Correlation between gastrointestinal symptoms and disease severity in patients with COVID-19: a systematic review and meta-analysis

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ABSTRACT

Objective To study the correlation between gastrointestinal (GI) symptoms and disease severity in patients with COVID-19.

Design We searched six databases including three Chinese and three English databases for all the published articles on COVID-19. Studies were screened according to inclusion and exclusion criteria. The relevant data were extracted and all the statistical analyses were performed using Revman5.3.

Result In a meta-analysis of 9 studies, comprising 3022 patients, 479 patients (13.7%, 95% CI 0.125 to 0.149) had severe disease and 624 patients (14.7%, 95% CI 0.136 to 0.159) had GI symptoms. Of 624 patients with GI symptoms, 118 patients had severe disease (20.5%, 95% CI 0.133 to 0.276) and of 2397 cases without GI symptoms, 361 patients had severe disease (18.2%, 95% CI 0.129 to 0.235). Comparing disease severity of patients with and without GI symptoms, the results indicated: I²=62%, OR=1.21, 95% CI 0.94 to 1.56, p=0.13; there was no statistically significant difference between the two groups. The funnel plot was symmetrical with no publication bias.

Conclusion Current results are not sufficient to demonstrate a significant correlation between GI symptoms and disease severity in patients with COVID-19.

Summary box

What is already known about this subject?
► The 2019 new coronavirus pneumonia is a new infectious clinical disease caused by a new coronavirus, called SARS-CoV-2.
► Fever and cough were the most common symptoms in patients with COVID-19, but some non-classical symptoms were underestimated.

What are the new findings?
► Gastrointestinal (GI) symptoms accounted for a certain proportion in patients with COVID-19, though fever and cough still were the main symptoms.
► There was no statistically significant difference in severity of COVID-19 between patients with and without GI symptoms, but the proportion of severe disease in patients with GI symptoms was higher than in patients without GI symptoms.

How might it impact on clinical practice in the foreseeable future?
► In clinical practice, the presence of GI symptoms in patients does not indicate a risk of disease progression, which cannot be a predictor.

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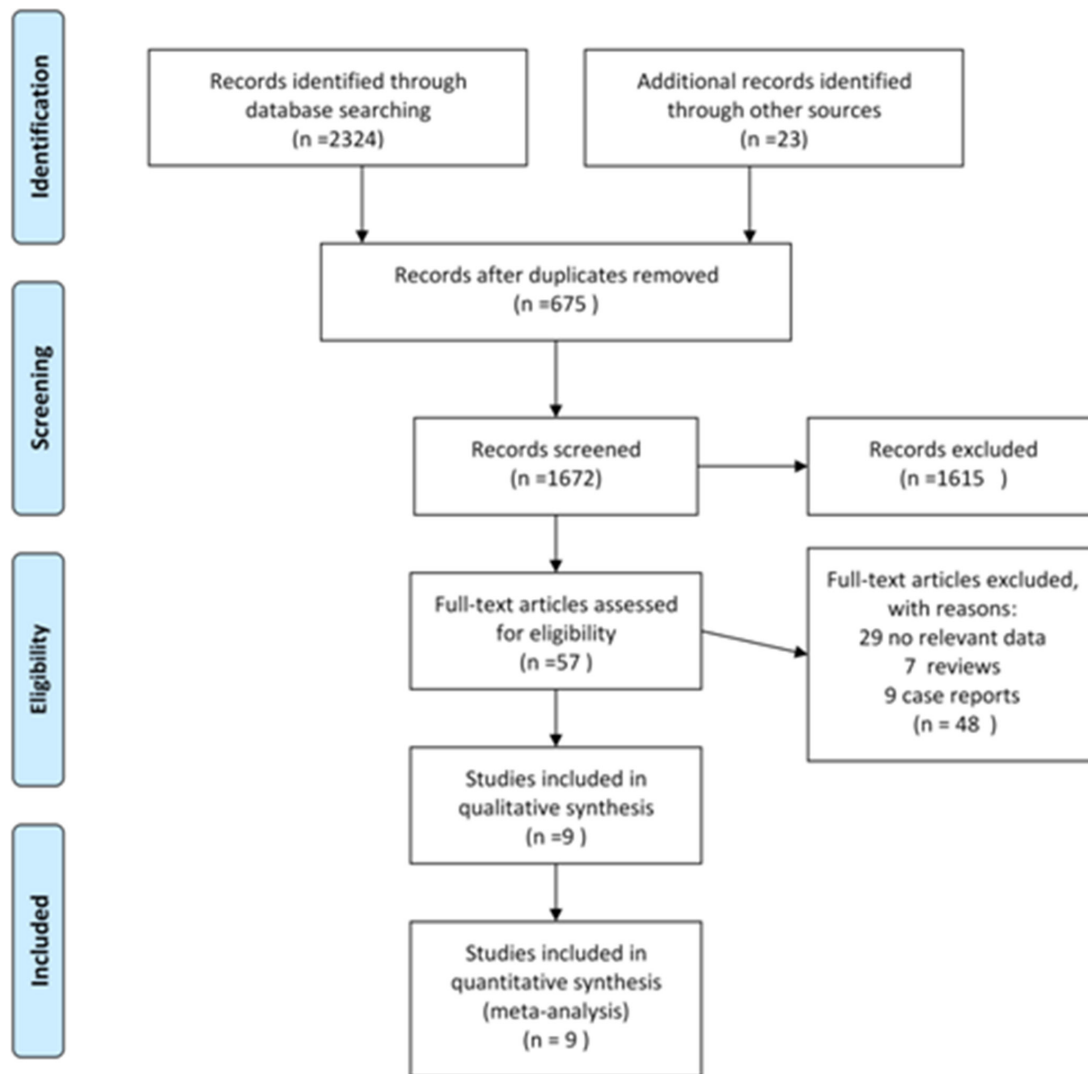**Correspondence to**
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INTRODUCTION

Since December 2019, novel coronavirus (SARS-CoV-2)-infected disease (COVID-19) has gradually swept the world. Morbidity and mortality are increasing due to the high infectivity of the disease worldwide. By 20 April 2020, a total of 2 291 281 infections and 160 044 deaths had been confirmed in 211 countries and regions, with a case fatality rate of 7%, and the number of infections and deaths was dramatically rising daily. SARS-CoV-2 belongs to the same coronavirus family as SARS-CoV and MERS-CoV.[1] But its transmission speed is higher than the other two, and transmission channels are more diversified, including respiratory and digestive tract.[2,3] Earlier studies indicated that the clinical symptoms of COVID-19 vary and not all appear as respiratory symptoms. In some cases, the main symptoms are gastrointestinal (GI) symptoms such as abdominal pain, diarrhoea, nausea and vomiting.[4] Moreover, there are many patients of severe disease with GI symptoms.[5] Hence, it is essential to explore the correlation between digestive symptoms and disease severity, so as to pre-estimate the disease severity and give appropriate early special care and treatment.

MATERIAL AND METHODS
Search strategy

Six medical databases were searched including three English databases (Pubmed, Cochrane Library and Embase) and three Chinese databases (CNKI, Wan Fang Data,

Figure 1 Diagram of documents retrieval.

China Science and Technology Journal Database). The keywords are as follows: 'COVID-19', 'gastrointestinal symptoms' and so on.

Inclusion/exclusion criteria
Inclusive criteria: (1) research types : cross-sectional studies, case control studies and case series; (2) research subjects: patients with confirmed COVID-19; (3) data items: including demographic characteristics (age and gender), clinical characteristics (fever, dry

cough, fatigue, nausea and vomiting, abdominal pain and diarrhoea) and comorbidities (hypertension and diabetes). Exclusive criteria: (1) the type of study is case report, review and so on; (2) repeated research; (3) lack of the above case data; (4) animal experiments.

Data extraction and paper quality evaluation
A total of 2324 articles were retrieved. Browse the titles and abstracts, remove duplicate references, leaving 57 studies. After reading the full text, 48 articles were
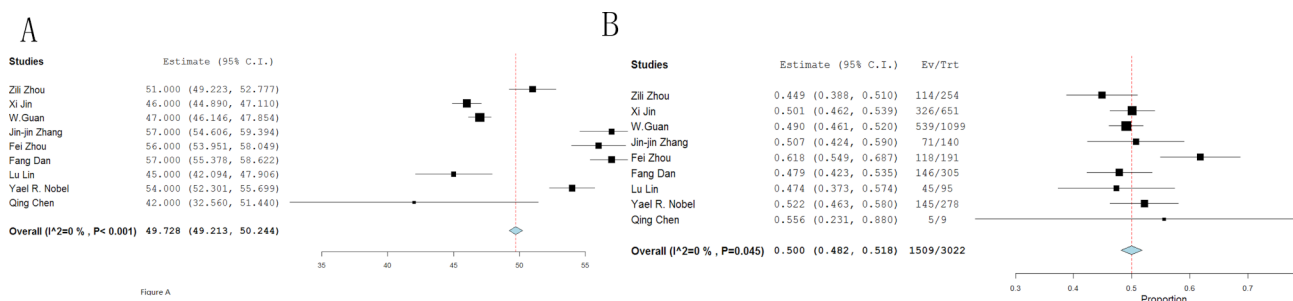

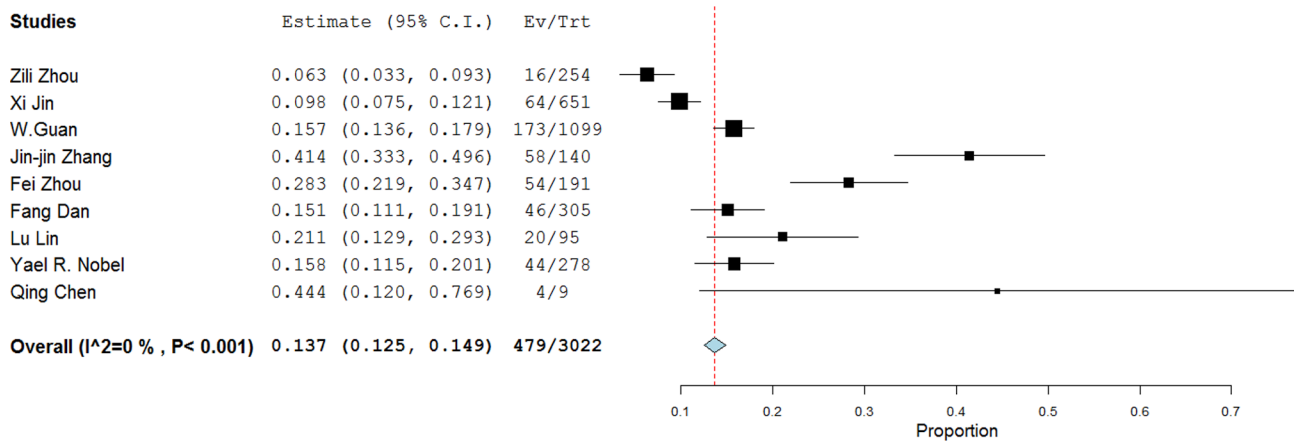**Figure 2** The forest plots of age (A) and male (B).

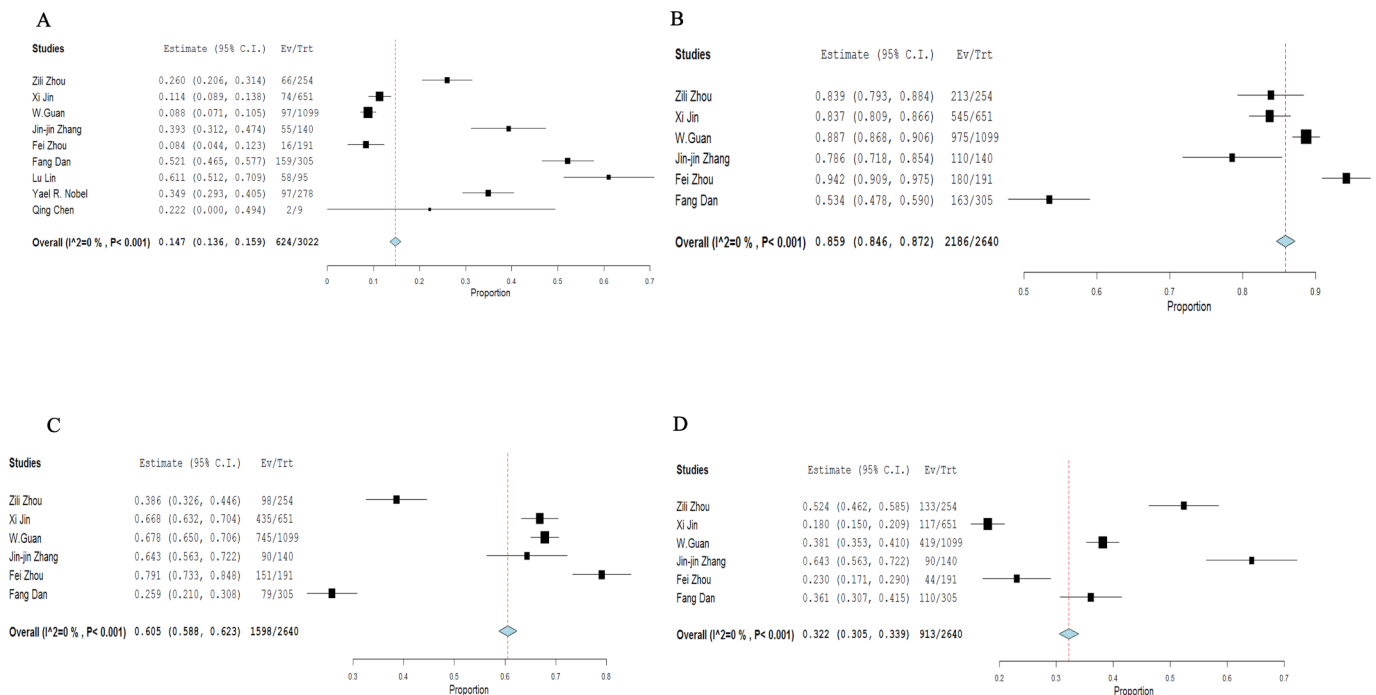**Figure 3** The incidence of severe type.

Figure 4 The incidence of clinical features: (A) GI symptoms, (B) fever, (C) dry cough and (D) fatigue. GI, gastrointestinal.

removed. Finally, a total of 9 studies[5–13] (including 8 English articles and 1 Chinese literature) and 3022 patients were included (figure 1). The Newcastle-Ottawa Scale (NOS) scoring system scored an average of 7.7 (6–8), indicating that the quality of selected studies was relatively high.

Statistical analysis

Meta-analysis was performed using Revman5.3. I² statistics are calculated to measure the proportion of total variation in study estimates attributed to heterogeneity. The combined OR and 95% CI (p<0.05) were calculated
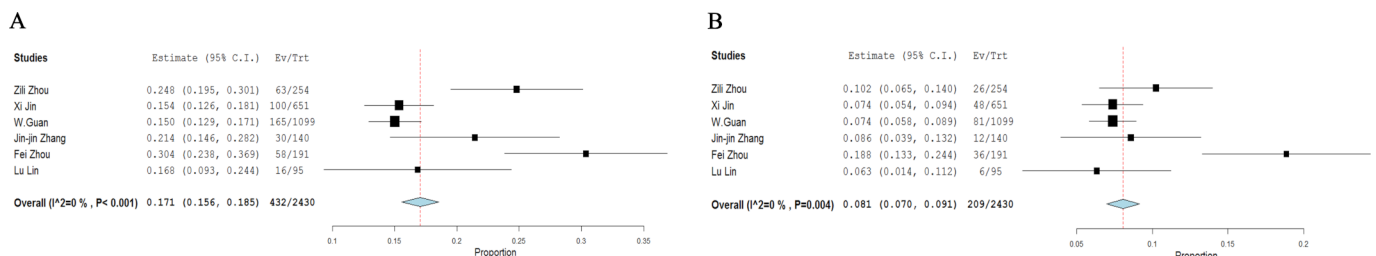

Figure 5 The incidence of comorbidities: (A) hypertension and (B) diabetes.

Table 1 Severe patients with and without GI symptoms

GI symptoms			No GI symptoms	
Study	Severe	No.	Severe	No.
Zhou et al[6]	4	66	12	188
Jin et al[5]	17	74	47	577
Guan et al[7]	22	97	151	1002
Zhang et al[8]	24	55	34	84
Zhou et al[9]	5	16	49	175
Fang et al[10]	17	159	29	146
Lin et al[11]	14	58	6	37
Nobel et al[12]	14	97	30	181
Chen et al[13]	1	2	3	7
Total	118	624	361	2397

GI, gastrointestinal.

for heterogeneity. The forest plot and funnel plot were developed to assess heterogeneity and publication bias.

RESULT
Demographical characteristics, clinical features and comorbidities

The main characteristics of all included studies are as follows: 50% patients are male (95% CI 0.482 to 0.518) and mean age of patients was 49.7 (95% CI 49.213 to 50.244) (figure 2). A total of 479 patients with COVID-19 (13.7%, 95% CI 0.125 to 0.149) had severe disease

(figure 3) and 624 patients (14.7%, 95% CI 0.136 to 0.159) had GI symptoms. The incidence of fever was 85.9% (95% CI 0.846 to 0.872), that of dry cough was 60.5% (95% CI 0.588 to 0.623) and that of fatigue was 32.2% (95% CI 0.305 to 0.339) (figure 4). The incidence of comorbidities, including hypertension and diabetes was 17.1% (95% CI 0.156 to 0.185) and 8.1% (95% CI 0.070 to 0.091), respectively (figure 5).

Gastrointestinal symptoms

As shown in table 1, of 624 patients with COVID-19 with GI symptoms, 118 patients had severe disease (20.5%, 95% CI 0.133 to 0.276) and of 2397 cases without GI symptoms, 361 patients were severe (18.2%, 95% CI 0.129 to 0.235) (figure 6). Comparing the severity of COVID-19 in patients with and without GI symptoms, the results indicated: I²=62%; the heterogeneity among studies was moderate. For OR=1.21, 95% CI 0.94 to 1.56, and p=0.13, there was no statistically significant difference in severity of COVID-19 between patients with and without GI symptoms (figure 7). The funnel plot was symmetrical with no publication bias(figure 8). The outcome showed that there was no significant correlation between GI symptoms and disease severity in patients with COVID-19.

DISCUSSION

In this study, fever (85.9%) and respiratory symptoms (60.5%) were still the main manifestations in patients with COVID-19, but GI symptoms (14.7%), such as nausea,
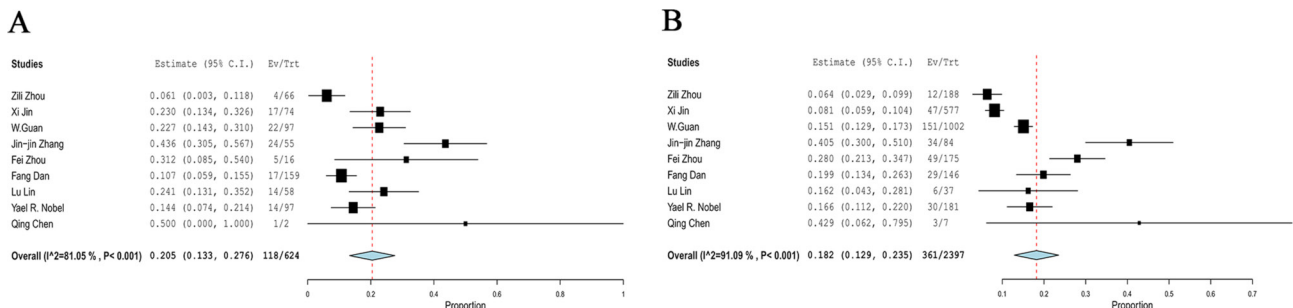

Figure 6 The severe type with and without GI symptoms: (A) severe type with GI symptoms and (B) severe type without GI symptoms. GI, gastrointestinal.
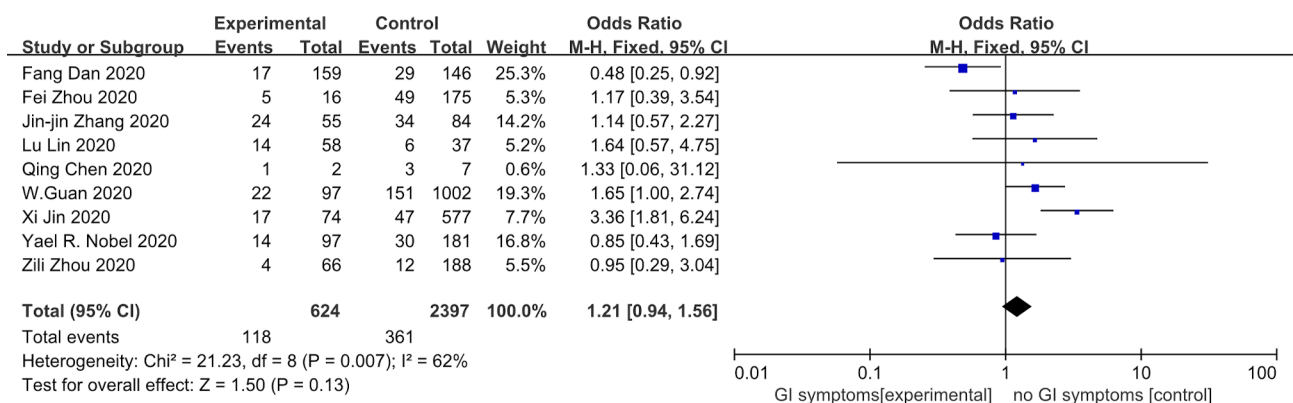

Figure 7 The correlation between the presence of GI symptoms and the severity of COVID-19. GI, gastrointestinal.
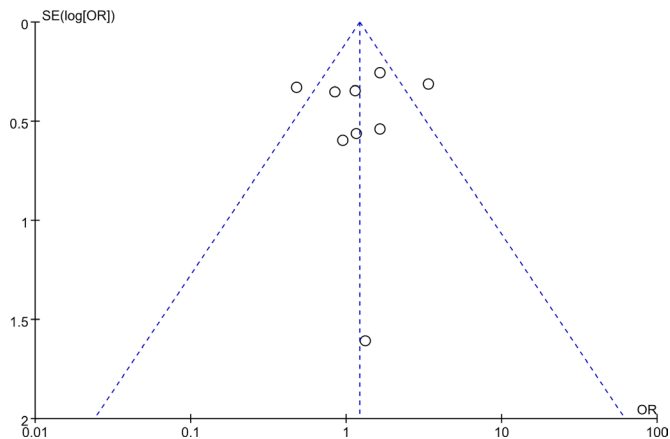
Figure 8 The funnel plot.

vomiting, diarrhoea and abdominal pain, also appeared in a considerable number of patients, which was consistent with the previous study that Huang et al[14] conducted. Wang et al[15] reported that abdominal pain was more frequent in patients who required intensive care unit care than those who did not. In addition, Holshue et al[16] and Gui et al[17] suggested that the crucial ACE2 receptor of SARS-CoV-2 infecting cells was expressed in lung AT2 cells and in intestinal epithelial cells. The study conducted by Lukassen et al showed that organs with ACE2 expressing cells may be considered as potential infection sites and transmission routes for SARS-CoV-2.[18] Liang et al[19] reported that due to the high ACE2 expression in proximal and distal enterocytes, intestine may be vulnerable to SARS-CoV-2 infection. GI symptoms, such as vomiting and diarrhoea, lead to the interruption of intestinal flora and electrolyte disturbance such as low potassium and imbalance of water and sodium. This is likely to worsen the patients' condition. However, the result of this meta-analysis showed that there was no statistical correlation between the presence of GI symptoms and the severity of COVID-19. Although there was no statistical significance, the result that the proportion of severe disease in patients with GI symptoms (20.5%) was higher than that in patients without GI symptoms (18.2%) was evident. This study also has some limitations: (1) the languages of retrieval literature are limited to Chinese and English and all the articles are limited to published literature and (2) GI symptoms may be under-reported in some studies, which may cause a lower pooled prevalence rate. Despite the limitations, this meta-analysis overcomes the shortcomings of small sample size and regional restrictions. The heterogeneity and publication bias among the studies are moderate and the results are relatively objective.

In summary, current findings are not sufficient to demonstrate a significant correlation between GI symptoms and disease severity in patients with COVID-19. Large multicentric prospective studies are required to confirm our findings.

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