GASTROINTESTINAL SYMPTOMS ARE ASSOCIATED WITH SEVERITY OF CORONAVIRUS DISEASE 2019: A SYSTEMATIC REVIEW

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Abstract
Background:
Aim: *This study aims to summarize and evaluate the association between GI symptoms in COVID-19 and disease severity.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2019–2023. Duplicate publications, review articles, and incomplete articles were excluded.*

Results: *Database searches identified a total of 17632 articles. Of these, 100 articles passed the screening process, resulting in 15 articles for full-text assessment. Among them, 6 articles did not evaluate the outcome of interest. Hence, we found 9 appropriate studies included.*

Conclusion: *Current findings are insufficient to establish a association between GI symptoms and disease severity in COVID-19 patients.*

Keywords: *Gastrointestinal symptoms, Gastro intestinal manifestation, COVID-19 severity, Mortality*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new coronavirus identified as severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2). The first case was reported in December 2019 in Wuhan, China. On 30 January 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern (PHEIC), and declared it a pandemic since 11 March 2020.[1] As of June 2023, WHO has reported more than 760 million confirmed cases of COVID-19 globally.[2]

Most patients (80–81%) had COVID-19 with a low to moderate severity, however 14% of patients had severe disease, and 5.1%–6.1% of patients had a serious condition.[3,4] Fever, coughing, and fatigue/myalgia are the most typical COVID-19 symptoms.[4] According to a number of studies, individuals with COVID-19 experience a variety of gastrointestinal (GI) symptoms including diarrhea, stomach pain, nausea, vomiting, and appetite loss.[5,6] Angiotensin-converting enzyme 2 (ACE2) receptor-expressing cells are the entry point for SARS-CoV-2. The idea that GI symptoms in COVID-19 patients are brought on by the invasion of SARS-CoV-2 into host GI cells is supported by the fact that ACE2 is highly expressed in the glandular cells of the colon, small intestine, duodenum, and stomach.[3,7]

Therefore, it is crucial to investigate the association between gastrointestinal symptoms and disease severity of COVID-19 in order to predict the severity of the condition and provide the necessary early special care and treatment.

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords used are "Gastrointestinal Symptoms" OR "Gastrointestinal manifestations" AND "COVID-19" AND "Severity" OR "Mortality". The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	"Gastrointestinal Symptoms" OR "Gastrointestinal manifestations" AND "COVID-19 Severity" OR "Mortality"	3043
Cochrane Library	"Gastrointestinal Symptoms" OR "Gastrointestinal manifestations" AND "COVID-19 Severity" OR "Mortality"	112
Google Scholar	"Gastrointestinal Symptoms" OR "Gastrointestinal manifestations" AND "COVID-19 Severity" OR "Mortality"	80.400

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were original articles (observational studies including cohort, case control, cross-sectional) published in the last 5 years between 2019 and 2023, full-text articles available, published in English, and studied the association between DED and smoking. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the focus of interest of this study. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection.

Data Extraction and Parameter Measured

All the authors extracted the data from the articles. The following datas are collected: Author, year of publication, study design, sample size, age of the study subjects, male to female ratio, number of severe COVID-19 patients, GI manifestations in severe and non-severe patients, and p-value. All disagreements regarding the methodology, article retrieval, and statistical analysis were resolved by consensus among the authors.

Results

The databases search identified a total of 18.058 articles (Table 1). Of these, 100 articles passed the screening process, resulting in 20 articles for full-text assessment. Among them, 11 articles did not evaluate the outcome of interest. Hence, we found 9 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 2.
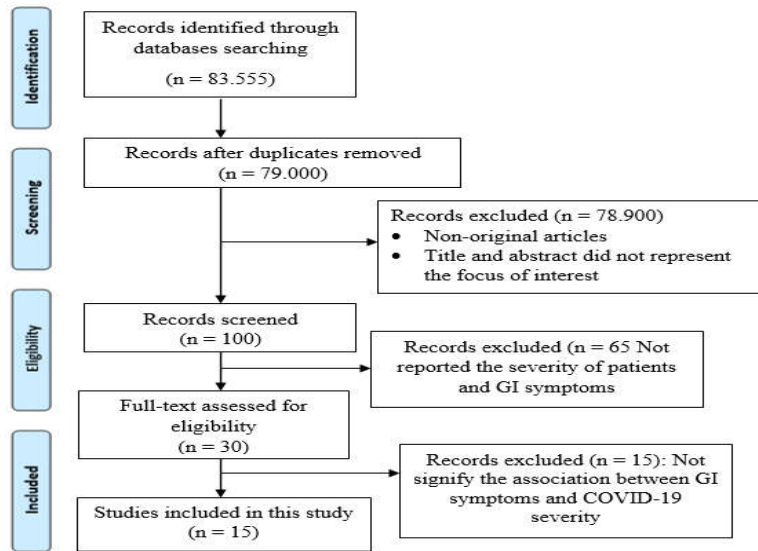
Figure 1. PRISMA flow diagram

Table 2. Summary of included studies

Author (Year)	Country	Study design	Sample size	Age (years)	Male/Female Ratio	Severe (ICU)	GI Manifestation in Severe/Critical Patients	GI Manifestation in Non-Severe Patients	p-value
C. Huang et al. 2020[8]	China	Case-control	41	Mean: 49	30/11	13	-	Diarrhea: 1	0.66
D. Wang et al. 2020[9]	China	Case-control	138	Mean: 56	75/63	36	Diarrhea: 6	Diarrhea: 8	0.20
							Abdominal pain: 3	Abdominal pain: 0	0.02*
							Nausea: 4	Nausea: 10	>.99
							Vomitting: 3	Vomitting: 2	0.13
G. Zhang et al. 2020[10]	China	Case-control	221	Mean: 55	108/113	55	Diarrhea: 9	Diarrhea: 16	0.172
							Abdominal pain: 2	Abdominal pain: 3	0.429
JJ Zhang et al. 2020[11]	China	Case-control	140	Mean: 57	69/72	58	Diarrhea: 9	Diarrhea: 9	0.406
							Abominal pain: 6	Abominal pain: 2	0.064
							Nausea: 5	Nausea: 19	0.027*
							Vomitting: 2	Vomitting: 5	0.700
L.Mao et al. 2020[12]	China	Case-control	214	Median: 52.7	87/127	88	Diarrhea: 13	Diarrhea: 28	0.17
							Abdominal pain: 6	Abdominal pain: 4	0.21
Q. Chen et al. 2020[13]	China	Case-control	145	Mean: 47.5	79/66	43	Diarrhea: 16	Diarrhea: 23	0.07
							Abdominal pain: 2	Abdominal pain: 6	1
							Nausea: 10	Nausea: 14	0.16
R. He et al. 2020[14]	China	Case-control	204	Median: 49	79/125	69	Diarrhea: 5	Diarrhea: 14	0.486
R. Zhang et al. 2020[15]	China	Case-control	120	Mean: 45.4	43/77	30	Diarrhea: 5	Diarrhea: 2	0.011*
							GI Discomfort: 5	GI Discomfort: 5	0.119
Y. Wan et al. 2020[16]	China	Cohort	230	Median: 47.5	129/101	61	Diarrhea: 26	Diarrhea: NR	<0·0001
Nobel et al. 2020[17]	America	Case-control	516	>18	253/263	NR	Diarrhea: 11	Diarrhea: 76	>0.20
							Nausea, vomiting: 8	Nausea, vomiting: 51	>0.20
Ghweil et al. 2020[18]	Egypt	Case-control	66	Mean: 55.5	48/18	30	Diarrhea: 0	Diarrhea: 1	0.358
J. Huang et al. 2020[19]	China	Case-control	308	>18	151/157	238	Diarrhea: 31	Diarrhea: 10	0.703
L.Yang et al. 2020[20]	China	Case-control	200	Mean: 55	98/102	29	Diarrhea: 3	Diarrhea: 11	0.54
							Nausea, vomiting: 2	Nausea, vomiting: 2	0.04*
J. Zhang et al. 2020[21]	China	Cohort	663	Mean: 55.6	321/342	409	Diarrhea: 36	Diarrhea: 25	0.003*
							Abdominal pain: 3	Abdominal pain: 2	0.643
							Nausea: 20	Nausea: 11	0.923
							Vomiting: 11	Vomiting: 6	0.895
Z. Zhong et al. 2020[22]	China	Case-control	48	>10	31/17	9	Diarrhea: 3	Diarrhea: 3	>0.1
							Nausea, vomiting: 0	Nausea, vomiting: 4	>0.5

Discussion

Due of its high infectivity, COVID-19 is causing a significant pandemic and is a serious health emergency. Respiratory symptoms are frequently prevalent in the patients. However, a lot of people also exhibit diarrhea, abdominal pain or discomfort, vomiting, and nausea. The prevalence of GI symptoms in COVID-19 patients was varied across many studies. According to Hossain et al., in a total of 3646 patients, GI symptoms were documented in (10.1%–16.2%) patients. The most prevalent GI symptom was diarrhea (47%).[23] Wang et al. reported that patients who required intensive care unit care experienced abdominal pain more frequently than those who did not.[9] There is conflicting evidence about the prevalence of GI symptoms in patients with severe COVID-19. According to Fang et al., high GI symptoms are common in both stable and severe patients, with prevalence rates of 85% and 79%, respectively.[24] A thorough examination of 1,099 patients revealed no variations in the percentage of GI symptoms in severe versus non-severe COVID-19 cases, which led researchers to notice a similar tendency.[25]

This study evaluates the association between GI symptoms and COVID-19 patient severity. Of 15 studies included, only five studies that found a statistically significant difference of GI symptoms among patients with severe disease versus those with non-severe disease. Our findings are insufficient to establish an association between GI symptoms and disease severity in COVID-19 patients. The previous systematic review also found a similar findings with our study.[26] However, other systematic review and meta-analysis that evaluate the association of COVID-19 disease severity and GI symptoms showed a significant association.[27,28]

The GI tract and liver may also be SARS-CoV-2's target organs, according to accumulated data on gastrointestinal complaints in COVID-19 patients. Although the cause is unknown, the potential to infect the GI tract is associated with ACE 2 expression in the stomach, ileum, and colon epithelial cells as well as the liver cholangiocyte. According to Xiao et al., who found significant viral staining in these regions, this theory is validated.[7] The SARS-CoV-2 virus may also harm the digestive tract by triggering an inflammatory response. Acute respiratory distress syndrome (ARDS) may result from this reaction, which is brought on by viremia, altering the gut flora, which in turn affects the respiratory flora. This "gut-lung axis" effect might be able to explain why COVID-19 individuals who have respiratory involvement also experience gastrointestinal symptoms.[23,29] According to Liang et al.19, increased ACE2 expression in proximal and distal enterocytes may make the gut susceptible to SARS-CoV-2 infection. Intestinal flora is disrupted by GI symptoms like vomiting and diarrhea, and electrolyte disturbances like low potassium and sodium and water balance are caused. This will probably make the patients' situation worse.[30] However, more research examining these underlying mechanisms of how GI symptoms associated with the disease severity of COVID-19 is required.

As the majority of included studies were conducted in hospital contexts in China, generalizability is one of the study's limitations. Recently, flawed methodology and a lack of a systematic approach have been reported in a number of studies, a trend driven by healthcare organizations with skepticism that require swift data dissemination with high-quality peer review.

Conclusion

Our findings are insufficient to establish an association between GI symptoms and disease severity in COVID-19 patients. Large prospective multicentric investigations are necessary to confirm our findings.

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