Are gastrointestinal symptoms associated with higher risk of Mortality in COVID-19 patients? A systematic review and meta-analysis

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Abstract

**Background:** Gastrointestinal symptoms have been reported in patients with COVID-19. Several clinical investigations suggested that gastrointestinal symptoms were associated with disease severity of COVID-19. However, the relevance of gastrointestinal symptoms and mortality of COVID-19 remains largely unknown. We aim to investigate the relationship between gastrointestinal symptoms and COVID-19 mortality.

**Methods:** We searched the PubMed, Embase, Web of science and Cochrane for studies published between Dec 1, 2019 and May 1, 2021, that had data on gastrointestinal symptoms in COVID-19 patients. Additional literatures were obtained by screening the citations of included studies and recent reviews. Only studies that reported the mortality of COVID-19 patients with/without gastrointestinal symptoms were included. Raw data were pooled to calculate OR (Odds Ratio). The mortality was compared between patients with and without gastrointestinal symptoms, as well as between patients with and without individual symptoms (diarrhea, nausea/vomiting, abdominal pain).

**Results:** Fifty-three literatures with 55,245 COVID-19 patients (4955 non-survivors and 50,290 survivors) were included. The presence of GI symptoms was not associated with the mortality of COVID-19 patients (OR = 0.88; 95% CI 0.71–1.09; P=0.23). As for individual symptoms, diarrhea (OR = 1.01; 95% CI 0.72–1.41; P=0.96), nausea/vomiting (OR = 1.16; 95% CI 0.78–1.71; P=0.46) and abdominal pain (OR = 1.55; 95% CI 0.68–3.54; P=0.3) also showed non-relevance with the death of COVID-19 patients.

**Conclusions:** Gastrointestinal symptoms are not associated with higher mortality of COVID-19 patients. The prognostic value of gastrointestinal symptoms in COVID-19 requires further investigation.

**Keywords:** Gastrointestinal symptom, COVID-19, Mortality, Prognosis

Background

The occurrence and rapid spread of novel coronavirus (SARS-CoV-2)-infected pneumonia (COVID-19) since December, 2019, has brought troublesome challenges to worldwide public health [1]. Globally, as of February 25, 2022, there have been 430,257,564 confirmed cases of COVID-19, including 5,922,049 deaths, reported to the WHO. In response to the alarming levels of its spread, severity and death threat of COVID-19, the WHO issued a statement of Public Health Emergency of International Concern on January 30, 2020 and further declared COVID-19 a pandemic on March 11, 2020 [2].

The most frequent symptoms in COVID-19 patients are respiratory manifestations. However, emerging studies have found that gastrointestinal (GI) symptoms including diarrhea, nausea/vomiting and abdominal pain,
are also commonly observed in patients with COVID-19, with a prevalence of up to 31.9% [3, 4].

As the major receptor of SARS-CoV-2, angiotensin-converting enzyme 2, is also expressed in the gastrointestinal tract [5]. Early evidence has identified gastrointestinal infection of SARS-CoV-2 via immunofluorescent [6]. Intriguingly, several case-control studies and meta-analysis suggested that COVID-19 patients with GI symptoms might be at a higher risk of clinical deterioration [7, 8]. Physicians are also anxious to find out whether GI symptoms in patients with COVID-19 indicate a higher probability of death. In the first few months of COVID-19 pandemic, Mao et al. performed a meta-analysis and found that COVID-19 patients with GI symptoms tended to have higher prevalence of death (OR (odds ratio) = 1.21) but without statistical significance (P = 0.52) [8]. The question remains controversial due to the limited number of studies and population at that time. Now with the numerous emerging publications reporting the characteristics and outcomes of COVID-19 patients, there is a pressing need to determine the role of GI symptoms in the prognosis of COVID-19. Hence, this meta-analysis is conducted to investigate the relationship between GI symptoms and the mortality of COVID-19 patients.

Methods
Search strategy and selection criteria
We searched PubMed, Embase, Web of Science and Cochrane databases on May 1, 2021 for articles published from Dec 1, 2019, using the keywords combination of “COVID-19”, “SARS-CoV-2”, “2019 novel coronavirus”, “2019-nCoV”, “coronavirus disease 2019”, “coronavirus disease-19”, “severe acute respiratory syndrome coronavirus” and “novel Coronavirus 2019” for COVID-19, and “gastrointestinal”, “vomiting”, “vomit”, “nausea”, “diarrhoea”, “diarrhea”, “appetite”, “anorexia”, “abdominal”, “abdomen”, “digestive” and “alimentary” for GI symptoms. The reference lists of relevant reviews, meta-analysis and included literatures were also screened manually to identify additional articles that might be missed in the database search. Search records were managed with EndNote (version X7) for excluding duplicates and further literature screening. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The protocol of this meta-analysis has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42020197032).

The eligibility for inclusion of literatures were determined by three authors (YW, YmL and YZ) independently, and dissonance were discussed with another author (YL) and subsequently resolved via consensus.

Articles reporting the mortality of COVID-19 patients with and without GI symptoms respectively were considered eligible for inclusion. Preprint studies without peer-review were excluded due to potential misinformation. The following literatures were excluded at title and abstract screening: reviews, meta-analysis, guidelines, case reports, letter, comment, editorial, protocol, clinical research with less than 20 patients, basic research and non-relevant literatures. Then full-text review was performed to exclude articles without needed data and those written in languages other than English.

Data extraction and definitions
Three authors (YW, YmL and YZ) independently extracted the data, and dissonance were resolved with another author (YL) by discussion and consensus. The following variables were extracted: first author, study location, number of patients, basic characteristics of study population, mortality of COVID-19 patients with and without GI symptoms, respectively (Additional file 1).

For studies only reporting individual symptoms such as diarrhea, nausea, vomiting and abdominal pain, “GI symptom” was defined as the most common one of these digestive symptoms. For studies reporting either nausea or vomiting but not nausea/vomiting, “nausea/vomiting” was defined as the more frequent one of the two symptoms.

Assessment of study quality
For included studies, Newcastle-Ottawa Scale (NOS) was used for the assessment of quality. NOS is a quality assessment tool for observational studies that has been endorsed by the Cochrane Collaboration [9, 10]. The studies were considered as high quality if they scored > 6 points, moderate quality if they scored 5 or 6 points, and poor quality if they scored < 5 points.

Data synthesis and statistical analysis
To ensure the accuracy of the results, analysis were performed by two authors (YW and YmL) independently. Dissonance was resolved by discussion. To evaluate the risk of mortality associated with GI symptoms, OR with 95% confidence intervals (CI) were calculated by the Cochrane Review Manager program (RevMan 5.3, Denmark) following the Mantel-Haenszel method. The heterogeneity of included literatures was detected by I² statistic.

Subgroup analysis was performed according to the study location, severity of disease, patient age and population size. Funnel-plot and Egger’s test were used to investigate the possibility of publication bias. P < 0.05 for Egger’s test was considered significant bias. If publication
bias was indicated, trim-and-fill method was used for adjusting OR. A sensitivity analysis was also performed by omitting each study using the meta package in R, version 4.0.2.

**Results**

**Search results and study characteristics**

The study selection process is depicted in Fig. 1. A total of 4,873 records were initially identified. After removal of duplicates, 3,756 remained. After screening by titles/abstracts and full-text review, 53 studies [11–63] were finally included for data analysis.

The characteristics of the included studies are shown in Table 1. Of the 53 included studies with a total of 55,245 patients, 21 were carried out in China, 12 in USA and 20 in other countries. One and four studies included pediatric and geriatric patients, respectively. Seven studies investigated COVID-19 combined with other disease history including chronic liver disease, cancer, kidney transplantation and interstitial lung disease. Six studies included critically ill patients. All papers were considered high quality with NOS score > 6.

Clinical features and outcomes of COVID-19 patients are listed in Table 2. Of the 55,245 patients, 4,955 non-survivors were reported. A total of 8,535 patients had GI symptoms. Individual GI symptoms included diarrhea (1,341 reported in 10,983 patients), nausea/vomiting (525 reported in 7,175 patients) and abdominal pain (92 reported in 5,012 patients). The cumulative incidences of GI symptom, diarrhea, nausea/vomiting and abdominal pain in COVID-19 patients were 25%, 16%, 7.5% and 3.6%, respectively.

**Association of GI symptoms with the mortality of COVID-19**

As shown in Fig. 2, presence of GI symptom was found to have no significant association with the mortality of COVID-19 (OR = 0.88; 95% CI 0.71–1.09; P = 0.23). There was substantial heterogeneity among the 53 studies included (I² = 78%, P < 0.001).

For individual GI symptoms, there were 24 studies reporting on diarrhea (Fig. 3a), 18 on nausea/vomiting (Fig. 3b), and 9 on abdominal pain (Fig. 3c). The pooled OR of diarrhea was 1.01 (95% CI 0.72–1.41; P = 0.96), of nausea/vomiting was 1.16 (95% CI 0.78–1.71; P = 0.46), and of abdominal pain was 1.55 (95% CI 0.68–3.54; P = 0.3). No substantial heterogeneity was found in the studies included for the analysis of nausea/vomiting and abdominal pain (I² = 34% and 50%, respectively). While moderate heterogeneity was observed for diarrhea (I² = 62%).

**Subgroup Analysis**

Since substantial heterogeneity was observed for GI symptom, we performed subgroup analysis to explore the source of heterogeneity. As shown in Table 3, as for studies conducted in different locations, the heterogeneity was moderate in the subgroups of Asia and America (I² = 54.7% and 42.7%, respectively). The heterogeneity remained significant in the subgroups of Europe and other continents (I² = 77% and 87.8%, respectively). Notably, data from Asian studies indicated that GI symptom was a significant risk factor for the death of COVID-19 patients (OR = 1.43, P = 0.01). On the contrary, American and European studies showed that GI symptom was associated with a lower mortality risk (OR = 0.64 and 0.4, respectively; P < 0.01 for both). The study location seemed to be a major source of heterogeneity. Meanwhile heterogeneity remained substantial in the other subgroups in terms of disease severity and population size, and GI symptom had no significant relevance with mortality in these subgroups. Nevertheless, in subgroup analysis Asian literatures indicate GI symptom is a significant risk factor for the mortality of COVID-19 (OR > 1, P < 0.05). Meanwhile European and American studies suggest that GI symptom is a significant protective factor (OR < 1, P < 0.05). The possible explanation for these contradictory observations has always been controversial. In an European research Crespo et al. found that patients with gastrointestinal COVID-19 phenotype recovered more frequently [19]. Several studies from the USA described that COVID-19 patients with GI...
| No. of study | First author | Study location | No. of patients | Age (year) | Male | Special patient population | NOS score |
|-------------|--------------|----------------|----------------|-----------|------|-----------------------------|-----------|
| 1           | Alizadehsani R et al. | Iran | 123 | 45 | 62 | None | 8 |
| 2           | An P et al. | China | 205 | 54 | 122 | None | 8 |
| 3           | Atlah E et al. | USA | 111 | 87 | 23 | Older patients | 7 |
| 4           | Caillard S et al. | France | 243 | 62 | 162 | Kidney transplant recipients | 7 |
| 5           | Chadalavada P et al. | USA | 84 | 60 | 52 | None | 8 |
| 6           | Chen R et al. | China | 1077 | 59 | 532 | None | 9 |
| 7           | Chen T et al. | China | 274 | 62 | 171 | Critically ill patients | 7 |
| 8           | Comoglu Ş et al. | Turkey | 1086 | 48 | 563 | None | 8 |
| 9           | Crespo M et al. | Spain | 414 | 62 | 265 | Kidney transplant recipients | 7 |
| 10          | Doganci S et al. | Turkey | 397 | 57 | 200 | None | 8 |
| 11          | Du H et al. | China | 182 | 6 | 120 | Pediatric patients | 7 |
| 12          | Elimian K et al. | Nigeria | 3215 | 36 | 2293 | None | 8 |
| 13          | Ferr S et al. | USA | 877 | 59 | 534 | None | 8 |
| 14          | Gayam V et al. | USA | 408 | 67 | 231 | African-Americans | 7 |
| 15          | Ghoshal U et al. | India | 252 | 40 | 204 | None | 8 |
| 16          | Hajfathalian K et al. | USA | 1059 | 61 | 611 | None | 8 |
| 17          | Huang H et al. | China | 49 | 37 | 23 | Patients with pre-existing ILD | 7 |
| 18          | Jiang Y et al. | China | 281 | 70 | 143 | Older severe patients | 7 |
| 19          | Jin X et al. | China | 651 | 46 | 331 | None | 9 |
| 20          | Kan M et al. | Korea | 118 | 59 | 52 | None | 8 |
| 21          | Kim D et al. | USA | 867 | 57 | 473 | Patients with chronic liver disease | 7 |
| 22          | Lanthier N et al. | Belgium | 50 | 88 | NA | Geriatric patients | 7 |
| 23          | Laszkowska M et al. | USA | 2804 | 66 | 1565 | None | 7 |
| 24          | Leal T et al. | Portugal | 201 | 71 | 113 | Symptomatic patients | 7 |
| 25          | Liang J et al. | China | 109 | 65 | 57 | Patients with cancer | 7 |
| 26          | Liu J et al. | China | 29393 | 47 | 15,501 | None | 8 |
| 27          | Livanos A et al. | USA | 634 | 61 | 369 | None | 8 |
| 28          | Luo S et al. | China | 1411 | 54 | 895 | None | 8 |
| 29          | Ma X et al. | China | 467 | 44 | 289 | None | 8 |
| 30          | Montazeri M et al. | Iran | 611 | 56 | 377 | None | 8 |
| 31          | Moura D et al. | Brazil | 400 | 56 | 225 | None | 8 |
| 32          | Nobel Y et al. | USA | 278 | NA | 145 | None | 7 |
| 33          | Pan L et al. | China | 204 | 53 | 107 | None | 9 |
| 34          | Peng X et al. | China | 49 | 63 | 17 | Critically ill patients | 7 |
| 35          | Ramachandran P et al. | USA | 150 | 57 | 83 | None | 8 |
| 36          | Redd W et al. | USA | 318 | 63 | 174 | None | 9 |
| 37          | Renelus B et al. | USA | 734 | 68 | 379 | None | 8 |
| 38          | Russell B et al. | UK | 156 | 65 | 90 | Patients with cancer | 7 |
| 39          | Schettino M et al. | Italy | 190 | 65 | 127 | None | 8 |
| 40          | Shang H et al. | China | 564 | 59 | 286 | None | 8 |
| 41          | Soares R et al. | Brazil | 1152 | NA | 494 | None | 8 |
| 42          | Sulaiman T et al. | Iraq | 140 | 45 | 100 | None | 8 |
| 43          | Tsibouris P et al. | Greece | 61 | 70 | 34 | None | 8 |
| 44          | Vena A et al. | Italy | 275 | 71 | 183 | None | 8 |
| 45          | Villanego F et al. | Spain | 1011 | 60 | 635 | Kidney transplant recipients | 7 |
| 46          | Vrillon A et al. | France | 52 | 90 | 34 | Older adults | 7 |
| 47          | Wan, Y et al. | China | 230 | 48 | 129 | None | 8 |
| 48          | Wang Z et al. | China | 59 | 67 | 38 | Critically ill patients | 7 |
| 49          | Yang X et al. | China | 52 | 60 | 35 | Critically ill adults | 7 |
| 50          | Zhang J et al. | China | 663 | 56 | 321 | None | 7 |
symptoms were younger, with less comorbidity [33, 37]. Therefore, we further reviewed the literatures in our analysis. Among the literatures that had data on the age of patients with/without GI symptoms, all of the European and American literatures (n = 8 of 8, 100%) [15, 19, 33, 34, 37, 45, 46, 49] reported that patients with GI symptoms were younger than those without. And OR values were < 1 in 7 [15, 19, 33, 34, 37, 46, 49] of these 8 literatures. On the other hand, 7 [12, 16, 18, 25, 29, 36, 57] of 13 Asian studies [12, 16, 18, 25, 29, 30, 36, 38, 40, 43, 50, 52, 57] reported that patients with GI symptoms were older, and OR values were > 1 in 6 [12, 16, 25, 29, 36, 57] of these 7 studies. It turns out that the studies carried out in different locations vary in the characteristics of included patients, especially in the age of patients with/without GI symptoms. Given that old age is an important risk factor for the death of COVID-19 patients [14], the discordance in the findings in different study locations may be due to the differences in the age of included patients.

To demonstrate the above finding, we explored the age related sub-analysis by study region. As shown in Table 3, the studies in Asia, America and Europe were divided into subgroups based on the age difference of included patients. Consistent with the age distribution, GI symptom was found to be a significant risk factor for mortality (OR > 1 and P < 0.05) in the subgroup that GI group was younger than non-GI group (Table 3, subgroup 1.1.1). Meanwhile, GI symptom was a significant protective factor (OR < 1 and P < 0.05) in the subgroups that GI group was younger than non-GI group (Table 3, subgroup 1.2.2 and subgroup 1.3.2). Since the number of studies in each subgroup was quite small, we also performed subgroup analysis based on the age difference of included patients irrespective of the study region. As shown in Table 3, three additional subgroups were determined: [1] subgroup 4.1 included the studies in which the patients in GI group were older than those in non-GI group; [2] subgroup 4.2 included the studies in which the patients in GI group were younger than those in non-GI group; [3] subgroup 4.3 included the studies without available information on the age of patients in GI and non-GI group. Interestingly, in subgroup 4.1, GI symptom was a significant risk factor for mortality (OR = 1.89, P = 0.02). On the contrary, in subgroup 4.2, GI symptom was a significant protective factor for mortality (OR = 0.61, P = 0.01). This finding further supports our deduction that the difference in the age of GI and non-GI groups leads to the discordance in the findings in different study locations. The forest plots of these additional subgroup analysis are available in the Supplementary Material (Additional file 2: Figs. S1 to S6).

As for individual symptoms including diarrhea, nausea/vomiting and abdominal pain, none of these symptoms showed significant correlation with mortality (P of OR > 0.05 for all subgroups).

Age stratification analysis
To further explore the relationship of GI symptom with mortality in different age groups, we performed additional age stratification analysis. As shown in Table 4, we stratified the studies into 5 groups according to the average age of the study population: 0–39, 40–49, 50–59, 60–69 and 70–+. We expected that with the increased population age, GI symptom might be a risk factor from mortality. However, the actual results were contrary to our expectation: in younger populations (0–39, 40–49 and 50–59), GI symptom seemed to be a risk factor (OR > 1) while in older populations (60–69 and 70–+) GI symptom showed a significant protective effect (OR < 1 and P < 0.05). The forest plots are available in Additional file 2.

To clarify this finding, we reviewed the included studies again. We found that the average age of GI group was older than non-GI group in most studies (83.3%) with younger populations (40–49); meanwhile the average age of GI group was younger than non-GI group in all studies (100%) with older populations (60–69 and 70–). Overall, we supposed that the potential patients selection bias in the age of patients with/without GI symptom led to the discordance in the results.

Publication bias analysis
The funnel plots (Fig. 4a) were found to be slightly asymmetric for GI symptom and nausea/vomiting. As shown in Table 5, Egger’s regression test also revealed publication bias for both factors (P = 0.05 and 0.04, respectively). Thus we performed trim-and-fill method to estimate missing studies (Fig. 4b) so as to make pooled OR more reliable. The P values of Egger’s test were > 0.05.
| No. of study | Author                        | No. of patients | No. of death | No. of GI symptom | No. of diarrhea | No. of nausea/vomiting | No. of abdominal pain |
|-------------|-------------------------------|-----------------|--------------|-------------------|----------------|------------------------|-----------------------|
| 1           | Alizadehsani R et al.         | 123             | 15 (12.2%)   | 11 (8.9%)         | NA             | NA                     | NA                    |
| 2           | An P et al.                   | 205             | 6 (2.9%)     | 79 (38.5%)        | NA             | NA                     | NA                    |
| 3           | Atalla E et al.               | 111             | 48 (43.2%)   | 8 (7.2%)          | 8 (7.2%)       | 2 (1.8%)               | NA                    |
| 4           | Caillard S et al.             | 243             | 43 (17.7%)   | 96 (39.5%)        | 96 (39.5%)     | NA                     | NA                    |
| 5           | Chadalavada P et al.          | 84              | 11 (13.1%)   | 44 (52.4%)        | NA             | NA                     | NA                    |
| 6           | Chen R et al.                 | 1077            | 85 (7.9%)    | 359 (33.3%)       | NA             | NA                     | NA                    |
| 7           | Chen T et al.                 | 274             | 113 (41.2%)  | 77 (28.1%)        | 77 (28.1%)     | 24 (8.8%)              | 19 (6.9%)             |
| 8           | Comoglu Ş et al.              | 1086            | 38 (3.5%)    | 78 (7.2%)         | 78 (7.2%)      | NA                     | NA                    |
| 9           | Crespo M et al.               | 414             | 109 (26.3%)  | 152 (36.7%)       | NA             | NA                     | NA                    |
| 10          | Doganci S et al.              | 397             | 34 (8.6%)    | 292 (73.6%)       | NA             | NA                     | NA                    |
| 11          | Du H et al.                   | 182             | 1 (0.5%)     | 20 (11.0%)        | 9 (4.9%)       | 7 (3.8%)               | 7 (3.8%)              |
| 12          | Elimian K et al.              | 3215            | 295 (9.2%)   | 132 (4.1%)        | 132 (4.1%)     | 103 (3.2%)             | 20 (0.6%)             |
| 13          | Fern S et al.                 | 877             | 208 (23.7%)  | 219 (25.0%)       | NA             | NA                     | NA                    |
| 14          | Gayam V et al.                | 408             | 132 (32.4%)  | 111 (27.2%)       | NA             | NA                     | NA                    |
| 15          | Ghoshal U et al.              | 252             | 5 (2.0%)     | 26 (10.3%)        | NA             | NA                     | NA                    |
| 16          | Hajifathalian K et al.        | 1059            | 147 (13.9%)  | 349 (33.0%)       | NA             | NA                     | NA                    |
| 17          | Huang H et al.                | 49              | 9 (18.4%)    | 3 (6.1%)          | 3 (6.1%)       | 1 (2.0%)               | NA                    |
| 18          | Jiang Y et al.                | 281             | 114 (40.6%)  | 33 (11.7%)        | 33 (11.7%)     | 13 (4.6%)              | NA                    |
| 19          | Jin X et al.                  | 651             | 1 (0.2%)     | 74 (11.4%)        | NA             | NA                     | NA                    |
| 20          | Kang M et al.                 | 118             | 6 (5.1%)     | 54 (45.8%)        | 54 (45.8%)     | NA                     | NA                    |
| 21          | Kim D et al.                  | 867             | 121 (14.0%)  | 181 (20.9%)       | NA             | 175 (20.2%)            | NA                    |
| 22          | Lanthier N et al.             | 50              | 26 (52.0%)   | 15 (30.0%)        | 12 (24.0%)     | 3 (6.0%)               | 3 (6.0%)              |
| 23          | Laszkowska M et al.           | 2804            | 542 (19.3%)  | 1084 (38.7%)      | NA             | NA                     | NA                    |
| 24          | Leal T et al.                 | 201             | 55 (27.4%)   | 60 (29.9%)        | NA             | NA                     | NA                    |
| 25          | Liang J et al.                | 109             | 23 (21.1%)   | 26 (23.9%)        | 26 (23.9%)     | 10 (9.2%)              | 5 (4.6%)              |
| 26          | Liu H et al.                  | 29,393          | 711 (2.4%)   | 2289 (7.8%)       | NA             | NA                     | NA                    |
| 27          | Livanos A et al.              | 634             | 151 (23.8%)  | 299 (47.2%)       | NA             | NA                     | NA                    |
| 28          | Luo S et al.                  | 1411            | 66 (4.7%)    | 183 (13.0%)       | NA             | NA                     | NA                    |
| 29          | Ma X et al.                   | 467             | 16 (3.4%)    | 25 (5.4%)         | 25 (5.4%)      | NA                     | NA                    |
| 30          | Montazeri M et al.            | 611             | 104 (17.0%)  | 155 (25.4%)       | NA             | NA                     | NA                    |
| 31          | Moura D et al.                | 400             | 89 (22.3%)   | 133 (33.3%)       | NA             | NA                     | NA                    |
| 32          | Nobel Y et al.                | 278             | 9 (3.2%)     | 97 (34.9%)        | 56 (20.1%)     | 63 (22.7%)             | NA                    |
| 33          | Pan L et al.                  | 204             | 36 (17.6%)   | 103 (50.5%)       | NA             | NA                     | NA                    |
| 34          | Peng X et al.                 | 49              | 16 (32.7%)   | 22 (44.9%)        | 11 (22.4%)     | 15 (30.6%)             | 3 (6.1%)              |
| 35          | Ramachandran P et al.         | 150             | 58 (38.7%)   | 31 (20.7%)        | NA             | NA                     | NA                    |
| 36          | Redd W et al.                 | 318             | 32 (10.1%)   | 195 (61.3%)       | NA             | NA                     | NA                    |
| 37          | Reneles B et al.              | 734             | 237 (32.3%)  | 231 (31.5%)       | NA             | NA                     | NA                    |
| 38          | Russell B et al.              | 156             | 34 (21.8%)   | 25 (16.0%)        | NA             | NA                     | NA                    |
| 39          | Schettino M et al.            | 190             | 41 (21.6%)   | 138 (72.6%)       | NA             | NA                     | NA                    |
| 40          | Shang H et al.                | 564             | 51 (9.0%)    | 157 (27.8%)       | 157 (27.8%)    | NA                     | NA                    |
| 41          | Soares R et al.               | 1152            | 456 (39.6%)  | 126 (10.9%)       | 126 (10.9%)    | NA                     | NA                    |
| 42          | Sulaiman T et al.             | 140             | 12 (8.6%)    | 78 (55.7%)        | NA             | NA                     | NA                    |
| 43          | Tsibouis P et al.             | 61              | 16 (26.2%)   | 11 (18.0%)        | 11 (18.0%)     | 4 (6.6%)               | 2 (3.3%)              |
| 44          | Vera A et al.                 | 275             | 120 (43.6%)  | 14 (5.1%)         | 14 (5.1%)      | 14 (4.0%)              | NA                    |
| 45          | Villanego F et al.            | 1011            | 220 (21.8%)  | 323 (31.9%)       | NA             | NA                     | NA                    |
| 46          | Viliron A et al.              | 52              | 17 (32.7%)   | 17 (32.7%)        | NA             | NA                     | NA                    |
| 47          | Wan, Y et al.                 | 230             | 6 (2.6%)     | 49 (21.3%)        | 49 (21.3%)     | NA                     | NA                    |
| 48          | Wang Z et al.                 | 59              | 41 (69.5%)   | 22 (37.3%)        | 22 (37.3%)     | 4 (6.8%)               | NA                    |
after trim-and-fill adjustment (Table 5), indicating that the publication bias was reduced. After adjustment for presumed un-published reports after trim-and-fill analysis (Table 5), GI symptoms and individual symptoms remained uncorrelated with the death risk of COVID-19 (OR close to 1, and \( P > 0.05 \) for all).

**Sensitivity analysis**

As depicted in Table 6, the results of GI symptom showed good stability with all OR estimates (ranging from 0.86 to 0.92) within the 95% CI of pooled OR. The OR estimates of diarrhea, nausea/vomiting and abdominal pain were also stable when omitting one study at a time. All of the estimates showed no statistical significance, which were also in accordance with the major conclusion that the relationship of GI symptoms and mortality was not significant.

**Discussion**

Several previous literatures have revealed that the GI symptoms might be associated with the prognosis with COVID-19 [7]. However, in the current meta-analysis, neither GI symptoms nor individual symptoms including diarrhea, nausea/vomiting and abdominal pain shows a significant relevance with the mortality of COVID-19 patients. Besides, the present data suggest that older age might be a significant predictor of poor prognosis in COVID-19 patients with GI symptoms. Based on the current available data, there is no convincing evidence that GI symptoms may be associated with higher risk of mortality in COVID-19 patients.

GI symptoms have been found common in COVID-19 patients in numerous studies [67], and are considered to indicate the involvement of digestive system by virus [68]. Xiao et al. identified the infection of SARS-CoV-2 in the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell by immunofluorescent staining of gastrointestinal tissues from hospitalized patients infected with SARS-CoV2 [6]. There have been views that GI symptoms might indicate a more invasive pattern of virus [7, 8, 69]. Quite a few clinical researches have observed the GI symptoms as a risk factor for disease severity of COVID-19. Jin et al. [29] found that for patients with GI symptoms (n = 74), 22.97% developed severe/critical type of disease; while for patients without GI symptoms (n = 577), only 8.14% were severe/critical type (\( P < 0.001 \)). The meta-analysis by Mao et al. also found GI symptoms a significant risk factor for disease severity (OR = 3.97; 95% CI 1.49–10.62; \( P = 0.006 \)) [8]. They included 4 studies to explore the influence of GI symptoms on mortality. Although they yielded an OR of 1.21, it was without statistical significance (95% CI 0.68–2.16; \( P = 0.52 \)). The limited number of included studies and death cases (n = 29) might restrict the statistical power. However, with more abundant patients who met the endpoint in our meta-analysis, the correlation of GI symptoms in COVID-19 patients and mortality is still non-significant.

Despite the points of view highlighting the importance of GI symptoms in COVID-19, there exist arguments. In another meta-analysis by Wang et al., no significant differences were detected in the prevalence of diarrhea (OR = 1.24; 95% CI 0.90 to 1.72; \( P = 0.19 \)) and nausea/vomiting (OR = 1.24; 95% CI 0.57 to 2.69; \( P = 0.58 \)) between non-severe and severe COVID-19 patients [70]. They held the view that GI symptoms were not associated with the COVID-19 progression, and SARS-CoV-2-induced liver injury deserved more attention [70]. Nobel et al. proposed that gastrointestinal symptoms were associated with a more indolent form of COVID-19 based on their clinical observation [42]. Although the digestive system

| No. of study | Author          | No. of patients | No. of death | No. of GI symptom | No. of diarrhea | No. of nausea/vomiting | No. of abdominal pain |
|--------------|-----------------|----------------|--------------|------------------|----------------|------------------------|-----------------------|
| 49           | Yang X et al.   | 52             | 32 (61.5%)   | 2 (3.8%)         | NA             | 2 (3.8%)               | NA                    |
| 50           | Zhang J et al.  | 663            | 25 (3.8%)    | 61(9.2%)         | 61 (9.2%)      | 31 (4.7%)              | 5 (0.8%)              |
| 51           | Zhang L et al.  | 409            | 102 (24.9%)  | 91 (22.2%)       | 91 (22.2%)     | 50 (12.2%)             | 28 (6.8%)             |
| 52           | Zhou F et al.   | 191            | 54 (28.3%)   | 9 (4.7%)         | 9 (4.7%)       | 7 (3.7%)               | NA                    |
| 53           | Zhou Z et al.   | 254            | 16 (6.3%)    | 66 (26.0%)       | NA             | NA                     | NA                    |
| Cumulative incidence |              |                |              | 25%              | 16%            | 7.5%                   | 3.6%                  |

GI, gastrointestinal; NA, not available
can be involved, most of the symptoms are mild and can be improved by supportive treatments, thus might have less impact upon disease severity. On the other hands, the respiratory tract is more commonly involved in COVID-19 and most patients died of respiratory failure. The gastrointestinal involvement might not be a prominent factor compared with other underlying diseases or respiratory failure.

There are several strengths of this meta-analysis. To the best of our knowledge, up to now this is a relatively large meta-analysis on the specific influence of GI symptoms on the mortality of COVID-19. We have included a large
Fig. 3 Forest plots showing pooled odds ratio of (A) diarrhea, (B) nausea/vomiting and (C) abdominal pain associated with the mortality of COVID-19.
Table 3  Subgroup analysis based on study location, type of participants and population size

| Subgroups | No. of studies | No. of patients | OR and P value for mortality of different symptoms |  |  |  |  |  |
|-----------|----------------|-----------------|---------------------------------------------------|---|---|---|---|---|
| 1. Study location |  |  |  |  |  |  |  |  |
| 1.1 Asia | 28 | 39,501 (72%) | 1.43, P<0.01 54.7% | 1.32, P=0.21 1.3, P=0.36 | 1.07, P=0.85 |
| Sub-subgroups for studies in Asia: |  |  |  |  |  |  |  |  |
| 1.1.1 GI group older than non-GI group | 7 | 32,894 | 2.43, P<0.01 66.9% |  |  |  |  |  |
| 1.1.2 GI group younger than non-GI group | 6 | 3048 | 1.2, P=0.29 15.8% |  |  |  |  |  |
| 1.2 America | 12 | 8324 (15%) | 0.64, P<0.01 42.7% | 0.81, P=0.37 0.84, P=0.8 | NA |
| Sub-subgroups for studies in America: |  |  |  |  |  |  |  |  |
| 1.2.1 GI group older than non-GI group | NA | NA | NA | NA |  |  |  |  |
| 1.2.2 GI group younger than non-GI group | 5 | 3990 | 0.55, P<0.01 30.6% |  |  |  |  |  |
| 1.3 Europe | 10 | 2653 (5%) | 0.4, P<0.01 77% | 0.51, P=0.07 0.7, P=0.51 | 0.61, P=0.76 |
| Sub-subgroups for studies in Europe: |  |  |  |  |  |  |  |  |
| 1.3.1 GI group older than non-GI group | NA | NA | NA | NA |  |  |  |  |
| 1.3.2 GI group younger than non-GI group | 3 | 805 | 0.23, P<0.01 84% |  |  |  |  |  |
| 1.4 Other | 3 | 4767 (8%) | 0.92, P=0.83 87.8% | 0.93, P=0.92 NA NA |  |  |  |  |
| 2. Only include critically ill patients? |  |  |  |  |  |  |  |  |
| 3.1 Yes | 6 | 1124(2%) | 1.42, P=0.36 74.6% | 1.3, P=0.45 0.92, P=0.71 | 0.75, P=0.45 |
| 3.2 No | 47 | 54,121 (98%) | 0.83, P=0.1 78.3% | 0.92, P=0.69 1.37, P=0.28 | 2.67, P=0.05 |
| 3. Population size |  |  |  |  |  |  |  |  |
| 4.1 <500 | 36 | 7436 (13%) | 0.93, P=0.66 72.1% | 1.05, P=0.82 1.19, P=0.51 | 1.04, P=0.92 |
| 4.2 >=500 | 17 | 47,809 (87%) | 0.84, P=0.25 85.7% | 0.94, P=0.83 1.16, P=0.68 | NA |
| 4. Average age of GI group and non-GI group |  |  |  |  |  |  |  |  |
| 4.1 GI group older than non-GI group | 8 | 33,294 (60%) | 1.89, P=0.02 69% |  |  |  |  |  |
| 4.2 GI group younger than non-GI group | 14 | 7843 (14%) | 0.61, P=0.01 80% |  |  |  |  |  |
| 4.3 Unknown | 31 | 14,058 (26%) | 0.89, P=0.36 64% |  |  |  |  |  |

Table 4  Age stratification analysis

| Age stratification | No. of studies | OR and 95% CI of GI symptom for mortality | P value of OR | No. of studies that average age: GI group > non GI group | No. of studies that average age: GI group < non-GI group |
|--------------------|----------------|------------------------------------------|--------------|--------------------------------------------------|--------------------------------------------------|
| 0–39 | 3 | 2.36 [0.88; 6.33] | 0.088 | NA | NA |
| 40–49 | 8 | 2.22 [0.96; 5.11] | 0.061 | 5 (83.3%) | 1 (16.7%) |
| 50–59 | 15 | 1.09 [0.85; 1.40] | 0.517 | 3 (33.3%) | 6 (66.7%) |
| 60–69 | 18 | 0.71 [0.54; 0.95] | 0.02 | 0 (0%) | 6 (100%) |
| 70~ | 7 | 0.40 [0.21; 0.76] | 0.006 | 0 | 1 (100%) |

OR, odds ratio; CI, confidence interval; GI, gastrointestinal; NA, not available because the studies in the subgroups did not report the age information of patients with/without GI symptoms
number of literatures, with patient population above fifty thousand and 4,955 non-survivors among them, spanning five continents. We have also excluded studies with small sample size (< 20), and most studies included in calculating the pooled OR estimates had more than 100 patients. Besides, the publication bias has been adjusted and the outcome remains the same, which make the conclusion more reliable.

Old age have been found to be independently associated with mortality in quite a few investigations [14]. As is known old age is related with increased incidence of comorbidities, cognitive impairment, dependence, and frailty. The immuno-senescence in the elderly might also lead to a different reaction against infections. The recent reports and the present meta-analysis have emphasized the differences in mortality for patients of a certain age exhibiting GI symptoms. It has been reported that adults over 60 years of age account for 96% of deaths caused by COVID-19 [71]. A significant portion of COVID-19 patients have digestive symptoms, mostly at presentation. Therefore, GI symptoms should also be taken into account so as to maintain a high level of suspicion to reach an early diagnosis and set up infection control measures to improve the prognosis of elderly patients with COVID-19.

This meta-analysis has two potential limitations. As mentioned, there might exist potential patients selection bias in the age of patients with/without GI symptoms in different countries. This might lead to the discordance in the results of different study subgroups. On the other hand, currently there are no studies designed to prospectively compare the mortality of COVID-19 patients with/without GI symptoms, thus we have to include retrospective reports, which might limit the quality of evidence. Future prospective observational studies are needed to further clarify the role of GI symptoms in COVID-19.

### Table 5 Publication bias analysis

|                  | No. of included literatures | OR   | P value for OR | P value of Egger's test |
|------------------|-----------------------------|------|----------------|------------------------|
| Original data    |                             |      |                |                        |
| GI symptom       | 53                          | 0.88 | 0.23           | 0.05                   |
| Diarrhea         | 24                          | 1.01 | 0.96           | 0.55                   |
| Nausea/vomiting  | 18                          | 1.16 | 0.46           | 0.04                   |
| Abdominal pain   | 9                           | 1.55 | 0.3            | 0.61                   |
| After trim-and-fill |                         |      |                |                        |
| GI symptom       | 56                          | 0.84 | 0.11           | 0.82                   |
| Diarrhea         | 24                          | 1.01 | 0.96           | 0.55                   |
| Nausea/vomiting  | 21                          | 1.02 | 0.91           | 0.9                    |
| Abdominal pain   | 11                          | 1.28 | 0.51           | 0.94                   |

OR, odds ratio; GI, gastrointestinal

**Fig. 4** Funnel plots for evaluation of publication bias. A shows the funnel plots of gastrointestinal symptoms, diarrhea, nausea/vomiting and abdominal pain. B shows the funnel plots after trim-and-fill method.
### Table 6  Sensitivity analysis

| Study omitted                        | GI symptom | Diarrhea | Nausea/vomiting | Abdominal pain |
|--------------------------------------|------------|----------|-----------------|----------------|
| Omitting Alizadehsani R et al.       | 0.88, P=0.25 | NA       | NA              | NA             |
| Omitting An P et al.                 | 0.86, P=0.17 | NA       | NA              | NA             |
| Omitting Atala E et al.              | 0.87, P=0.22 | 1, P=0.98 | 1.13, P=0.55    | NA             |
| Omitting Caillard S et al.           | 0.89, P=0.28 | 1.04, P=0.81 | NA           | NA             |
| Omitting Chadalavada P et al.        | 0.88, P=0.25 | NA       | NA              | NA             |
| Omitting Chen R et al.               | 0.87, P=0.2  | NA       | NA              | NA             |
| Omitting Chen T et al.               | 0.89, P=0.27 | 1.04, P=0.83 | 1.23, P=0.33   | 1.91, P=0.17  |
| Omitting Comoglu Ş et al.            | 0.88, P=0.25 | 1.02, P=0.9 | NA            | NA             |
| Omitting Crespo M et al.             | 0.9, P=0.31  | NA       | NA              | NA             |
| Omitting Doganci S et al.            | 0.86, P=0.15 | NA       | NA              | NA             |
| Omitting Du H et al.                 | 0.87, P=0.18 | 0.99, P=0.96 | 1.08, P=0.63   | 1.42, P=0.42  |
| Omitting Elimian K et al.            | 0.86, P=0.16 | 0.96, P=0.82 | 1.05, P=0.82   | 1.05, P=0.9   |
| Omitting Ferry S et al.              | 0.88, P=0.28 | NA       | NA              | NA             |
| Omitting Gayam V et al.              | 0.88, P=0.23 | NA       | NA              | NA             |
| Omitting Ghoshal U et al.            | 0.86, P=0.15 | NA       | NA              | NA             |
| Omitting Hajfathalian K et al.       | 0.9, P=0.32  | NA       | NA              | NA             |
| Omitting Huang H et al.              | 0.87, P=0.21 | 1, P=0.98  | 1.12, P=0.57    | NA             |
| Omitting Jiang Y et al.              | 0.89, P=0.29 | 1.05, P=0.77 | 1.23, P=0.3   | NA             |
| Omitting Jin X et al.                | 0.87, P=0.18 | NA       | NA              | NA             |
| Omitting Kang M et al.               | 0.89, P=0.27 | 1.04, P=0.83 | NA            | NA             |
| Omitting Kim D et al.                | 0.88, P=0.26 | 1.03, P=0.88 | 1.25, P=0.32  | NA             |
| Omitting Lanther N et al.            | 0.9, P=0.31  | 1.06, P=0.72 | 1.15, P=0.5  | 1.77, P=0.16  |
| Omitting Laszkowska M et al.         | 0.9, P=0.32  | NA       | NA              | NA             |
| Omitting Leal T et al.               | 0.9, P=0.34  | NA       | NA              | NA             |
| Omitting Liang J et al.              | 0.87, P=0.22 | 1, P=0.99  | 1.14, P=0.54    | 1.46, P=0.42  |
| Omitting Liu J et al.                | 0.86, P=0.14 | NA       | NA              | NA             |
| Omitting Livanos A et al.            | 0.9, P=0.33  | NA       | NA              | NA             |
| Omitting Luo S et al.                | 0.88, P=0.25 | NA       | NA              | NA             |
| Omitting Ma X et al.                 | 0.87, P=0.19 | 0.98, P=0.9 | NA           | NA             |
| Omitting Montazeri M et al.          | 0.87, P=0.19 | NA       | NA              | NA             |
| Omitting Moura D et al.              | 0.88, P=0.24 | NA       | NA              | NA             |
| Omitting Nobel Y et al.              | 0.89, P=0.27 | 1.03, P=0.87 | 1.19, P=0.37  | NA             |
| Omitting Pan L et al.                | 0.87, P=0.22 | NA       | NA              | NA             |
| Omitting Peng X et al.               | 0.85, P=0.13 | 0.97, P=0.84 | 1.1, P=0.64   | 1.42, P=0.44  |
| Omitting Ramachandran P et al.       | 0.87, P=0.21 | NA       | NA              | NA             |
| Omitting Redd W et al.               | 0.89, P=0.28 | NA       | NA              | NA             |
| Omitting Renelus B et al.            | 0.89, P=0.29 | NA       | NA              | NA             |
| Omitting Russell B et al.            | 0.86, P=0.18 | NA       | NA              | NA             |
| Omitting Schettino M et al.          | 0.92, P=0.43 | NA       | NA              | NA             |
| Omitting Shang H et al.              | 0.86, P=0.17 | 0.97, P=0.85 | NA           | NA             |
| Omitting Soares R et al.             | 0.9, P=0.32  | 1.08, P=0.66 | NA           | NA             |
| Omitting Sulaiman T et al.           | 0.88, P=0.24 | NA       | NA              | NA             |
| Omitting Tibbouris P et al.          | 0.89, P=0.27 | 1.04, P=0.83 | 1.17, P=0.45   | 1.49, P=0.38  |
| Omitting Vena A et al.               | 0.88, P=0.23 | 1.01, P=0.95 | 1.23, P=0.32  | NA             |
| Omitting Villaneo F et al.           | 0.89, P=0.29 | NA       | NA              | NA             |
| Omitting Vllion A et al.             | 0.89, P=0.3  | NA       | NA              | NA             |
| Omitting Wan Y et al.                | 0.86, P=0.15 | 0.96, P=0.78 | NA           | NA             |
| Omitting Wang Z et al.               | 0.86, P=0.16 | 0.96, P=0.8 | 1.13, P=0.53  | NA             |
| Omitting Yang X et al.               | 0.88, P=0.24 | NA       | 1.18, P=0.43    | NA             |
**Conclusions**
In summary, we have shown in this meta-analysis that the presence of GI symptoms is not associated with the risk of mortality in COVID-19 patients. The prognostic value of GI symptoms in COVID-19 might not be as significant as other factors such as age, concomitant underlying diseases and respiratory manifestations. Further investigations are needed to clarify the role of gastrointestinal involvement in the disease course of COVID-19, and to explore its therapeutic implications.

**Competing interests**
The authors declare that they have no competing interests.

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**Supplementary Information**
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**Additional 1.** Lists all the extracted data which were used to generate all the results of this study.

**Additional 2.** Contains the supplementary forest plots and the corresponding figure legends.

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**Authors’ contributions**
YW, YmL, YL and YZ collected the literatures and extracted the data. YW and YmL did the data analysis and drafted the manuscript. YlL designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

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**Availability of data and materials**
The dataset generated and analysed during the current study is available in the Additional file 1.

**Declarations**

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