ORIGINAL ARTICLE

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

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Key words
Coronavirus disease 2019, gastrointestinal symptoms, meta-analysis.

Accepted for publication 10 August 2022.

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Declaration of conflict of interest: None.

Author contribution: Shafquat Zaman, Shahin Hajibandeh, Shahab Hajibandeh, and Andrew D Beggs were involved in study conception and design. Shafquat Zaman, Shahin Hajibandeh, and Ali Yasen Y Mohamedahmed were involved in acquisition of data. Shafquat Zaman, Shahin Hajibandeh, Shahab Hajibandeh, Mohammed E El-Asrag were involved in analysis and interpretation of data. All authors were involved in drafting the manuscript, critical revision of the manuscript, and final approval of the manuscript.

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 = 6,544) 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, and a pandemic on 11 March 2020.1,2 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.3 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 sequelae may also develop in
the adult population (MIS-A). GI signs and symptoms such as abdominal pain, nausea/vomiting, and diarrhea can appear prominence as presenting features of MIS-C. 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). Our methodology respected the Cochrane Handbook for Systematic Reviews of Interventions and standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

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, ClinicalTrials.gov, and ISRCTN Register 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). 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 ($\chi^2$) 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. 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 dropouts, 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 ($\chi^2$). 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 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. The remainder 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 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. For the remaining five studies, 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 Table 4.

Figure 1 PRISMA flow diagram
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 (I² = 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 (I² = 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 1  Study characteristics

| Author          | Year | Country | Study design           | Study population | Total SARS-CoV-2 positive (n) | Gastrointestinal symptoms (n) | Timing of GI symptoms assessment |
|-----------------|------|---------|------------------------|------------------|------------------------------|------------------------------|---------------------------------|
| Ghoshal et al.  | 2020 | India   | Observational (prospective) | Hospitalized/ambulatory | 252                          | 26                           | 226                              |
| 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 (retrospective) | 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 (retrospective) | 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/ambulatory | 1059                         | 349                          | 710 Initial presentation        |
| Bishehsari et al. | 2022 | United States | Observational (retrospective) | Hospitalized/ambulatory | 921                          | 206                          | 715 Initial presentation        |
| Delavari et al. | 2022 | Iran    | Observational (prospective) | Hospitalized/ambulatory | 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.
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 (I² = 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 (I² = 53%, P = 0.005).

Coronary artery disease: Ten studies provided data on the number of patients with coronary artery disease in the 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 (I² = 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 (I² = 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 (I² = 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 (I² = 84%, P < 0.00001).

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 | Abdominal pain, nausea, vomiting, abdominal pain                                        |

GI, gastrointestinal.
| 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.
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 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 symptom group.

Moreover, we conducted meta-regression analysis, which indicated that the baseline difference in age and diabetes between...
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%. Moreover, the literature on the association between these

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.
Gastrointestinal symptoms in COVID-19

S Zaman et al.

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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. 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. 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. 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.