>18	318	33.64	41.82	34.59	14.46
Shen et al. (2020)	Hong Kong	22-96	10	40	–	–	–
Shi et al. (2020)	Wuhan/ China	49.5	81	3.70	4.93	1.23	–
Song et al. (2020)	Shanghai/ China	49.0	51	9.80	5.88	17.64	–
Wang et al. (2020)	Wuhan/China	56.0	138	10.14	10.14	39.85	2.17
Wu et al. (2020)	Yancheng/China	46.1	80	1/25	1.25	–	–
Xiao et al. (2020)	Guangzhou/China	10-78	73	35.61	–	–	–
Xiong et al. (2020)	Wuhan/China	14-49	42	23.80	–	–	–
Xu et al. (2020)	Wuhan/China	50.0	90	5.55	7.77	–	–
Yang et al. (2020)	Wuhan/China	59.7	52	3.84	–	–	–
Zhang et al. (2020b)	Wuhan/China	57.0	139	12.94	17.26	12.23	5.57
Zhao et al. (2020)	Beijing/China	47.0	75	12	–	–	–
Zhou et al. (2020)	Wuhan/China	51.0	254	18.11	8.26	–	1.18
Zou et al. (2020)	Zhuhai/China	59.0	18	5.55	5.55	5.55	–

and animals or adapted in a way that allows pathogenesis among humans. Common symptoms in studies on COVID-19 patients' gastrointestinal disorders such as diarrhea, nausea, and vomiting have been reported (Chang *et al.*, 2020; Chen *et al.*, 2020; Cheung *et al.*, 2020; Fang *et al.*, 2020; Gou *et al.*, 2020; Guan *et al.*, 2020; Han *et al.*, 2020; Wang *et al.*, 2020; An *et al.*, 2021). Anorexia was the most common gastrointestinal symptom in adults, while diarrhea was reported as the most common symptom in both adults and children, and vomiting was more common in children than adults (Liu *et al.*, 2020; Pan *et al.*, 2020; Wu *et al.*, 2020; Xiao *et al.*, 2020; Xiong *et al.*, 2020).

On average, gastrointestinal bleeding was reported in 4-13.7% of the cases, whereas abdominal pain was more common in patients with critical conditions. It is thought that due to prolonged hypoxemia, cell necrosis induced by tissue hypoxia may damage the gastrointestinal mucosa cells, resulting in ulceration and malaise (Dorgalaleh, 2020). Most studies show that the SARS-CoV-2 virus enters intestinal enterocyte cells and respiratory tract cells by binding to the ACE-2 protein as a receptor. The ACE-2 receptor, located in the cell membrane, helps regulate blood pressure by controlling the level of the protein angiotensin, causing blood vessels to constrict, and thus increasing blood pressure (Junior *et al.*, 2021). Viruses enter intestinal cells after binding to ACE-2 via a spike protein. Spike proteins are a structural component of viruses that play a vital role in infiltrating host cells and initiating infection; once inside the cell, the virus uses the cell's ability to multiply (Zhang *et al.*, 2021). The spread of SARS-Cov-2 particles from infected cells releases cytokines. Cytokines are small proteins that play a key role in the inflammatory process. This inflammatory process causes gastrointestinal symptoms (Costela-Ruiz *et al.*, 2020). Gastrointestinal complications may also occur as a result of damage to the gastrointestinal tract caused by the virus, especially symptoms such as pain, nausea, and diarrhea (Nobel *et al.*, 2020; Zhang *et al.*, 2020a).

Some researchers suggested that COVID-19 may alter the gut microbiota (Liu *et al.*, 2022; Dhar and Mohanty, 2020). Microbiotas are a population of microbes that live naturally and beneficially in the gut (Liu *et al.*, 2022). Upon entering the gastrointestinal tract, the virus can pass through the portal vein. This can allow viruses to affect the vagus nerve and cause nausea. There is evidence that SARS-CoV-2 may also be transmitted through fecal-oral (Cuicchi *et al.*, 2021). The stool sample of the first person with SARS-CoV-2 in the United States contained virus particles. Some studies suggest that the virus may still be present in the stool even when it is undetectable in the upper respiratory tract, e.g., the lungs, nose, and throat. Still, more research is required to prove whether these viral particles are infectious (Cuicchi *et al.*, 2021).

People with gastrointestinal symptoms are more likely to develop heart disease, sustain kidney damage, or die when hospitalized. Many gastrointestinal diseases may also make it easier to develop gastrointestinal infections because they damage or weaken the lining of the gut or stomach. Some of these conditions, e.g., irritable bowel syndrome (IBS), can damage or weaken the lining of the gut due to weakness in the epithelial cells which also causes the overexpression of ACE-2 and gives viruses more time to enter the cells (Hu *et al.*, 2020). There are also several times more ACE-2 in the gastrointestinal tract than in the respiratory tract, which can lead to more virus accumulation in this area and more infection (Hu *et al.*, 2020). People who experience gastrointestinal symptoms may be more prone to coronary heart disease. A study conducted in November 2020 shows that experiencing these symptoms increases the risk of developing acute respiratory distress syndrome. This study also reported that experiencing gastrointestinal complications increases the risk of ventilation and intubation. Another study, conducted in late January 2021, found that people with these symptoms were more likely to develop coronary heart disease and die from it (Wang *et al.*, 2020).

CONCLUSION

The findings of the present review revealed that contrary to what was initially assumed in the COVID-19 outbreak, this infection does not manifest only as respiratory but also gastrointestinal symptoms. Therefore, clinicians and gastroenterologists must be alert of these unusual cases and the fecal-oral transmission during the COVID-19 pandemic and implement preventive strategies.

LIMITATIONS

The main limitation of this review study was the inadequate distribution of studies, as more than 70% of the studies were conducted in China. Further studies in different parts of the world are needed to reach such a conclusion.

ACKNOWLEDGEMENTS

The authors would like to thank the researchers at the University of Tabuk, the Research Centre at King Faisal Specialist Hospital and Research Center and Shaqra University for their assistance. The authors also extend their appreciation to the Deanship of Scientific Research (DSR), University of Tabuk, for funding this work through grant number: S-1441-0080.

Competing interests

The authors declare that they have no competing interests.

Funding

The Deanship of Scientific Research (DSR), the University of Tabuk for funding this work through grant No. S-1441-0080.

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