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ORIGINAL ARTICLE

Meta-analysis of the demographic and prognostic significance of gastrointestinal symptoms in COVID-19 patients

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Abstract

Background and Aim: To evaluate the demographic and prognostic significance of gastrointestinal (GI) symptoms in patients with coronavirus disease 2019 (COVID-19).

Methods: A systematic search of electronic information sources was conducted. Combined overall effect sizes were calculated using random-effects models for baseline demographic factors and outcomes including mortality, intensive care unit (ICU) admission, and length of hospital stay.

Results: Twenty-four comparative observational studies reporting a total of 51 522 COVID-19 patients with (n = 6544) or without (n = 44 978) GI symptoms were identified. The patients with GI symptoms were of comparable age (mean difference [MD]: 0.25, 95% confidence interval [CI] −2.42 to 2.92, P = 0.86), rate of pre-existing hypertension (odds ratio [OR]: 1.11, 95% CI 0.86–1.42, P = 0.42), diabetes mellitus (OR: 1.14, 95% CI 0.91–1.44, P = 0.26), and coronary artery disease (OR: 1.00, 95% CI 0.86–1.16, P = 0.98) compared with those without GI symptoms. However, there were significantly more male patients in the GI symptoms group (OR: 0.85, 95% CI 0.75–0.95, P = 0.005). The presence of GI symptoms was associated with similar risk of mortality (OR: 0.73; 95% CI 0.47–1.13, P = 0.16), ICU admission (OR: 1.15; 95% CI 0.67–1.96, P = 0.62), and length of hospital stay (MD: 0.43; 95% CI −0.73 to 1.60, P = 0.47) when compared with their absence.

Conclusion: Meta-analysis of the best possible available evidence demonstrated that GI symptoms in COVID-19 patients do not seem to affect patients with any specific demographic patterns and may not have any important prognostic significance. Although no randomized studies can be conducted on this topic, future high-quality studies can provide stronger evidence to further understand the impact of GI symptoms on outcomes of COVID-19 patients.

Introduction

Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was declared a Public Health Emergency of International Concern on 30 January 2020,[1] and a pandemic on 11 March 2020.[2]

Clinical manifestations of COVID-19 are variable from asymptomatic/mild cases to patients becoming critically ill with fulminant pneumonia and acute respiratory distress. All ages are susceptible with more severe disease generally seen in older males with underlying comorbidities. Common symptoms include fever, fatigue, and dry cough.[2] Other symptoms that have been reported include anosmia, ageusia, sputum production, chest discomfort, and gastrointestinal (GI) manifestations such as nausea, vomiting, abdominal discomfort, and diarrhea,[3] which can be chronic and disabling.

COVID-19 can involve persistence (long COVID), sequelae, and other medical complications that last weeks to months after initial recovery. One study estimated a total of 55 long-term effects associated with COVID-19 including fatigue, headache, joint pain, and digestive tract symptoms.[4]

Medical complications include the development of rare but severe disorders such as multisystem inflammatory syndrome in children (MIS-C), associated with current or recent SARS-CoV-2 infection.[5] MIS-C seems to show a male predilection with no significant racial predisposition.[6] Although this syndrome was first described in children, these sequalae may also develop in

the adult population (MIS-A).[7] GI signs and symptoms such as abdominal pain, nausea/vomiting, and diarrhea can appear prominently as presenting features of MIS-C.[8] Prompt recognition and specialist treatment are required to prevent shock and multi-organ failure.

The incidence of GI symptoms in the acute setting in patients with COVID-19 varies and considering the existence of several confounding factors, estimation of the true incidence can be challenging. Although the respiratory tract appears to be the primary target of the novel coronavirus, the impact of GI symptoms on the severity of disease and outcomes remains undetermined.

We aimed to conduct a comprehensive systematic review and meta-analysis of baseline characteristics and reported outcomes to evaluate the demographic and prognostic significance of GI symptoms in patients with COVID-19.

Methods

The eligibility criteria, methodology, and investigated outcome parameters of this study were highlighted in a review protocol, which was registered at the International Prospective Register of Systematic Reviews (registration number: CRD42021283173).[9] Our methodology respected the Cochrane Handbook for Systematic Reviews of Interventions[10] and standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11]

Study design: Considering that COVID-19 with GI symptoms is a condition rather than an intervention, performing a randomized controlled trial (RCT) on the topic of the current study is not possible. Therefore, all comparative observational studies comparing the demographic factors and outcomes of COVID-19 with and without associated GI symptoms were considered eligible for inclusion.

Population: Patients of any age or gender with a confirmed acute diagnosis of COVID-19.

Exposure of interest: Presence of one or more GI symptoms at the time of presentation to a healthcare provider.

Comparison of interest: Absence of GI symptoms at the time of presentation.

The baseline demographic factors of interest: Age, gender, hypertension, diabetes mellitus, and coronary artery disease.

The outcome measures of interest: Mortality, intensive care unit (ICU) admission, and length of hospital stay.

Literature search strategy. A comprehensive search strategy was structured based on thesaurus headings, search operators, and limits in PubMed, Web of Science (WOS), and EMBASE. Two authors conducted the literature search via the above databases and searched World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/, ClinicalTrials.gov http://clinicaltrials.gov/, and ISRCTN Register http://www.isrctn.com/ to identify ongoing and unpublished studies. Moreover, the same reviewers independently evaluated the reference lists of included studies and reviews to identify relevant trials. The last literature search was conducted on 08/05/2022. Appendix 1 presents the search strategy that was used to perform the literature search.

Selection of studies. The title and abstract of articles found as a result of the literature search were assessed by two authors. When deemed necessary, the full texts of relevant articles were retrieved and carefully assessed against the eligibility criteria of this review. Studies that met the inclusion criteria were considered for inclusion. Disagreements in this process were resolved by discussion between the authors. However, if the disagreement still existed, an independent author was consulted.

Data extraction and management. An electronic data extraction spreadsheet according to the Cochrane's recommendations for intervention reviews was created and was pilot tested in randomly selected articles and adjusted accordingly. The following information was extracted from each of the included studies by two independent reviewers:

- study-related data;
- baseline demographic and clinical information of the study populations;
- primary and secondary outcome data.

Discrepancies in this stage were resolved following consultation with an additional author.

Assessment of risk of bias. As all the included studies were observational, assessment of their methodological quality and risk of bias were carried out by two authors using the Newcastle–Ottawa scale (NOS).[12] The NOS is a star-based scoring system (maximum score: 9), which enables review authors to evaluate an observational study in the following aspects: the selection of the study groups, the comparability of the groups, and the ascertainment of outcome of interest. Studies with score of nine stars were deemed to be at low risk of bias, studies with score of seven or eight stars were deemed to be at medium risk of bias, and those that scored six or less were judged to be at high risk of bias. Disagreements in this stage were resolved by discussion between the assessing authors. A third reviewer was consulted if the discrepancies remained unresolved.

Summary measures and synthesis. Analyses were conducted using Review Manager 5.4 software. Mean difference (MD) was computed for continuous outcome variables and odds ratio (OR) was calculated for dichotomous outcome variables. The I^2 using Cochran Q test (χ^2) was used to quantify heterogeneity. When mean values were not available for continuous outcomes, data on median and interquartile range (IQR) were extracted and subsequently converted to mean and SD using the well-practiced equation described by Hozo *et al.*[13] Random-effects modeling was used for analysis. We reported the results of our analysis for each outcome parameter in a forest plot with 95% confidence intervals (CIs).

The unit of analysis regarding all evaluated outcomes was an individual participant. Where possible, data regarding drop-outs, withdrawals, and other missing information were recorded. We planned to contact authors of the included studies where information about our outcome of interest was not reported.

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0–50% might not be important; 50–75% may represent moderate heterogeneity;

75–100% may represent substantial heterogeneity. Moreover, where more than 10 studies were available for analysis of an outcome parameter, funnel plots were constructed to assess their symmetry to visually evaluate publication bias.

We conducted sensitivity analyses to explore potential sources of heterogeneity and assess the robustness of our results. We evaluated the effect of each study on the overall effect size and heterogeneity by repeating the analysis after excluding one study at a time (leave-one-out sensitivity analysis).

Meta-regression analysis of effect estimates were modeled to assess whether the difference in age, gender, hypertension, coronary artery disease, and diabetes between the two groups affected the effect estimates.

Results

The literature search resulted in 9609 articles. Of those, 102 studies were shortlisted for potential inclusion following assessment of their titles, abstracts, or full texts. Further, 78 studies were excluded as 61 were single-arm studies and 17 did not provide sufficient data. Therefore, 24 comparative observational studies[14–37] were deemed appropriate for inclusion (Fig. 1). The total number of included patients was 51 522 patients of whom 6544 patients had COVID-19 with GI symptoms and 44 978 patients had COVID-19 without GI symptoms.

Of the 24 studies included in this review, 20 reported on hospitalized patients only.[15–32,34,36] The remainder[14,33,35,37] provided data on a mixed cohort of patients including those hospitalized (in-patients) and those not admitted (outpatients/ambulatory).

Moreover, 18 of our included studies[15–18,22,24–27,29–37] assessed GI symptoms only once at the time of presentation to a healthcare facility. One study assessed GI symptoms both on presentation and during hospital admission.[21]

For the remaining five studies,[14,19,20,23,28] timing of assessment of GI symptoms was not explicitly stated. Although one can reasonably infer that this was once only at the point of admission/presentation. Tables 1 and 2 present the date of publication and country of origin, study design, and sample size of the included studies along with the definition of GI symptoms.

Risk of bias in included studies. Table 3 highlights the outcomes of methodological quality assessment based on the NOS.

Demographic factors. Demographic factors are summarized in Figure 2.

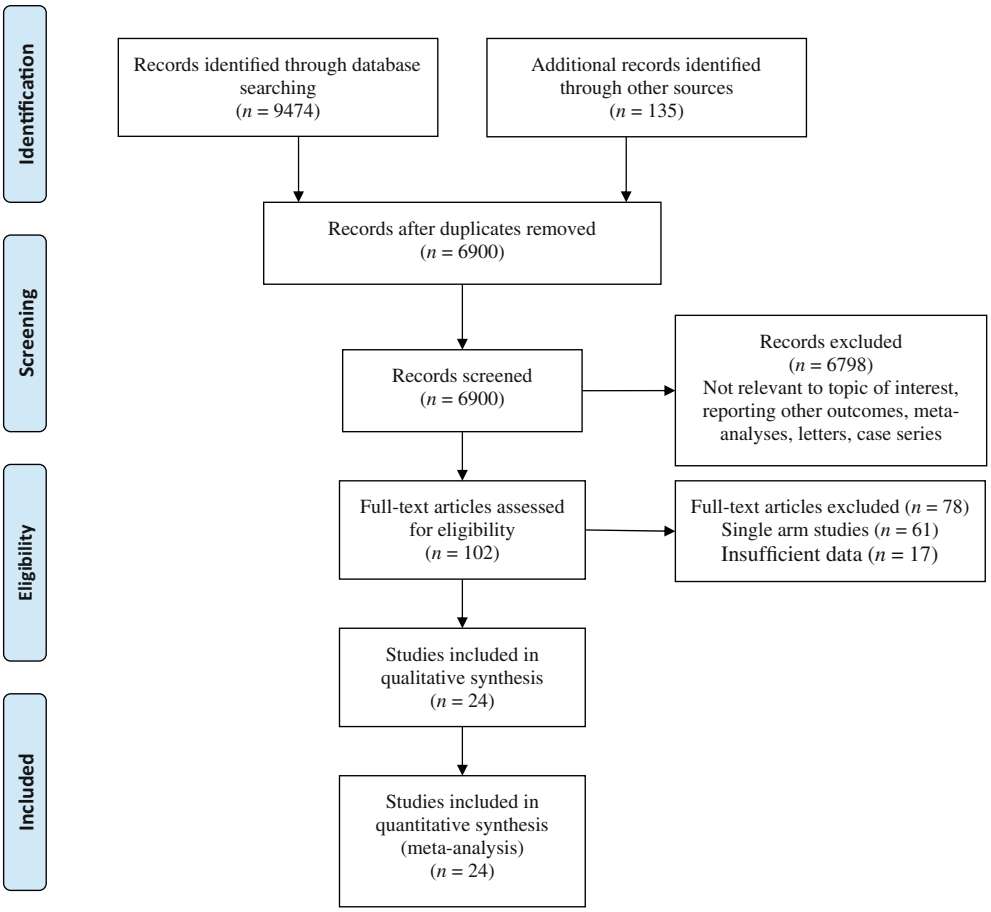


Figure 1 PRISMA flow diagram

Table 1 Study characteristics

Author	Year	Country	Study design	Characteristics of included studies				
				Study population	Total SARS-CoV-2 positive (*n*)	Gastrointestinal symptoms (*n*)		Timing of GI symptoms assessment
						Present	Absent	
Ghoshal *et al.*	2020	India	Observational (prospective)	Hospitalized/ ambulatory	252	26	226	NR
Kang *et al.*	2020	Korea	Observational (retrospective)	Hospitalized	118	54	64	Initial presentation
Jin *et al.*	2020	China	Observational (retrospective)	Hospitalized	651	74	577	Initial presentation
de Moura *et al.*	2020	Brazil	Single-center cohort study (prospective)	Hospitalized	400	133	267	Initial presentation
Ramachandran *et al.*	2020	United States	Single-center cohort study (retrospective)	Hospitalized	150	31	119	Initial presentation
Zhang *et al.*	2020	China	Observational (retrospective)	Hospitalized	505	164	341	NR
Cao *et al.*	2020	China	Observational	Hospitalized	157	63	94	NR
Lin *et al.*	2020	China	Single-center cohort study (retrospective)	Hospitalized	95	58	37	Initial presentation and during hospital admission
Wan *et al.*	2020	China	Multi-center observational study (retrospective)	Hospitalized	230	49	181	Initial presentation
Wei *et al.*	2020	China	Single-center cohort study (retrospective)	Hospitalized	84	26	58	NR
Han *et al.*	2020	China	Single-center cohort study (retrospective)	Hospitalized	206	117	89	Initial presentation
Pan *et al.*	2020	China	Descriptive, cross-sectional, multi-center study	Hospitalized	204	103	101	Initial presentation
Grover *et al.*	2021	United States	Multi-center cohort study (prospective)	Hospitalized	395	23	13	Initial presentation
Zheng *et al.*	2020	China	Observational (retrospective)	Hospitalized	1320	192	1128	Initial presentation
Zhou *et al.*	2020	China	Single-center cohort study	Hospitalized	254	66	188	NR
Xiong *et al.*	2021	China	Observational (prospective)	Hospitalized	244	34	210	Initial presentation
Gonzalez Jimenez *et al.*	2020	Spain	Multi-center, descriptive, observational study	Hospitalized	101	58	43	Initial presentation
Redd *et al.*	2020	United States	Multi-center cohort study (prospective)	Hospitalized	318	195	123	Initial presentation
Schettino *et al.*	2021	Italy	Single-center cohort study (prospective)	Hospitalized	190	138	52	Initial presentation
Hajifathalian *et al.*	2020	United States	Observational (retrospective)	Hospitalized/ outpatients	1059	349	710	Initial presentation
Bishehsari *et al.*	2022	United States	Observational (retrospective)	Hospitalized/ outpatients	921	206	715	Initial presentation
Delavari *et al.*	2022	Iran	Observational	Hospitalized/ outpatients	42 964	4187	38 777	Initial presentation
Fallouh *et al.*	2022	United States	Single-center cohort study (retrospective)	Hospitalized	382	154	228	Initial presentation
Patel *et al.*	2022	United States	Observational (retrospective)	Hospitalized	1672	44	637	Initial presentation

GI, gastrointestinal; NR, not recorded.

Age: Eighteen studies reported data on age of the included populations. Pooled analysis of 36 240 patients demonstrated no significant difference in age between GI symptoms and no GI symptoms groups (MD: 0.25, 95% CI −2.42 to 2.92, $P = 0.86$). Cochran Q test revealed a significant level of between-study heterogeneity ($I^2 = 92\%$, $P < 0.00001$).

Male gender: Twenty-three studies provided data on gender of the included populations. Pooled analysis of 38 296 patients showed significantly higher number of males in patients with GI symptoms compared with those without GI symptoms (OR: 0.85, 95% CI 0.75–0.95, $P = 0.005$). Cochran Q test revealed a low level of between-study heterogeneity ($I^2 = 24\%$, $P = 0.15$).

Hypertension: Seventeen studies provided data on the number of hypertensive patients in their study groups. Pooled analysis of 35 694 patients did not show any significant

Table 2 Study characteristics

Author	Year	Country	Definition of GI symptoms
Ghoshal *et al.*	2020	India	Anorexia, nausea, vomiting, diarrhea, abdominal pain/ discomfort
Kang *et al.*	2020	Korea	Diarrhea
Jin *et al.*	2020	China	At least one of: nausea, vomiting, diarrhea
de Moura *et al.*	2020	Brazil	Diarrhea, nausea, anorexia, vomiting, abdominal pain, dysphagia, weight loss, GI bleed, constipation
Ramachandran *et al.*	2020	United States	Nausea, vomiting, diarrhea, or abdominal pain
Zhang *et al.*	2020	China	Not specified
Cao *et al.*	2020	China	One or more of: anorexia, nausea, diarrhea
Lin *et al.*	2020	China	Not specified
Wan *et al.*	2020	China	Diarrhea
Wei *et al.*	2020	China	Not specified but divided into diarrhea *versus* non-diarrhea group
Han *et al.*	2020	China	One or more including: anorexia, vomiting, diarrhea, abdominal pain
Pan *et al.*	2020	China	Lack of appetite, diarrhea, vomiting, abdominal pain
Grover *et al.*	2021	United States	Not specified
Zheng *et al.*	2020	China	Diarrhea, abdominal pain, nausea & vomiting, anorexia
Zhou *et al.*	2020	China	Not specified
Xiong *et al.*	2021	China	At least one of: diarrhea, nausea & vomiting, abdominal pain, decreased feeding
Gonzalez Jimenez *et al.*	2020	Spain	Not specified
Redd *et al.*	2020	United States	Not specified
Schettino *et al.*	2021	Italy	Abdominal pain, diarrhea, nausea, vomiting, hyporexia/anorexia
Hajifathalian *et al.*	2020	United States	Nausea, vomiting, diarrhea, or abdominal pain
Bishehsari *et al.*	2022	United States	Diarrhea, nausea/vomiting, abdominal pain
Delavari *et al.*	2022	Iran	Any self-reported stomach pain, nausea, vomiting, diarrhea, anorexia, and fever
Fallouh *et al.*	2022	United States	Abdominal pain, nausea, vomiting, or diarrhea
Patel *et al.*	2022	United States	Diarrhea, nausea, vomiting, abdominal pain

GI, gastrointestinal.

difference in the number of hypertensive patients between the two groups (OR: 1.11, 95% CI 0.86–1.42, $P = 0.42$). Cochran Q test revealed a moderate level of between-study heterogeneity ($I^2 = 66\%$, $P < 0.0001$).

Diabetes mellitus: Seventeen studies provided data on the number of diabetic patients in their study groups. Pooled analysis of 35 692 patients did not show any significant difference in the number of diabetic patients between the two groups (OR: 1.14, 95% CI 0.91–1.44, $P = 0.26$). Cochran Q test revealed a moderate level of between-study heterogeneity ($I^2 = 53\%$, $P = 0.005$).

Coronary artery disease: Ten studies provided data on the number of patients with coronary artery disease in their study groups. Pooled analysis of 33 108 patients did not show any significant difference in the number of patients with coronary artery disease between the GI symptoms and no GI symptoms groups (OR: 1.00, 95% CI 0.86–1.16, $P = 0.98$). Cochran Q test revealed a low level of between-study heterogeneity ($I^2 = 0\%$, $P = 0.60$).

Outcome synthesis. Outcomes are summarized in Figures 3 and 4.

Mortality: Fourteen studies reported mortality of their patients as an outcome. The mortality rate in patients with GI symptoms was 8.0%, while it was 10.5% in patients without GI symptoms. Pooled analysis of 34 853 patients demonstrated no significant difference in mortality rate between the two groups (OR: 0.73; 95% CI 0.47–1.13, $P = 0.16$). Cochran Q test revealed a significant level of between-study heterogeneity ($I^2 = 79\%$, $P < 0.00001$).

ICU admission: Eleven studies reported rate of ICU admission as an outcome. The rate of ICU admission in patients with and without GI symptoms were 20.3 and 18.7%, respectively. Pooled analysis of 5168 patients demonstrated no significant difference in ICU admission rate between the two groups (OR: 1.15; 95% CI 0.67–1.96, $P = 0.62$). Cochran Q test revealed a significant level of between-study heterogeneity ($I^2 = 83\%$, $P < 0.00001$).

Length of hospital stay: Ten studies reported length of hospital stay of the patients as an outcome. The mean length of stay in patients with and without GI symptoms were 15.7 ± 6.7 days and 15.1 ± 5.4 days, respectively. Pooled analysis of 34 117 patients demonstrated no significant difference in length of hospital stay between the two groups (MD: 0.43; 95% CI −0.73 to 1.60, $P = 0.47$). Cochran Q test revealed a significant level of between-study heterogeneity ($I^2 = 84\%$, $P < 0.00001$).

Table 3 Risk of bias assessment

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis controlled for confounders	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts
Ghoshal *et al.* (2020)	*	*	*	*	**	*		*
Kang *et al.* (2020)	*	*	*		*	*	*	*
De Moura *et al.* (2020)	*	*	*		*	*	*	*
Ramachandran *et al.* (2020)	*	*	*		*	*		*
Zhang *et al.* (2020)	*	*	*		*	*		*
Cao *et al.* (2020)	*	*	*		*	*		*
Lin *et al.* (2020)	*	*	*			*		*
Jin *et al.* (2020)	*	*	*	*	**	*		*
Wan *et al.* (2020)	*	*	*		*	*		*
Wei *et al.* (2020)	*	*	*			*		*
Han *et al.* (2020)	*	*	*		**	*	*	*
Pan *et al.* (2020)	*	*	*		*	*	*	*
Grover *et al.* (2021)	*	*	*		**	*		*
Zheng *et al.* (2020)	*	*	*		*	*	*	*
Zhou *et al.* (2020)	*	*	*		*	*	*	*
Xiong *et al.* (2021)	*	*	*		*	*		
Gonzalez Jimenez *et al.* (2020)	*	*			*	*		*
Redd *et al.* (2020)	*	*	*			*	*	*
Schettino *et al.* (2021)	*	*	*		*	*	*	*
Hajifathalian *et al.* (2020)	*	*	*		*	*		*
Bishehsari *et al.* (2022)	*	*	*		*	*		*
Delavari *et al.* (2022)	*	*	*		**	*	*	*
Fallouh *et al.* (2022)	*	*	*		*	*		*
Patel *et al.* (2022)	*	*	*			*		*

* = 1 point.

** = 2 points.

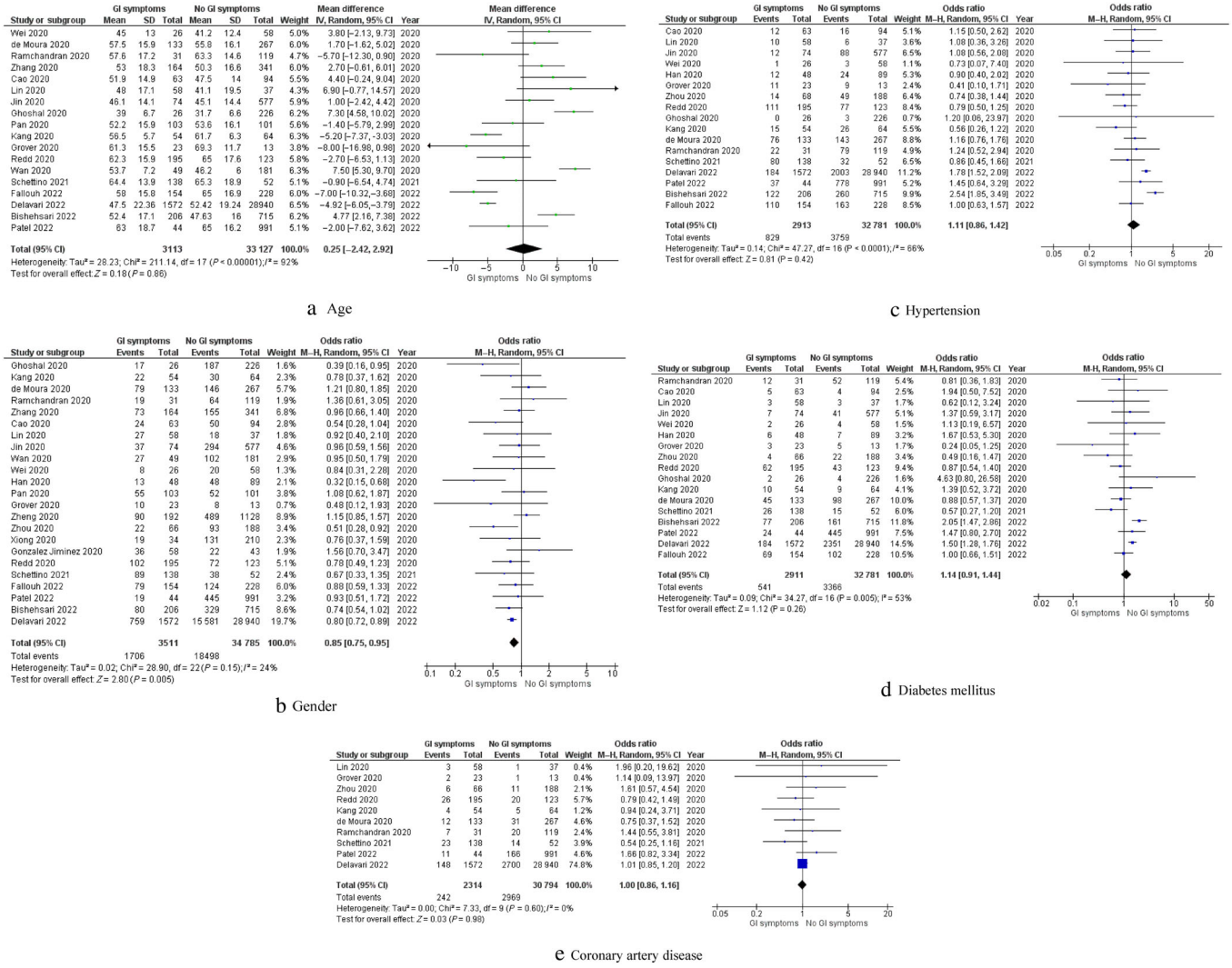


Figure 2 Forest plots of comparison of (a) age, (b) gender (c) hypertension, (d) diabetes mellitus, and (e) coronary artery disease. The solid squares denote the odds ratio, the horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size. GI, gastrointestinal; M–H, Mantel–Haenszel test

Sensitivity analysis. The direction of pooled effect size remained unchanged when the OR, risk ratio (RR), or risk difference (RD) was calculated or during leave-one-out sensitivity analysis.

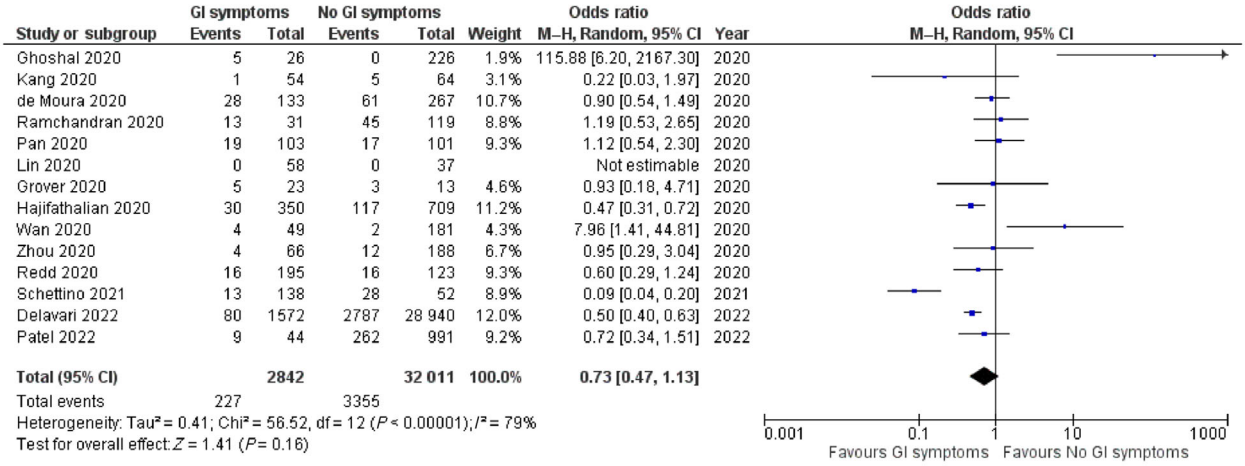
Meta-regression analysis. Meta-regression analyses suggested that the baseline difference in age ($P = 0.046$) and diabetes ($P = 0.003$) between the two groups affected the effect estimate for mortality, but the effect estimate for mortality was not affected by baseline difference in gender ($P = 0.904$), hypertension ($P = 0.200$), or coronary artery disease ($P = 0.139$).

Discussion

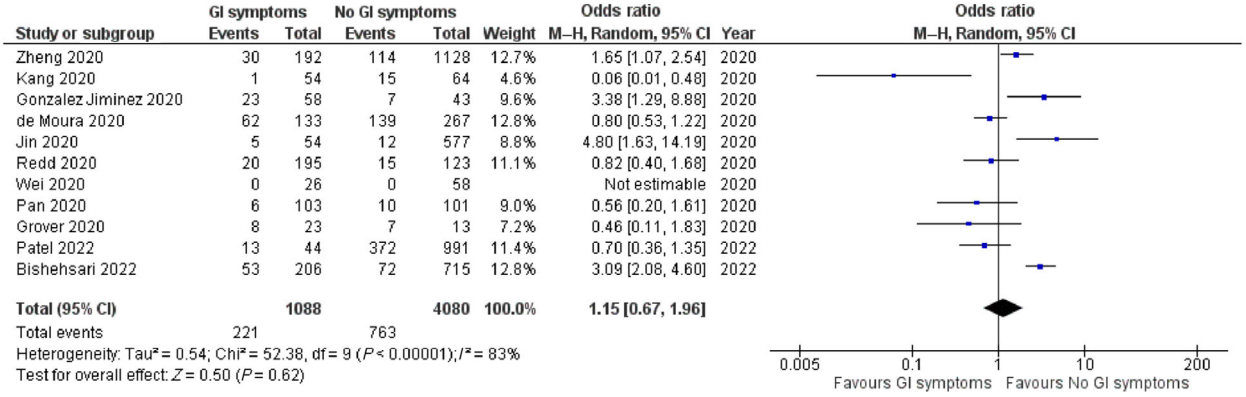
In view of unknown prognostic significance of GI symptoms associated with COVID-19, we conducted a comprehensive literature search and identified 24 comparative observational studies[14–37] reporting a total of 51 522 COVID-19 patients of whom 6544 patients had GI symptoms and 44 978 patients did not have any GI symptoms. The subsequent meta-analysis of outcomes demonstrated that the presence of GI symptoms was associated with similar risk of mortality, ICU admission, and length of hospital stay when compared with their absence. The between-study heterogeneity was significant in the analysis of all the evaluated outcomes.

Furthermore, alongside the outcome parameters, we objectively evaluated the baseline characteristics of the study populations and demonstrated that the patients with GI symptoms were of comparable age, rate of pre-existing hypertension, coronary artery disease, and diabetes mellitus compared with those without GI symptoms although there were more male patients in the GI symptoms group.

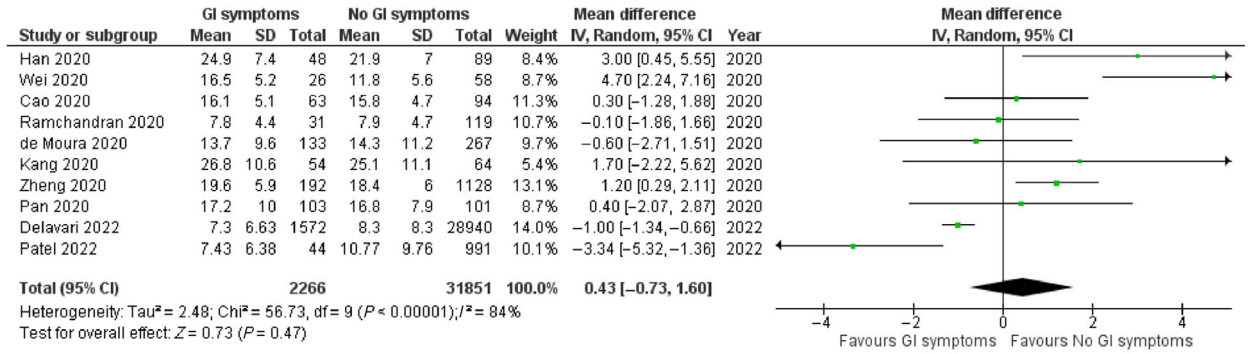
Moreover, we conducted meta-regression analysis, which indicated that the baseline difference in age and diabetes between



a Mortality



b Proportion of patients admitted to ITU



c Length of hospital stay

Figure 3 Forest plots of comparison of (a) mortality, (b) proportion of patients admitted to intensive therapy unit, and (c) length of hospital stay. The solid squares denote the odds ratio or mean difference. The horizontal lines represent the 95% confidence intervals (CIs), and the diamond denotes the pooled effect size. GI, gastrointestinal; M–H, Mantel–Haenszel test

the two groups affected the effect estimate for mortality, but the effect estimate for mortality was not affected by baseline difference in gender, hypertension, or coronary artery disease.

The reported incidence of GI symptoms in COVID-19 patients varies with estimates ranging between 3 and 39%.[38] Moreover, the literature on the association between these

symptoms and COVID-19 disease severity is also conflicting. Some studies have suggested a "protective" effect with patients experiencing a mild/moderate illness,[39] while others have found more severe symptoms of pneumonia.[22] This may in part reflect on the quality and type of studies commenting on this association (largely observational retrospective data).

A study on the significance of GI symptoms in COVID-19 patients found 22.4% of their cohort reporting at least one symptom at the onset of infection, with diarrhea being the most common complaint (70%). This group (compared to absence of GI symptoms) were older with higher BMI and more prevalent rates of diabetes and hypertension.[35]

Even after adjustment for demographics, comorbidities, and other clinical symptoms, the presence of GI symptoms and in particular diarrhea and/or abdominal pain were independently linked to poor outcomes including hospitalization, intensive therapy unit (ITU) admission, acute respiratory distress syndrome (ARDS), and increased rate of intubation.[35]

A meta-analysis of 21 articles[38] (mainly from China) suggested regional differences in the relationship between diarrhea and COVID-19 severity. Overall analysis showed a severe rate of COVID-19 in patients with diarrhea of 41.1% with a pooled OR reaching statistical significance. However, further subgroup and sensitivity analysis failed to show a significant association.

The authors did demonstrate a significant correlation between abdominal pain and disease severity. A 2.8-fold increased risk of severe COVID-19 was estimated in patients with abdominal pain. However, due to the variable reporting a significant association between nausea and vomiting, disease severity was not established.[38]

A further review showed a similar significant association between abdominal pain and severe COVID-19. The incidence of other common GI symptoms showed no difference between severe and mild–moderate cases.[40]

In terms of GI symptom frequency in patients infected with SARS-CoV-2, a large systematic review (158 studies, $n = 78\,798$) reported as follows: diarrhea (16.5%), nausea (9.7%), anorexia/loss of appetite (1.6%), vomiting (1.5%), and abdominal pain (4.5%). They also failed to demonstrate a significant association between the presence of GI symptoms and indicators of severe disease such as admission to ITU and increased mortality rate.[41]

Cumulative incidence of GI symptoms occurring in COVID-19 patients was estimated as follows by Wang *et al.*[42]: diarrhea (25%), nausea (16%), vomiting (7.5%), and abdominal pain (3.6%). In keeping with previous conclusions, no significant correlation between the presence of GI symptoms and mortality was demonstrated.

Finally, Mao *et al.*[43] reported a pooled prevalence of GI symptoms of 15% in patients with COVID-19 at diagnosis and these were associated with a significantly increased risk of developing ARDS. However, pooled rates of hospital discharge, length of stay, and mortality rates were unaffected by the presence of digestive symptoms. In keeping with the above findings, abdominal pain seemed to have a higher prevalence in patients with severe disease compared with non-severe COVID-19.

In summary, from the published literature, it is difficult to determine disease severity and risk stratify COVID-19 patients based on the presence or absence of GI symptoms. Some evidence suggests a possible link between abdominal pain and increased COVID-19 severity. This link remains unclear, and the "gut–lung" axis has been proposed as a potential mechanism. Altered gut flora secondary to viral invasion may lead to changes in immune regulation and effects on the respiratory system, but this warrants further investigation.

Overall, the analysis of best available evidence does not seem to demonstrate a significant correlation between GI symptoms and disease severity in patients with COVID-19. Our results agree with previous studies and show no real prognostic significance of GI symptoms in patients with COVID-19.

We did find a higher proportion of males in the GI symptoms group. A large-scale global analysis[44] showed that both sexes were at equivalent risk of infection, but male sex was associated with the development of severe disease as measured by ITU admission and death. Sex differences have previously been reported in both the innate and adaptive immune systems.[44] Robust antiviral interferon response and increased adaptive immunity toward viral antigens in females may help to contain and localize the infection and may account for the differences seen in risk of developing GI symptoms.

Diarrhea, whether on presentation or developing during hospital admission, is an important consideration for healthcare professionals. Viral colonization of the gut and viral shedding in the stool (even after it becomes undetectable in the upper respiratory tract) has clinical implications for possible fecal–oral mode of transmission.

Infection prevention and control principles therefore become necessary to prevent further viral propagation and include screening, triaging, and regular testing of both patients and healthcare providers. Correct personal protective equipment, compliance with good hand hygiene, use of single rooms (where possible), regular decontamination of the care environment including toilets/commodes and frequently touched surfaces should all help in minimizing the risk of spread.

Therefore, GI symptoms and in particular diarrhea in addition to the commonly reported respiratory complaints should be monitored as a sign of an actively infectious state.

COVID-19 has had (and continues to have) an enormous impact on healthcare resources worldwide, including critical care facilities. The need to risk stratify patients early and identify those potentially becoming critically ill for closer monitoring and early intervention is vital to reduce morbidity and mortality.

The coronavirus virion is made up of several structural proteins, including the nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins.[45] Angiotensin-converting enzyme 2 (ACE2) is the obligate receptor for SARS-CoV-2 entry into host cells. ACE2 was originally identified in 2003 and acts as the receptor for other alpha- and beta-coronaviruses. Viral entry including attachment to host cell membrane and fusion are mediated by the S glycoprotein. This process is also dependent on transmembrane protease, serine 2 (TMPRSS2).[45] Receptor expression in the GI tract and the demonstration in human small intestinal organoid models producing infectious virions is thought to be the mechanism responsible for GI symptoms. Moreover, viral RNA and proteins have been observed in biopsies from different parts of the GI tract and show infiltration of plasma cells and lymphocytes in the lamina propria.[46]

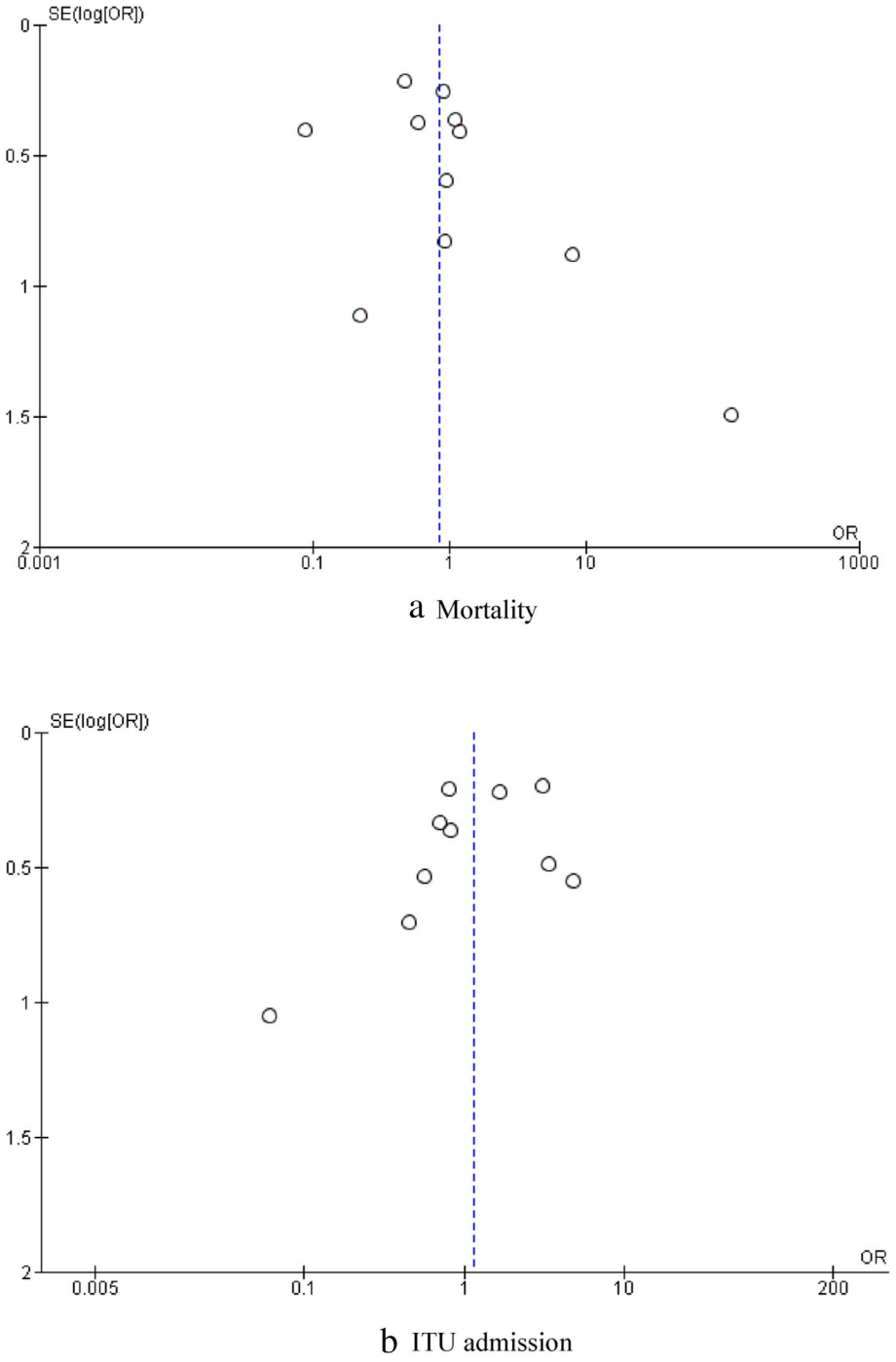


Figure 4 Funnel plot of comparison of (a) mortality and (b) intensive therapy unit (ITU) admission. OR, odds ratio

It remains unclear whether the GI tract is affected primarily by the virus, or the dysfunction occurs secondary to critical illness, and its associated systemic inflammation [systemic inflammatory response syndrome (SIRS) response], hypoperfusion, coagulopathy, and treatments.[46]

Changes in the gut microbiota may also play a role. COVID-19 patients have significantly reduced bacterial diversity and in particular a reduction in species with immunomodulatory potential and relative increases in opportunistic pathogens. Data suggesting altered microbiome may be related to COVID-19 severity and biochemical markers of inflammation.[46] However, future well-designed studies are needed to explore this further.

The current study has some limitations that should be considered when interpreting its findings. The best available evidence comes mainly from retrospective observational studies that are subject to selection bias. Other inherent problems with this

study design include recall bias and missing data. They are often subject to confounding factors and unable to determine causation being limited to association. Moreover, temporal relationships are difficult to assess.

In several of our included studies GI symptoms were not clearly defined and, in the majority, they were assessed once only at the time of initial presentation and not repeatedly throughout the study period. The definition of what constitutes severe COVID-19 compared with mild/moderate cases also varied between studies introducing heterogeneity. Additionally, due to lack of data, subgroup analysis based on severity of illness in patients with and without GI symptoms was not feasible.

Furthermore, there is heterogeneity in the cohort of patients included in this review. Most of the included data were from hospitalized patients but a small number of studies also included ambulatory/outpatients. Due to a lack of data, it was not feasible to perform separate subgroup analysis for these groups.

Following hospital admission, extraneous factors other than COVID-19 such as antibiotic or antiviral treatments, associated infections can potentially result in the development of GI symptoms. Future analyses in carefully selected studies considering GI symptoms at presentation and subsequent development during admission and their impact on outcomes and prognosis would be interesting. Similarly, association with disease severity in matched cohorts would provide for further valuable insight into this topic.

Finally missing data may result in less precise and possibly biased effect estimates in single studies. This bias arising from individual studies with incomplete outcome datasets can then be propagated into subsequent meta-analyses. To address this, we attempted to contact corresponding authors of the included studies where information about our outcome of interest was not reported.

Some studies reported their continuous parameters as median and IQR. We have calculated the mean and SD from median and IQR applying a widely acceptable equation described by Hozo *et al*.[13] This might have introduced some bias to our findings.

In conclusion, GI symptoms are an important clinical feature of COVID-19 and in some patients can be particularly debilitating leading to a prolonged recovery. However, our meta-analysis of the best possible available evidence (level 2) demonstrated that GI symptoms in COVID-19 do not seem to affect patients with any specific demographic pattern and may not have any important prognostic significance. However, in hospitalized patients, especially in the presence of diarrhea, the necessary precautions need to be taken to prevent further disease transmission and disruption of healthcare provision.

Although no randomized studies can be conducted on this topic, future high-quality studies can provide stronger evidence to further understand the impact of GI symptoms on outcomes of COVID-19 patients.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Appendix S1. Search strategy.