Digestive symptoms and liver injury in patients with coronavirus disease 2019 (COVID-19): A systematic review with meta-analysis

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Key words
COVID-19, digestive symptoms, liver injury, meta-analysis.

Accepted for publication 20 September 2020.

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Declaration of conflict of interest: None.

Author contribution: Jian Wan and Jie Liang formulated the research questions and designed the study. Jian Wan, Xuan Wang, and Jie Liang developed the search strategy. Jian Wan and Xuan Wang collected and analyzed the data. Yujie Zhang, Yirong Jin, and Yanting Shi verified the data. Jian Wan, Xuan Wang, and Song Su drafted the manuscript. Yujie Zhang, Kaichun Wu, and Jie Liang revised the paper. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

Guarantor of the article: Jie Liang.

Funding support: National Key Research and Development Plan of China, 2017YFC0908300

Abstract

Although most COVID-19 patients typically present with respiratory symptoms, many patients could experience digestive symptoms as the major complaint. We performed a systematic review and meta-analysis to investigate the exact prevalence of digestive symptoms and liver injury in COVID-19 patients and compare the difference between patients with and without digestive symptoms. PubMed, Embase, Ovid, Wanfang data, and CNKI were searched until 24 April 2020 to identify studies that reported digestive symptoms and liver injury in COVID-19 patients. A random-effect model was used to combine the data. Finally, 64 studies with 15 141 patients were included. The pooled rate of digestive symptoms and liver dysfunction was 31.8% (95 CI 21.0–42.5%, \(I^2 = 76\%\)) and 27.4% (95 CI 16.9–37.9%, \(I^2 = 97.9\%\)), respectively. Patients with digestive symptoms were more likely to present with fatigue (OR 2.28, 95 CI 1.16–4.51, \(P = 0.02\), \(I^2 = 78\%\)) and acute respiratory disease syndrome (ARDS) (OR 2.94, 95 CI 1.17–7.40, \(P = 0.02\), \(I^2 = 0\)) and had a trend to present as severe/critical type (OR 1.87, 95 CI 0.98–3.57, \(P = 0.06\), \(I^2 = 58\%\)). Severe/critical patients were more likely to present with diarrhea (OR 2.02, 95 CI 1.16–3.50, \(P = 0.01\), \(I^2 = 64\%\)) and have high alanine aminotransferase (ALT) (OR 2.08, 95 CI 1.55–2.81, \(P < 0.00001\), \(I^2 = 13\%\), and aspartate aminotransferase (AST) (OR 3.57, 95 CI 2.76–4.51, \(P < 0.00001\), \(I^2 = 0\)). The pooled rate of patients with digestive symptoms was 28.7% (95 CI 17.6–39.8%) and 42.8% (95 CI 23.4–62.3%) in studies from China and out of China, respectively. COVID-19 patients had a high rate of digestive symptoms and liver injury. Patients with digestive symptoms had a trend to develop severe/critical illness.

Introduction

Currently, the pandemic of novel coronavirus disease (COVID-19) has developed as a big threat to global health. Although the majority of COVID-19 patients typically present with respiratory symptoms and signs, many patients could experience extrapulmonary symptoms such as digestive symptoms, including diarrhea, loss of appetite, nausea/vomiting, and abdominal pain, as the major complaints. These features may be attributable to the following fact: 1) COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its receptor angiotensin converting enzyme 2 (ACE2) was found to be highly expressed in gastrointestinal (GI) epithelial cells, providing a prerequisite for SARS-CoV-2 infection and 2) SARS-CoV-2 viral RNA has been found in the stool specimens of infected patients, and 20% of patients showed prolonged presence of SARS-CoV-2 RNA in fecal samples after testing negative for the virus in the respiratory system. There findings suggest that SARS-CoV-2 may be able to actively infect and replicate in the GI tract.

Moreover, GI infection could be the first manifestation antedating respiratory symptoms, and six patients only suffering digestive symptoms but no respiratory symptoms as clinical
manifestation were reported.\textsuperscript{1} Thus, the implications of digestive symptoms in patients with COVID-19 absolutely has significant importance. To date, there are increasing data showing that the GI tract and liver can be involved in COVID-19 and that the infected patients could have corresponding organ damage and symptoms.\textsuperscript{6} However, the prevalence of digestive symptoms and liver injury varied remarkably among studies. The percentage of patients with GI tract manifestations was reported to be 7.5–61.1\%,\textsuperscript{7,8} and liver injury was identified in 2.5–55.0\%\textsuperscript{9,10} of patients with COVID-19. Thus, the exact prevalence of digestive symptoms and liver injury in COVID-19 remains unclear. Furthermore, several studies reported that COVID-19 patients with digestive symptoms tended to suffer a worse clinical outcome and higher risk of mortality compared to those without digestive symptoms, as well as a have a longer time from symptom onset to admission.\textsuperscript{1} In addition, the prevalence of diarrhea and abdomen pain was significantly higher in severe patients than that in mild patients.\textsuperscript{2,5} However, these studies are basically conducted in a single center from a single country involving patients from a single ethical background. In addition, the sample size of most studies was relatively small.

Therefore, we performed a systematic review and meta-analysis using global-wide data and aimed to comprehensively investigate 1) the exact prevalence of digestive symptoms and liver injury in COVID-19 patients and 2) the relationship between digestive symptoms and clinical characteristics, especially the presence or absence of severe disease.

**Materials and methods**

**Search strategy and studies selection.** This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.\textsuperscript{11} PubMed, Ovid, Embase, Wanfang data, and China National Knowledge Infrastructure (CNKI) were searched for studies from December 2019 to March 27, 2020 to identify all case studies. Article language limit was not set. An updated search was performed on 24 April 2020. The search terms used were: 2019 novel coronavirus,

![Flow diagram](image-url)

**Figure 1** Flow diagram of the search results and study selection.
Table 1 Characteristics of studies

| Author                  | Published language | Cases across centers | Female Age | Digestive comorbidities | Liver comorbidities | Quality score |
|-------------------------|--------------------|----------------------|------------|-------------------------|---------------------|---------------|
| Min Li15                | Chinese            | Hubei, 1             | 30 (4)     | 20                      | 35 ± 8              | 6             |
| Hansheng Xie56          | English            | Hubei, 1             | 79 (28)    | 35                      | 60 (range 48–66)    | 6             |
| Fei Zhou59              | English            | Hubei, 1             | 219 (119)  | 1 (72)                  | 56 (IQR 34–67)      | 9             |
| Xiaobo Yang60           | English            | Hubei, 1             | 52 (52)    | 17                      | 59.7 ± 13.3         | 8             |
| Heshui Shi65            | English            | Hubei, 1             | 2 (81)     | 39                      | 49.5 ± 11.0         | 7             |
| Chaomin Wu54            | English            | Hubei, 1             | 201 (73)   | 51 (IQR 34–60)          | 7             |
| Tao Chen21              | English            | Hubei, 1             | 274 (103)  | 62 (IQR 44–70)          | 14 (range 2–83)     | 7             |
| Ling Mao37              | English            | Hubei, 1             | 3 (214)    | 127                     | 52.7 ± 15.5         | 7             |
| Qian Li32               | Chinese            | Hubei, 2             | 30 (12)    | 6 (range 0–14)          | 7             |
| Gui Liu34               | Chinese            | Hubei, 9             | 137 (76)   | 57 (range 20–83)        | 7             |
| Dan Fang25              | Chinese            | Hubei, 1             | 305 (159)  | 57 (range 18–95)        | 6             |
| Lei Pan1                | English            | Hubei, 3             | 204 (97)   | 52.91 ± 15.98           | 7             |
| Yuanmei Guo77           | Chinese            | Hubei, 1             | 663 (342)  | 58 (IQR 44–69)          | 31 (range 25–87)    | 7             |
| Jinh-jin Zhang64        | English            | Hubei, 1             | 140 (69)   | 57 (range 25–87)        | 4             |
| Xiaoling Zhao18         | English            | Hubei, 1             | 171 (67)   | 6.7 (range 1 day–15)    | 6             |
| Min Bai17               | Chinese            | Hubei, 1             | 472 (257)  | 50.7 ± 11.6             | 6             |
| Shi Chen20              | Chinese            | Hubei, 1             | 109 (61)   | 52.5 ± 10.8             | 7             |
| Gemin Zhang63           | English            | Hubei, 1             | 95 (42)    | 49 (range 39–58)        | 8             |
| Zili Zhou50             | English            | Hubei, 1             | 254 (139)  | 50.6 (range 15–87)      | 7             |
| K. Wang51               | English            | Hubei, 1             | 114 (56)   | 53 (range 23–78)        | 6             |
| Zhongliang Wang52       | Chinese            | Hubei, 1             | 69 (37)    | 42 (IQR 35–62)          | 6             |
| Fenghua Xu57            | Chinese            | Hubei, 1             | 251 (119)  | 59.9 ± 15.7             | 4             |
| Rong Wang64             | Chinese            | Hubei, 1             | 96 (50)    | NA                      | 7             |
| Pingzheng Mo58          | English            | Hubei, 1             | 155 (69)   | 54 (IQR 42–66)          | 7             |
| Dawei Wang59            | Chinese            | Hubei, 1             | 138 (63)   | 56 (IQR 42–68)          | 4             |
| Wei-je Guan50           | English            | China, 522           | 1099 (459) | 47 (IQR 35–58)          | 9             |
| Dahai Zhao58            | English            | Hubei, 1             | 19 (8)     | 48 (IQR 27–56)          | 1             |
| Yalin Li414             | Chinese            | Anhui, 1             | 49 (21)    | 45 (range 14–82)        | 3             |
| De Chang18              | English            | Beijing, 3           | 13 (3)     | 34 (IQR 34–48)          | 6             |
| Zhi En59                | Chinese            | Beijing, 1           | 46 (19)    | 41.8 ± 16.3             | 6             |
| Xi Xu59                 | English            | Guangdong, 1         | 90 (51)    | 50 (range 18–86)        | 7             |
| Jing Yuan62             | English            | Guangdong, 1         | 94 (52)    | 40 (range 1–78)         | 8             |
| Lu Lin5                  | English            | Guangdong, 1         | 95 (50)    | 45.3 ± 18.3             | 8             |
| Rui Zhao57              | Chinese            | Guangxi, 1           | 28 (17)    | 44.5 (range 11–68)      | 5             |
| Chan Sun46              | Chinese            | Henan, 16            | 150 (83)   | 45 ± 16                 | 6             |
| Ye Zhao50               | Chinese            | Henan, 1             | 106 (40)   | 48.9 ± 13.1             | 8             |
| Feng Zheng68            | English            | Hunan, 1             | 161 (81)   | 45 (range 33.5–57)      | 6             |
| Xin Tan47               | Chinese            | Hunan, 1             | 13 (1)     | 8 (range 1–7)           | 6             |
| Dan Li31                | Chinese            | Hunan, NA            | 80 (40)    | 47.5 (range 3–90)       | 6             |
| Tianmin Xu58            | English            | Jiangsu, 1           | 51 (26)    | 35 (IQR 29–51) (n = 15) | 6             |
| Miao Zhu15              | Chinese            | Jiangsu, 1           | 23 (13)    | 50.0 ± 13.0             | 5             |
| Jian Wu10               | English            | Jiangsu and Anhui, 4 | 280 (83)   | 43.12 ± 19.02           | 7             |
| Tianxin Xiang55         | Chinese            | Jiangxi, 1           | 49 (9)     | 42.9 (range 18–78)      | 6             |
| Shuxiang Zhang65        | Chinese            | Ningxia, 1           | 34 (14)    | 41 ± 17                 | 7             |
| Na Yao5                 | Chinese            | Shaanxi, 1           | 40 (15)    | 53.9 ± 15.8             | 6             |
| Jun Chen19              | English            | Shanghai, 1          | 249 (123)  | 51 (IQR 36–64)          | 2             |
| Dan Li20                | Chinese            | Liaoning, 1          | 30 (12)    | 43 (range 21–72)        | 6             |
| Xiaochun Dong23         | Chinese            | Tianjin, NA          | 135 (63)   | 48.6 ± 16.8             | 5             |
| Kelvin Kai-Wang20        | English            | Hongkong, 2          | 23 (10)    | 62 (range 37–75)        | 8             |
| Xi Jin28                | English            | Zhejiang, NA         | 651 (320)  | 46.1 ± 14.2 (n = 74)    | 5             |
| Xiaolong Qi51           | English            | China, 9             | 70 (31)    | 41 (IQR 27.5–50) (n = 32)| 6             |
| Duan Wang60             | Chinese            | China, 21            | 31 (0)     | 7.1 (range 0.5–17)      | 5             |

Continues
Table 1 (Continued)

| Author                                | Published language | Center | Cases (severe) | Female Age | Digestive comorbidities | Liver comorbidities | Quality score |
|----------------------------------------|--------------------|--------|----------------|------------|------------------------|--------------------|--------------|
| Chuan Liu53                            | Chinese            | China 7| 32 (4)         | 12         | 38.5 (IQR 26.3–45.8)   | —                  | 7            |
| Suxin Wan49                            | Chinese            | Chongqing, 1 | 135 (40)   | 63         | 47 (IQR 36–55)         | —                  | 2            |
| Jing Yuan16                            | Chinese            | Chongqing, 1 | 223 (31)   | 117        | 46.5 ± 16.1            | —                  | 8            |
| Maria Effenberger24                    | English            | Austria, 1 | 40          | 16         | 58.4 ± 17.1 (n = 18)   | —                  | 5            |
| The COVID-19 Investigation Team48      | English            | America, 6 | 12          | 4          | 53 (range 21–68)       | —                  | 5            |
| Safiya Richardson43                    | English            | America, 12 | 5700       | 2263       | 63 (IQR 52–75)         | —                  | 6            |
| George Cholankeril22                   | English            | America, 1 | 116         | 54         | 50 (IQR 35–67)         | —                  | 5            |
| Walker D. Redd45                       | English            | America, 9 | 318         | 144        | 63.4 ± 16.6            | 122                | 5            |
| Yael R. Nobel29                        | English            | America, 1 | 278         | 133        | Range 18–30 (n = 31); 31–50 (n = 69); 51–70 (n = 103); >70 (n = 75) | —                  | 5            |
| Mario Fernández-Ruiž26                 | English            | Spain   | 18           | 4          | 72 (range 39–80)       | 7                  | 7            |
| Rachael Pung30                         | English            | Singapore, 1 | 17          | 10         | 40 (IQR 36–51)         | —                  | 6            |
| BE Young61                             | English            | Singapore, 4 | 18          | 9          | 47 (range 31–73)       | —                  | 7            |

1Including the patients with liver comorbidities.

IQR, interquartile range; NA, not available;

2019-nCoV, COVID-19, COVID19, SARS-CoV-2, SAR2, Coronavirus disease 2019, Coronavirus 2019, and Wuhan coronavirus. Studies meeting all the following criteria were included: (a) reported digestive manifestations in COVID-19 patients; (b) the sample size of COVID-19 patients was more than 10; (c) and full-text articles that were peer reviewed. Exclusion criteria were as follows: (a) research data were missing; (b) duplicate reported data or paper; (c) case report, letters, editorials, reviews, and meta-analyses not presenting original data; and (d) abstracts from conferences and commentary articles. We also reviewed the references of included articles to guarantee the comprehensiveness and accuracy of our research.

Data extraction. After performing the literature search independently, the two investigators (Jian Wan and Xuan Wang) used EndNote X 9.0 software to exclude duplicate records. After screening the title and abstract of the articles independently, two authors (Jian Wan and Xuan Wang) reviewed the full text to select potentially eligible studies and then, using predesigned standard forms, extracted data from the eligible studies independently. They captured the names of the authors, published year, type of study, country, study design, characteristics of the patients (including their number, the number of severe/critical type patients, age, gender, comorbidities, symptoms), digestive symptoms (such as diarrhea, nausea, vomiting, abdominal pain, and loss of appetite), and liver function [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBil)]. Any disagreements were resolved by discussion with the third reviewer (Jie Liang).

Outcomes of interest. The primary outcome was the rate of various digestive symptoms and liver function in COVID-19 patients. Secondary outcomes included the difference between patients with and without digestive symptoms and between normal/mild and severe/critical patients with COVID-19.

Quality assessment. Two reviewers (Jian Wan and Xuan Wang) used an 11-item checklist that was recommended by the Agency for Healthcare Research and Quality (AHRQ).12 Article quality was assessed as follows: low quality (0–3), moderate quality (4–7), and high quality (8–11).

Statistical analysis. The data on all outcomes of interest were analyzed using Review Manager version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and Stata software version 12.0 (Stata Corporation, College Station, TX, USA). Heterogeneity among studies was tested using the Cochran Chi-square test and $\chi^2$. A random-effect model was used to combine the outcomes of interest because of the heterogeneity within and between studies. A random-effect model would give a more conservative estimate of the 95% confidence interval (CI). Data were presented with odds ratio (OR) and 95% CI using forest plots. $\chi^2$ statistic and Cochran’s Q test were used to assess statistical heterogeneity. The statistical significance level was set at $P < 0.05$. Statistical heterogeneity was set at $P < 0.10$ for the $\chi^2$ test and $\chi^2 > 50\%$ for the $\chi^2$ value.13

Results

Characteristics of included studies. Based on the previous search strategy, a total of 22,493 studies were obtained from the databases. After deleting duplicate records and screening the abstract and title, 150 articles were selected for full-text assessment. Finally, 64 studies1,2,5,7,10,14–70 were included in the meta-analysis, including data from 15,141 patients. A flow diagram of the search results and study selection is shown in Figure 1. The main characteristics of the included studies and...
Table 2  Characteristics of digestive symptoms and liver function of the study patients

| Author, year   | Cases | Diarrhea | Nausea and/or Vomiting | Abdominal pain | Loss of appetite | Digestive symptoms | Elevated ALT | Elevated AST | Elevated TBil | Abnormal liver functions |
|----------------|-------|----------|------------------------|----------------|----------------|--------------------|--------------|--------------|---------------|--------------------------|
| Min Liu        | 30    | —        | —                      | —              | —              | 9/30               | —            | —            | —             | —                        |
| Hansheng Xie   | 79    | 7        | —                      | —              | —              | 25/79              | 28/79        | 4/79         | —             | —                        |
| Fei Zhou       | 191   | 9        | 7                      | —              | —              | 59/189             | —            | —            | —             | —                        |
| Xiaobo Yang    | 52    | —        | 2                      | —              | —              | —                  | —            | —            | —             | —                        |
| Heshui Shi     | 81    | 3        | 4                      | —              | 1              | —                  | 43/81        | —            | —             | —                        |
| Chaomin Wu     | 201   | —        | —                      | —              | —              | 43/198             | 59/198       | 10/198       | —             | —                        |
| Tao Chen       | 274   | 77       | 24,16                 | 19             | 66             | —                  | 60/274       | 84/274       | —             | —                        |
| Ling Mao       | 214   | 41       | 10                     | 68             | —              | —                  | —            | —            | —             | —                        |
| Qian Li        | 30    | 2        | 2                      | —              | —              | —                  | —            | —            | —             | —                        |
| Kui Li         | 137   | 11       | —                      | —              | —              | —                  | —            | —            | —             | —                        |
| Min Liu        | 35    | —        | —                      | —              | —              | 9/30               | —            | —            | —             | 7/30                      |
| Hansheng Xie   | 56    | 79       | 7                      | —              | —              | 25/79              | 28/79        | 4/79         | —             | —                        |
| Fei Zhou       | 191   | 9        | 7                      | —              | —              | 59/189             | —            | —            | —             | —                        |
| Xiaobo Yang    | 52    | —        | 2                      | —              | —              | —                  | —            | —            | —             | —                        |
| Heshui Shi     | 81    | 3        | 4                      | —              | 1              | —                  | 43/81        | —            | —             | —                        |
| Chaomin Wu     | 201   | —        | —                      | —              | —              | 43/198             | 59/198       | 10/198       | —             | —                        |
| Tao Chen       | 274   | 77       | 24,16                 | 19             | 66             | —                  | 60/274       | 84/274       | —             | —                        |
| Ling Mao       | 214   | 41       | 10                     | 68             | —              | —                  | —            | —            | —             | —                        |
| Qian Li        | 30    | 2        | 2                      | —              | —              | —                  | —            | —            | —             | —                        |
| Kui Li         | 137   | 11       | —                      | —              | —              | —                  | —            | —            | —             | —                        |

(Continues)
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Table 2 (Continued)

| Author, year | Cases | Diarrhea | Nausea and/or vomiting | Abdominal pain | Loss of appetite | Digestive symptoms | Elevated ALT | Elevated AST | Elevated TBil | Abnormal liver functions |
|--------------|-------|----------|------------------------|---------------|-----------------|-------------------|-------------|-------------|-------------|-------------------------|
| Maria Effenberger24 | 40 | 22 | 11.5 | — | — | — | — | — | — | — |
| The COVID-19 Investigation Team46 | 12 | 1 | 1 | — | — | — | — | — | — | — |
| Safiya Richardson43 | 5700 | — | — | — | — | — | — | — | — | — |
| George Cholankeril22 | 116 | 12 | 12 | 10 | 22 | 37/116 | — | — | — | 26/65 |
| Walker D. Redd42 | 318 | 107 | 84.49 | 46 | 110 | 195/318 | — | — | — | — |
| Yael R. Nobel29 | 278 | 56 | 63 | — | — | 97/278 | — | — | — | — |
| Mario Fernández-Ruiz26 | 18 | 4 | 1 | — | — | — | — | — | — | — |
| Rachael Pung30 | 17 | 4 | 1 | — | — | — | — | — | — | — |
| BE Young61 | 18 | 3 | — | — | — | — | — | — | — | — |

1No. of patients with nausea, No. of patients with vomiting.
2Excluded from the meta-analysis (many patients presented with diarrhea after using oseltamivir and/or abidor).

AST, aspartate aminotransferase; ALT, alanine aminotransaminase; TBil, total bilirubin;

patients are shown in Tables 1 and 2, respectively. Fifty-five studies were from China, and nine were from out of China (Austria: 1, America: 5, Spain: 1, and Singapore: 2). Twenty-five studies were published in Chinese, and the other 39 were published in English. The quality assessment of the studies is summarized in Table 1.

**Digestive symptoms.** The pooled results of 14 studies (2535 patients) showed that the rate of patients with digestive symptoms was 31.8% (95 CI 21.0–42.5%, 97.6%, heterogeneity  $P = 0.000$) (Fig. S1a). The main digestive symptoms were diarrhea (53 studies, 8604 patients: 11.2%, 95 CI 9.3–13.1%, 90.7%, heterogeneity  $P = 0.000$) (Fig. S1c), nausea and/or vomiting (33 studies, 6165 patients: 10.0%, 95 CI 7.6–12.3%, 94.4%, heterogeneity  $P = 0.000$) (Fig. S1f), loss of appetite (15 studies, 2203 patients: 46.6%, 95 CI 2.7–6.5%, 82.5%, heterogeneity  $P = 0.000$) (Fig. S1d), and abdominal pain (14 studies, 2203 patients: 46.6%, 95 CI 2.7–6.5%, 82.5%, heterogeneity  $P = 0.000$) (Fig. S1e). The pooled estimate of digestive disease comorbidities was 11.2% (95 CI 6.1–16.3%, 95.2%, heterogeneity  $P = 0.000$, 9 studies, 2107 patients) (Fig. S1b) (Table 3).

**Liver injury.** The pooled results of 12 studies (1878 patients) showed that the rate of patients with abnormal liver function was 27.4% (95 CI 16.9–37.9%, 97.9%, heterogeneity  $P = 0.000$) (Fig. S2a). The pooled results demonstrated that the rate of high ALT was 25.3% (95 CI 21.3–29.2%, 87.8%, heterogeneity  $P = 0.000$, 23 studies, 3973 patients) (Fig. S2c), the rate of high AST was 25.4% (95 CI 16.1–34.6%, 98.8%, heterogeneity  $P = 0.000$, 23 studies, 9650 patients) (Fig. S2d), and the rate of high TBil was 8.8% (95 CI 5.1–12.5%, 91.5%, heterogeneity  $P = 0.000$, 9 studies, 1975 patients) (Fig. S2e). The pooled rate of liver diseases comorbidities was 2.5% (95 CI 1.8–3.3%, 75%, heterogeneity  $P = 0.000$, 29 studies, 10 839 patients) (Fig. S2b) (Table 3).

**Subgroup analysis of comparing COVID-19 patients with and without digestive symptoms.** There were eight studies1,7,8,27,28,42,57,70 including 2542 patients focusing on the differences between patients with and without digestive symptoms. Patients with digestive symptoms were more likely to present with fatigue (OR 2.28, 95 CI 1.66–3.14, $P < 0.00001$, 97.6%, heterogeneity  $P = 0.32$, 5 studies, 1975 patients) (Fig. S2).
patients) and myalgia (OR 1.96, 95 CI 1.06–3.65, \( P = 0.03, I^2 = 69\%), heterogeneity \( P = 0.04, 3 \text{ studies, 1223 patients} \) (Fig. S3). There was no significance between patients with and without digestive symptoms in age, gender, fever, sore throat, cough, sputum production, chest tightness, dyspnea, headache, dizziness, hemoptysis, and comorbidities. When comparing the difference in complications, patients with digestive symptoms were more likely to present with ARDS (OR 2.94, 95 CI 1.17–7.40, \( P = 0.02, I^2 = 0\), heterogeneity \( P = 0.59, 2 \text{ studies, 905 patients} \) (Fig. 2). No difference was found in shock, acute heart

![Figure 2](image-url)

**Figure 2** Comparison of complications between COVID-19 patients with and without digestive symptoms.
**Figure 3** Comparison of normal/mild and severe/critical patients with COVID-19.
failure, arhythmia, pneumonia, and liver injury. Patients with digestive symptoms had a trend to present as severe/critical type (OR 1.87, 95 CI 0.98–3.57, P = 0.06, I² = 58%, heterogeneity P = 0.07, 4 study, 1515 patients) (Fig. 2). When comparing the difference in treatments, patients with digestive symptoms were more likely to be treated with immunoglobulins (OR 2.39, 95 CI 1.53–3.72, P = 0.0001, I² = 0, heterogeneity P = 0.34, 2 study, 458 patients). No difference was found in mechanical ventilation, antibiotics, glucocorticoids, antivirals, extracorporeal membrane oxygenation (ECMO), and intensive care unit admission (Fig. S3).

**Subgroup analysis: Severe/critical versus mild/normal type.** Patients with severe/critical type were more likely to present with diarrhea (OR 2.02, 95 CI 1.16–3.50, P = 0.01, I² = 64, heterogeneity P = 0.0003, 16 studies, 3849 patients) and have high ALT (OR 2.08, 95 CI 1.55–2.81, P < 0.00001, I² = 13%, heterogeneity P = 0.33, 8 studies, 1830 patients) and AST (OR 3.53, 95 CI 2.76–4.51, P < 0.00001, I² = 0, heterogeneity P = 0.57, 8 studies, 1959 patients) (Fig. 3). No difference was found in nausea and/or vomiting, abdominal pain, loss of appetite, and TBil (Fig. 5).

**Subgroup analysis: China versus out of China.** The pooled rate of patients with digestive symptoms was 28.7% (95 CI 17.6–39.8%) and 42.8% (95 CI 23.4–62.3%) in studies from China and out of China, respectively (Fig. S1a). The pooled rate of patients with diarrhea was 9.6% (95 CI 7.9–11.4%) and 23.5% (95 CI 14.2–32.9%) in studies from China and out of China, respectively (Fig. S1c). The pooled rate of patients with loss of appetite was 20.5% (95 CI 12.8–28.2%) and 27.0% (95 CI 11.7–42.3%) in studies from China and out of China, respectively (Fig. S1d). The pooled rate of patients with abdominal pain was 3.2% (95 CI 1.8–4.6%) and 11.8% (95 CI 6.1–17.5%) in studies from China and out of China, respectively (Fig. S1e). The pooled rate of patients with nausea and/or vomiting was 7.6% (95 CI 5.6–9.5%) and 19.4% (95 CI 7.6–31.7%) in studies from China and out of China, respectively (Fig. S1f). The pooled rate of patients with high AST was 23.6% (95 CI 18.9–28.3%) and 57.2% (95 CI 56.0–58.5%) in studies from China and out of China, respectively (Fig. S2d). The pooled rate of patients with liver dysfunction was 27.9% (95 CI 16.7–39.1%) and 22.4% (95 CI 14.8–30.0%) in studies from China and out of China, respectively (Fig. S2a).

**Publication bias.** The Begg funnel plot for the rate of diarrhea in COVID-19 patients is shown in Figure S4. There was no publication bias for Begg’s test (P = 1.000) and Egger’s test (P = 0.945). Publication bias was also analyzed in the digestive symptom-related outcomes, which included more than 10 studies. No publication bias was found in the rate of nausea and/or vomiting (Begg’s test P = 0.215, Egger’s test P = 0.254), loss of appetite (Begg’s test P = 0.274, Egger’s test P = 0.429), abdominal pain (Begg’s test P = 1.000, Egger’s test P = 0.752), and digestive symptoms (Begg’s test P = 0.669, Egger’s test P = 0.411).

**Discussion.** In this meta-analysis, we demonstrated that the pooled rate of digestive symptoms and abnormal liver function was 31.8 and 27.4%, respectively. The most common digestive symptom was loss of appetite and diarrhea. COVID-19 patients with digestive symptoms are more likely to present with fatigue, myalgia, and ARDS when compared with patients without digestive symptoms. Furthermore, severe/critical patients are more likely to present with diarrhea and liver dysfunction.

A previous meta-analysis summarizing the clinical, laboratory, and imaging features of COVID-19 showed that the pooled rate of diarrhea, elevated AST, and liver diseases in COVID-19 patients was 6, 33, and 3%, respectively. This meta-analysis included only 19 studies, and only 6 studies had reported diarrhea in COVID-19 patients. None of other digestive symptoms were analyzed, such as nausea, vomiting, and loss of appetite, which were also common symptoms in COVID-19 patients. After the meta-analysis was published, several large sample studies focusing on the clinical features, especially the digestive features, were published. So, a further meta-analysis with more concise results was needed to obtain a deeper understanding of the digestive symptoms in the COVID-19 patients.

When we performed the presented meta-analysis, a similar study from Hong Kong was published. We included liver injury in our study and excluded studies from the same department of the same hospital, which differed from the Hong Kong study. For example, many patients in Chen et al.’s study were also included in Zhou et al.’s study and Wu et al.’s study. We excluded Chen et al.’s study and Hu et al.’s study to make our results more precise, and when calculating the rate of digestive symptoms, we included the studies that mentioned the studied patients reporting digestive symptoms. However, in Cheung et al.’s meta-analysis, they also included the studies that did not mention patients having definite digestive symptoms and then counted the number of the most frequent single digestive symptom (like diarrhea, vomiting…) to calculate the prevalence of digestive symptoms. This significantly reduced the rate of digestive symptoms, which can explain why the rate of digestive symptoms in our study (28.8%) was much higher than Cheung et al.’s meta-analysis (17.6%).

Fever and cough were the most emphasized symptoms, and the screening of patients with SAR-COV-2 infection started by measuring body temperature. Patients with uncommon symptoms might be misdiagnosed, which could pose a great potential danger to the whole society. Overlooking the digestive symptoms by the public or the physicians might contribute to transmission as some patients only presented with digestive symptoms. Among the 204 COVID-19 patients in Pan et al.’s study, 6 patients presented with only digestive symptoms in the absence of respiratory symptoms (one patient even without fever). Luo et al.’s study reported that 183 (16%) patients only presented with GI symptoms of the 1141 confirmed COVID-19 cases. Jin et al.’s study demonstrated that 11.4% patients presented with at least one GI tract symptom (nausea, vomiting, and diarrhea), and diarrhea was the most common GI symptom. In the present meta-analysis, we confirmed that a large number of COVID-19 patients could present with digestive symptoms. Patients with digestive symptoms seemed to have a high rate of fatigue, liver
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injury, and ARDS. This might be of great significance to the treatment of COVID-19. Currently, few studies focused on the difference between COVID-19 patients with and without digestive symptoms. Our results need to be confirmed by a large-sample, well-designed study.

Patients with digestive symptoms had a tendency to develop severe/critical illness in our study ($P = 0.06$). When comparing with the normal/mild patients, severe/critical patients had a higher rate of diarrhea. Patients with digestive symptoms had a longer time from onset to admission (8.95 days vs 7.26 days). This may be because uncommon digestive symptoms led to a delay in diagnosis and treatment for COVID-19. These results highlight the importance of recognition of the digestive symptoms associated with COVID-19.

COVID-19 patients had a high rate of liver injury, especially the severe patients. Huang et al.’s study demonstrated that the rate of elevated AST was 37%, and the rate was up to 62% in severe patients. In a national multicenter study, the rate of elevated ALT, AST, and TBil was 21.3%, 22.2%, and 10.5%, respectively. The rate of elevated ALT, AST, and TBil was higher in severe patients than in nonsevere patients. Our study also showed that COVID-19 patients had a high rate of liver dysfunction, and severe/critical patients had a higher rate of liver dysfunction than normal/mild patients, which was consistent with previous studies. Monitoring and assessment of liver function should be strengthened when treating COVID-19 patients, especially in critically ill patients.

The major strengths of this study are listed as follows: First, we excluded studies from the same department of the same hospital to make our results more reliable. Furthermore, COVID-19 patients reported at the time were mainly Chinese, and a considerable number of case was summarized and published in Chinese journals; in this study, we specifically included 18 studies published in Chinese, with a total of 208 patients, to demonstrate a more precise prevalence and impact of GI involvement in patients with COVID-19. Moreover, this is the first meta-analysis comparing the difference between COVID-19 patients with and without digestive symptoms. In addition, there were some limitations in our study. First, all studies included in this meta-analysis were retrospective studies with large heterogeneity. Second, most patients in our meta-analysis were Chinese, and whether our results were applicable to patients in other countries was unknown.

Conclusions

In summary, digestive symptoms are common, with a prevalence of about 30%, in patients with COVID-19. Patients with digestive symptoms are more likely to present with fatigue, myalgia, and ARDS and have a tendency to develop severe/critical illness. Furthermore, severe/critical patients are more likely to present with diarrhea and liver dysfunction.

Acknowledgements

Our study was supported by the National Natural Science Foundation of China (81421003, 81627807, 81772650, 81322037, and 81572302) and the National Key Research and Development Plan of China (2017YFC0908300).

Ethics approval

Ethical approval was not required as this study is a meta-analysis of published studies.

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Supporting information

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

Figure S1 Meta-analysis of the rate of (a) digestive symptoms, (b) digestive comorbidities, (c) diarrhea, (d) loss of appetite, (e) abdominal pain, and (f) nausea and/or vomiting in COVID-19 patients.

Figure S2 Meta-analysis of the rate of (a) abnormal liver function, (b) liver comorbidities, (c) high ALT, (d) high AST, and (e) high TBil in COVID-19 patients.

Figure S3 Comparison of COVID-19 patients with and without digestive symptoms.

Figure S4 Begg funnel plot for the rate of diarrhea in COVID-19 patients