The Prevalence of Gastrointestinal Symptoms, Abnormal Liver Function, Digestive System Disease and Liver Disease in COVID-19 Infection

A Systematic Review and Meta-Analysis

Zi-yuan Dong, MD, Bing-Jie Xiang, MD, Min Jiang, PhD, Ming-jun Sun, PhD, and Cong Dai, PhD

Background: The worldwide outbreak of COVID-19 infected millions of people. Some patients had gastrointestinal (GI) symptoms, abnormal liver function, digestive system disease and liver disease. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased in patients with COVID-19. We aimed to conduct a systematic review and meta-analysis of the prevalence of GI symptoms, abnormal liver function, digestive system disease, and liver disease in patients with COVID-19.

Aim: To investigate the prevalence of GI symptoms, abnormal liver function, digestive system disease and liver disease in patients with COVID-19 by a systematic review and meta-analysis.

Methods: We searched PubMed, Ovid Embase, Medline, and 2 Chinese databases. Primary outcomes were the prevalence of GI symptoms, abnormal liver function, digestive system disease, and liver disease. Different studies were included in different subset analysis. The prevalence of nausea and vomiting, diarrhea, abnormal liver function, digestive system disease, liver disease was more prevalent in Wuhan group. The prevalence of diarrhea was higher in non-China group.

Results: Thirty-one studies involving 4682 patients were included. The most significant GI symptoms were diarrhea (0.08, 95% CI: 0.06-0.11) and anorexia (0.17, 95% CI: 0.06-0.27). A total of 5% of the patients had abnormal liver function, 18% of the patients had abnormal liver function was increased alanine aminotransferase (ALT) (0.25, 95% CI: 0.16-0.33). A total of 5% of the patients had liver damage, 95% of the patients had liver damage (95% CI: 0.02-0.08). A total of 3% of the patients had liver damage (95% CI: 0.02-0.05). The prevalence of nausea and vomiting, diarrhea, abnormal liver function, digestive system disease, and liver disease was higher in Wuhan group. Patients in severe/intensive care unit group were more likely to have diarrhea, anorexia, abdominal pain increased aspartate aminotransferase, and increased ALT.

Conclusion: The most significant GI symptoms were diarrhea and anorexia. The most significant abnormal liver function was increased ALT. Severe patients were more likely to have GI symptoms and abnormal liver function.

Key Words: COVID-19, gastrointestinal symptoms, liver function, digestive system disease, meta-analysis

DOI: 10.1097/MCG.000000000001424

J Clin Gastroenterol • Volume 55, Number 1, January 2021 www.jcge.com

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.
prevalence of GI symptoms, abnormal liver function, digestive system disease, and liver disease in patients with COVID-19, also to compare the difference based on region and severity of disease.

METHODS

Search Strategy
We systematically searched PubMed, Ovid Embase, Medline, 2 Chinese databases (CNKI and Wanfang Data) since inception up to April 6, 2020. Search terms were “COVID-19,” “SARS-CoV-2,” “2019-nCoV,” “2019 novel coronavirus,” and “novel coronavirus pneumonia.”

Inclusion Criteria and Exclusion Criteria
We included studies which met criteria as follows: (1) studies aimed at COVID-19; (2) studies provided information about GI symptoms, abnormal liver function, digestive system disease, and liver disease; (3) studies designed by randomized controlled trials (RCTs), prospective cohorts, retrospective cohorts, and open-label; (4) full text. The exclusion criteria were as follows: (1) studies published as reviews, letters, case reports, editorials, comments, conference abstracts, and family-based studies; (2) studies only describe these situations such as GI symptoms, abnormal liver function, digestive system disease, liver disease, and lacks specific data.

Data Extraction
Information was extracted from each study, including baseline characteristics such as age, sex, region, severity of disease, clinical outcome, date of cases collection, GI symptoms such as nausea, vomiting, diarrhea, abdominal pain, anorexia, belching and constipation, abnormal liver function such as increased AST, ALT, and TBil, digestive system disease, and liver disease. We defined studies performed in Wuhan as Wuhan group, studies performed outside Wuhan in China as non-Wuhan group, studies performed in China as China group and studies performed outside China as non-China group. We defined the patients who had severe symptoms or received ICU care as severe/ICU group, the patients who had general symptoms or did not receive ICU care as general/non-ICU group. Primary outcome was the prevalence of GI symptoms. Secondary outcomes were the prevalence of abnormal liver function, digestive system disease, and liver disease.

Statistical Analysis
The data was analyzed by Stata SE 15.1, the proportion and 95% confidence interval (CI) was used to calculate the prevalence. Forest plots were used to present data visually. Heterogeneity was evaluated using the Cochran’s Q test and $I^2$ statistics. $P$-value $< 0.10$ or $I^2 > 50\%$ means the heterogeneity was significant. The random-effects model was used if heterogeneity was significant, otherwise, the fixed-effects model was adopted. Publication bias was assessed with funnel plots and Egger’s test. Subgroup analysis were performed based on region. Odds ratio (OR), 95% CI, and $P$-value were computed to compare the difference based on severity of disease. $P$-value $< 0.05$ means the difference between groups was statistically significant. Different studies were included in different subset analysis.

RESULTS

Study Selection and Baseline Characteristics
We initially retrieved 3154 unique citations from PubMed, Ovid Embase, Medline, and 2 Chinese databases (CNKI and Wanfang Data). A total of 569 studies were excluded in the first screening because of duplication. After reading the titles, abstracts, and full-text of citations, 2554 literatures were excluded and 31 studies with a total of 4682 patients were included (Fig. 1). In this meta-analysis, the time span of cases collection was from December 11, 2019 to February 28, 2020. The median age of patients ranged from 36 to 62 years, 55% of the patients were male (Table 1).

Prevalence of GI Symptoms
In total, 26 studies were included to analyze the prevalence of nausea, vomiting, diarrhea, abdominal pain, and anorexia which we focused on in this meta-analysis. In addition, the study of Zhang et al$^{13}$ reported 7 patients with belching. The study of Wang et al$^{24}$ reported a patient with constipation. The prevalence of nausea and vomiting was 7% (95% CI: 0.04-0.09), the funnel plot and Egger’s test revealed evidence of publication bias ($t = 2.57$, 95% CI: 0.46-4.55, $P = 0.019$). The prevalence of diarrhea was 8% (95% CI: 0.06-0.11), heterogeneity was significant ($P < 0.0001$, $I^2 = 86.4\%$) (Fig. 2), the funnel plot and Egger’s test revealed the evidence of publication bias ($t = 3.02$, 95% CI: 0.77-4.13, $P = 0.006$). The prevalence of abdominal pain was 3% (95% CI: 0.01-0.05), heterogeneity was significant ($P = 0.005$, $I^2 = 73.4\%$), the funnel plot and Egger’s test revealed no evidence of publication bias ($t = 2.86$, 95% CI: -0.46 to 8.77, $P = 0.064$). The prevalence of anorexia was 17% (95% CI: 0.06-0.27), heterogeneity was significant ($P < 0.0001$, $I^2 = 95.6\%$) (Fig. S1 in Supplementary Appendix, Supplemental Digital Content 1, http://links.lww.com/JCG/A622), the funnel plot and Egger’s test revealed no evidence of publication bias ($t = 2.10$, 95% CI: -1.31 to 13.34, $P = 0.089$). We utilized random-effect model to analyze the prevalence of GI symptoms.

Prevalence of Abnormal Liver Function
Fourteen studies were included to analyze the prevalence of increased AST, ALT, and TBil. The upper limit of normal value of AST, ALT, and TBil was 40 U/L, 40 to 64 U/L, and 17.1 to 26 μmol/L, respectively. In total, 24% of the patients had increased AST (95% CI: 0.16-0.32), heterogeneity was significant ($P < 0.0001$, $I^2 = 94.7\%$) (Fig. S2 in Supplementary Appendix, Supplemental Digital Content 2, http://links.lww.com/JCG/A623), the funnel plot and Egger’s test revealed no evidence of publication bias ($t = 1.49$, 95% CI: -1.61 to 8.30, $P = 0.165$). A total of 25% of the patients had increased ALT (95% CI: 0.16-0.33), heterogeneity was significant ($P < 0.0001$, $I^2 = 92.9\%$) (Fig. 3), the funnel plot and Egger’s test revealed no evidence of publication bias ($t = 0.99$, 95% CI: -3.21 to 7.80, $P = 0.356$). A total of 13% of the patients had increased TBil (95% CI: 0.05-0.20), heterogeneity was significant ($P < 0.0001$, $I^2 = 92.5\%$), the funnel plot and Egger’s test revealed evidence of publication bias ($t = 1.12$, 95% CI: -11.69 to 19.89, $P = 0.38$). All the results were analyzed by random-effect model.

Prevalence of Digestive System Disease and Liver Disease
Seventeen studies were included to analyze the prevalence of digestive system disease and liver disease. The disease categories were not mentioned in most studies. The study of Easom et al$^{16}$ reported 3 patients with gastroenteritis. The study of Wang et al$^{24}$ reported 1 patient with fatty liver. The study of Zhang et al$^{13}$ reported 8 patients with fatty liver and abnormal liver function, 7 patients with chronic gastritis and gastric ulcer, and 6 patients with cholelithiasis. In this meta-analysis, 5% of the patients had digestive system disease (95% CI: 0.02-0.08),
heterogeneity was significant ($P < 0.0001$, $I^2 = 76.5\%$) (Fig. 4), the funnel plot and Egger’s test revealed evidence of publication bias ($t = 5.61$, 95% CI: 1.68-4.53, $P = 0.002$). In total, 3% of the patients had liver disease (95% CI: 0.02-0.05), heterogeneity was significant ($P = 0.023$, $I^2 = 50.6\%$) (Fig. 5), the funnel plot and Egger’s test revealed no evidence of publication bias ($t = 2.18$, 95% CI: −0.03 to 2.83, $P = 0.054$). Both the results were analyzed by fixed-effects model.

Subgroup Analysis by Region

Fourteen studies were performed in Wuhan, 14 studies were performed outside Wuhan in China. Only 1 study was performed in United Kingdom. Two studies including patients in and outside Wuhan in China, however, the difference of clinical characteristics between patients in and outside Wuhan in China were not mentioned. Ultimately, 28 studies were included to analyze the difference between Wuhan group and non-Wuhan group. And 31 studies were included to analyze the difference between China group and non-China group.

In Wuhan group, 58% of the patients were male. The prevalence of nausea and vomiting was 8% (95% CI: 0.04-0.12), the prevalence of diarrhea was 10% (95% CI: 0.05-0.14), and the prevalence of anorexia was 17% (95% CI: 0.05-0.28). The prevalence of increased AST, ALT, and TBil were 40% (95% CI: 0.31-0.49), 38% (95% CI: 0.23-0.52), and 18% (95% CI: 0.11-0.26), respectively. The prevalence of digestive system disease and liver disease were 7% (95% CI: 0.00-0.14) and 4% (95% CI: 0.02-0.06), respectively. In non-Wuhan group, 53% of the patients were male. The prevalence of nausea and vomiting was 5% (95% CI: 0.02-0.09), the prevalence of diarrhea was 7% (95% CI: 0.03-0.10), and the prevalence of anorexia was 18% (95% CI: 0.10-0.26).
| References     | Date (mm dd, yy)                | Sample Size | Age, Mean | Sex, Male | Nausea and Vomiting | Diarrhea | Abdominal Pain | Anorexia | Increased AST | Increased ALT | Increased Tbil | Digestive System Disease | Liver Disease |
|---------------|--------------------------------|-------------|-----------|-----------|---------------------|----------|----------------|----------|--------------|--------------|----------------|---------------------|---------------|-------------------|
| Bai et al     | Jan 6, 2020-Feb 20, 2020       | 219         | 44.8      | 119       | 1                   | 2        |                |          | 35           | 28           | 18               | 11               |                  |
| Chen et al    | Jan 1, 2020-Jan 20, 2020       | 99          | 55.5      | 67        | 1                   | 2        |                |          | 35           | 28           | 18               | 11               |                  |
| Chen et al    | Jan 13, 2020-Feb 28, 2020      | 274         | 62        | 171       | 40                  | 77       | 19             | 66       | 84           |              |                | 3                |                |                  |
| Chu et al     | Jan 7, 2020-Feb 11, 2020       | 54          | 39        | 36        | 1                   | 3        | 1              | 3        | 33           |              |                | 3                |                |                  |
| Chung et al   | Jan 18, 2020-Jan 27, 2020      | 21          | 51        | 13        | 1                   |          | 1              | 1        |              |              |                | 3                |                |                  |
| Dong et al    | Jan 20, 2020-Feb 14, 2020      | 11          | 36.6      | 5         | 1                   | 2        |                |          |              |              |                | 3                |                |                  |
| Easom et al   | Dec 29, 2020-Feb 24, 2020      | 68          | 42.5      | 32        | 2                   | 9        |                |          | 2            |              |                | 3                |                |                  |
| Guan et al    | Dec 21, 2019-Feb 29, 2020      | 1099        | 47        | 637/1096  | 55                  | 42       |                |          | 168/757      | 158/741       | 76/722          | 1                  |                |                  |
| Huang et al   | Dec 16, 2019-Jan 2, 2020       | 41          | 49        | 30        | 1/38                |          |                |          | 15           |              |                | 1                |                |                  |
| Liu et al     | Jan 17, 2020-Feb 12, 2020      | 788         | 45.3      | 45        | 21                  | 23       | 17             |          | 4            | 5            | 22              | 1                |                |                  |
| Liu et al     | Dec 30, 2019-Jan 24, 2020      | 137         | 55        | 61        | 2                   | 3        |                |          | 2            |              |                | 1                |                |                  |
| Liu et al     | Dec 26, 2019-Jan 21, 2020      | 12          | 53.7      | 8         | 2                   | 2        |                |          | 3            | 2            |                | 1                |                |                  |
| Mo et al      | Jan 1, 2020-Feb 5, 2020        | 155         | 54        | 86        | 6                   | 7        | 3              |          | 4            |              |                | 1                |                |                  |
| Peng et al    | Jan 20, 2020-Feb 15, 2020      | 112         | 62        | 53        | 4                   | 3        |                |          | 43           |              |                | 7                |                |                  |
| Shi et al     | Dec 20, 2019-Jan 23, 2020      | 81          | 49.5      | 42        | 4                   | 3        | 1              |          |              |              |                | 4                |                |                  |
| Wang et al    | Jan 1, 2020-Feb 28, 2020       | 138         | 56        | 75        | 19                  | 14       | 3              | 55       |              |              |                | 4                |                |                  |
| Wang et al    | Jan 21, 2020-Feb 24, 2020      | 4           | 44.3      | 3         | 1                   |          |                |          | 4            |              |                | 1                |                |                  |
| Wu et al      | Jan 22, 2020-Feb 14, 2020      | 80          | 46.1      | 39        | 1                   |          | 1              |          | 3            |              |                | 1                |                |                  |
| Xu et al      | Jan 23, 2020-Feb 4, 2020       | 90          | 50        | 39        | 7                   |          |                |          | 5            |              |                | 1                |                |                  |
| Xu et al      | Jan 10, 2020-Jan 26, 2020      | 62          | 41        | 36        | 3                   |          |                |          | 10           |              |                | 7                |                |                  |
| Yang et al    | Jan 17, 2020-Feb 10, 2020      | 149         | 45.1      | 81        | 2                   | 11       |                |          | 27           | 18           | 4               | 8                |                |                  |
| Yang et al    | Dec 24, 2019-Jan 26, 2020      | 52          | 59.7      | 35        | 2                   |          |                |          |              |              |                | 1                |                |                  |
| Zhang et al   | Jan 16, 2020-Feb 25, 2020      | 95          | 49        | 53        |                    |          |                |          | 45           | 52           |                |                  |                |                  |
| Zhang et al   | Jan 16, 2020-Feb 3, 2020       | 140         | 57        | 71        | 31/139              | 18/139   | 8/139          | 17/139   | 13           |              |                | 8                |                |                  |
| Zhang et al   | Jan 18, 2020-Feb 3, 2020       | 9           | 36        | 5         | 1                   |          |                |          |              |              |                | 13               | 8               |                  |
| Zhao et al    | Jan 23, 2020-Feb 5, 2020       | 19          | 48        | 11        | 1                   |          |                |          | 5/18         | 5/18         |                |                  |                |                  |
| Zhao et al    | Dec 29, 2019-Jan 31, 2020      | 191         | 56        | 119       | 7                   | 9        |                |          | 59/189       |              |                |                  |                |                  |
| Zhou et al    | Dec 20, 2019-Feb 9, 2020       | 254         | 50        | 115       | 36                  | 46       | 3              |          | 3            |              |                |                  |                |                  |
| Total         | 4682                           | 2570        | 309       | 161       | 443                 | 336      | 120            | 47       | 77           |              |                |                  |                |                  |
| Propotion (%) | 55                             | 7           | 7         | 3         | 3                   | 24       | 4              | 25       | 13           | 5            | 3               |                  |                |                  |

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; Tbil, total bilirubin.
The prevalence of increased AST, ALT, and TBil were 13% (95% CI: 0.06-0.21), 14% (95% CI: 0.06-0.22), and 13% (95% CI: -0.08 to 0.33), respectively. The prevalence of digestive system disease and liver disease were 5% (95% CI: 0.03-0.07) and 3% (95% CI: 0.02-0.05), respectively (Fig. S3-S8 in Supplementary Appendix, Supplemental Digital Content 3, http://links.lww.com/JCG/A624, Supplemental Digital Content 4, http://links.lww.com/JCG/A625, Supplemental Digital Content 5, http://links.lww.com/JCG/A626, Supplemental Digital Content 6, http://links.lww.com/JCG/A627, Supplemental Digital Content 7, http://links.lww.com/JCG/A628, Supplemental Digital Content 8, http://links.lww.com/JCG/A629).

In China group, 55% of the patients were male. The prevalence of nausea and vomiting was 7% (95% CI: 0.05-0.09), the prevalence of diarrhea was 8% (95% CI: 0.06-0.11). The prevalence of increased AST and digestive system disease were 26% (95% CI: 0.18-0.34) and 6% (95% CI: 0.02-0.09), respectively. In non-China group, 47% of the patients were male. The prevalence of nausea and vomiting was 3% (95% CI: -0.01 to 0.07), the prevalence of diarrhea was 13% (95% CI: 0.05-0.21) (Fig. S9, Supplemental Digital Content 9, http://links.lww.com/JCG/A630). The prevalence of increased AST and digestive system disease were 3% (95% CI: -0.01 to 0.07) and 4% (95% CI: 0.00-0.09).

**Difference Between General/Non-ICU Group and Severe/ICU Group**

Only 8 studies were included, the prevalence of nausea and vomiting, diarrhea, abdominal pain, anorexia, increased AST, increased ALT, and liver disease were analyzed. There was no significant difference between general/non-ICU group and severe/ICU group for the prevalence of nausea and vomiting (OR = 0.97, 95% CI: 0.45-2.08, P = 0.927) and liver disease (OR = 1.20, 95% CI: 0.48-2.97, P = 0.695). Patients in severe/ICU group were more likely to have diarrhea (OR = 1.65, 95% CI: 1.04-2.62, P = 0.033), anorexia (OR = 2.19, 95% CI: 1.21-3.93, P = 0.009), abdominal pain (OR = 6.38, 95% CI: 1.77-22.91, P = 0.005), increased AST (OR = 2.98, 95% CI: 2.11-4.21, P < 0.0001) and increased ALT (OR = 2.66, 95% CI: 1.11-6.37, P = 0.029) compared with the patients in general/non-ICU group (Fig. S10-S14 in Supplementary Appendix, Supplemental Digital Content 10, http://links.lww.com/JCG/A631, Supplemental Digital Content 11, http://links.lww.com/JCG/A632, Supplemental Digital Content 12, http://links.lww.com/JCG/A633, Supplemental Digital Content 13, http://links.lww.com/JCG/A634, Supplemental Digital Content 14, http://links.lww.com/JCG/A635). Heterogeneity was not significant in the above analysis apart from the prevalence of nausea and vomiting and increased ALT.
DISCUSSION

In the last 2 decades, the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) had a great effect on global health, the emergence of 2019-nCoV marked the third introduction of a highly morbillivorous coronavirus which could cause epidemics with variable severity of respiratory and extra-respiratory symptoms into the human population. 2019-nCoV is the seventh member of the human-infecting coronaviruses family which had 88% identity with 2 bat-derived SARS-like coronaviruses, bat-SL-CoVZC45, and bat-SL-CoVZXC21, and was 79% related to SARS-associated coronavirus.
(SARS-CoV), 50% related to MERS-associated coronavirus (MERS-CoV), respectively. The main mode of COVID-19 transmission is via droplets and contact, positive reverse-transcription polymerase chain reaction (RT-PCR) test for viral RNA from oropharyngeal or nasopharyngeal swabs can help doctors make a quick diagnosis. Notably, laboratories in China declared that they isolated 2019-CoV from stool specimens of patients with COVID-19. A study of 18 patients in Singapore shown that 2019-nCoV was detectable in the stools in 50% of the patients. The first confirmed case in the United State had a history of nausea and vomiting for 2 days followed by diarrhea and abdominal discomfort. Patients could have negative PCR test in oropharyngeal swabs together with positive results in stools. The existence duration of viral RNA in patients’ stool specimens is longer than in oropharyngeal swabs, which was essential during convalescence. Besides, angiotensin converting enzyme II (ACE2) which was the cell entry receptor of SARS-CoV has also been confirmed as the cell entry receptor of 2019-nCoV, which could influence the expression of neutral amino acid transporters in gut, change the composition of the gut microbiota, and cause diarrhea and intestinal inflammation. All the information revealed that COVID-19 could influence GI manifestations, and fecal-oral might contribute to the transmission of COVID-19.

Common GI symptoms include nausea, vomiting, diarrhea, abdominal pain, and anorexia. The study of Guan et al showed that 5% of the patients had nausea and vomiting and 3.8% of the patients had diarrhea. The study of Zhang et al showed that 12.2% of the patients had anorexia, 5.8% of the patients had abdominal pain, and 5% of the patients had belching. However, the study of Wang et al showed that 10.1% of the patients had nausea and diarrhea, 39.9% of the patients had anorexia. In this meta-analysis, 7% of the patients had nausea and vomiting, 8% of the patients had diarrhea, 3% of the patients had abdominal pain, and 17% of the patients had anorexia. After reviewing previous studies, we found that the prevalence of GI symptoms of COVID-19 was lower than that of SARS and MERS. Previous studies showed that 40% to 70% of the patients had self-limited watery diarrhea, and 20% to 35% of the patients had nausea and vomiting in SARS infection. Besides, at least one-third of the patients got GI symptoms in MERS infection. Just as the description in above paragraph, ACE2 was identified as cell receptor of 2019-nCoV. Previous study showed that abundant presentation of ACE2 was discovered in esophagus keratinocytes, stomach epithelial cells, intestinal epithelial cells, and colon colonocytes. ACE2 might provide possible routes of entry for 2019-nCoV and played an important role in the GI infection of COVID-19. In order to treat the disease, multiple types of antiviral agents and antibiotic agents were used. Pharmacy expert consensus in China indicated that lopinavir and ritonavir could cause nausea, diarrhea, and vomiting. A previous study showed that the most common adverse events (AEs) of combination therapy of oseltamivir, amantadine, and ribavirin for the treatment of influenza were nausea, diarrhea, and vomiting. The use of antibiotic agents could change the composition and metabolic function of the intestinal microflora, which was essential to the immunity and metabolism. Antibiotic agents might cause dysbacteriosis and contributed to antibiotic-associated diarrhea (AAD). The clinical manifestations of AAD varied from mild to severe, severe AAD could have nausea, fever, abdominal pain, and severe watery diarrhea.
some patients could have megacolon, even death. Common opportunistic pathogen of severe AAD was *Clostridium difficile*, a meta-analysis revealed that the most commonly used antibiotic agents were clindamycin, fluoroquinolones, and cephalosporins in clinical practice, and the frequency of *clostridium difficile* among AAD was 20.2%.35 Therefore, it is necessary to avoid blindly using medicine, especially the abuse of combination therapy of antiviral agents or antibiotics. A meta-analysis shown that probiotics could reduce risk of AAD in adults, however, the effect in elderly population was not significant.36 It reminded us that probiotics could be used to relieve GI symptoms.

A considerable number of patients could have abnormal liver function, primarily presented as increased AST, ALT, and TBil. Besides, some patients with normal liver function at baseline could have liver insufficiency during the disease process. In the study of Guan et al,8 the prevalence of increased AST, ALT, and TBil were 22%, 21.3%, and 10.5%, respectively. In the study of Chen et al,7 1 patient had severe liver function damage with extremely increased ALT (7590 U/L) and AST (1445 U/L). Besides, the study of Zhao et al33 reported 44.44% of the patients had increased γ-glutamyl, and compared with other types of pneumonia, COVID-19 could cause liver dysfunction more frequently. The study of Liu et al39 indicated that 17% of the patients, who did not have liver damage at baseline, got liver dysfunction during the process of disease. In this meta-analysis, 24% of the patients had increased AST, 25% of the patients had increased ALT, and 13% of the patients had increased TBil. Reviewing previous studies of SARS and MERS, we found that up to 60% patients could have abnormal liver function in SARS, large numbers of virus particles was found in liver, the liver function impairment was associated with the direct attack of coronavirus or the immune response of viral infection in SARS.77,58 The study of Assiri et al39 shown that 15% of the patients had increased AST and 11% of the patients had increased ALT in MERS. MERS-CoV could bind with host cell dipeptidyl peptidase 4 (DPP4) receptor to enter host cells, and DPP4 was widely expressed on the tissues of liver, which might explain the liver impairment by MERS-CoV.60,61 In COVID-19, the liver damage might be associated with several factors. The previous studies shown that ACE2 could express in liver cells and biliary epithelial cells, the level of expression in biliary epithelial cells was similar to that in alveolar type 2 cells in lung, and higher than that in liver cells, which might explain the liver damage in COVID-19.60,61 Besides, pharmacy expert consensus in China indicated that lopinavir and ribavirin should be used with caution with the AEs of liver damage.72 There was a case report of liver dysfunction and alimentary tract hemorrhage caused by osetamivir in a child, although the AEs of the drug were mostly mild.93 Therefore, it is essential to monitor the liver function and avoid intensive use of drugs which could cause liver damage, especially in severe patients. Protecting liver therapy could be applied if necessary.

Some patients had digestive system disease and liver disease at the baseline. The study of Chen et al7 showed that 11% of the patients had digestive system disease. The study of Zhang et al31 showed that 5.7% of the patients had fatty liver and abnormal liver function, 5% of the patients had chronic gastritis and gastric ulcer, 4.3% patients had cholecystitis, and 6.4% of the patients received cholecystectomy at the baseline. Compared with other types of viral pneumonia, patients infected by COVID-19 had similar prevalence for liver disease in the study of Bai et al.11 In this meta-analysis, 5% of the patients had digestive system disease and 3% of the patients had liver disease. A meta-analysis revealed that the pooled mean prevalence of fatty liver disease was 16.73% in China.64 The prevalence of gastro-oesophageal reflux symptoms was 2.5% in China.65 The prevalence of gallstone diseases ranged from 4% to 73% around the world.66 Although we did not acquire all the epidemiological data of digestive system disease and liver disease, it seemed that we could not say people with digestive system disease and liver disease were more likely to have COVID-19.

Compared with non-Wuhan group, the prevalence of nausea and vomiting, diarrhea, abnormal liver function, and digestive system disease was higher in Wuhan group of Wuhan region, severe patients were admitted to designated hospitals in concentrated way, such as Jinyintan Hospital and Zhongnan Hospital, and the studies included in Wuhan group were mostly from these designated hospitals. The proportion of severe patients in these hospitals might be higher than hospitals in other provinces whose patients were more sporadic. The study of Huang et al69 which included patients infected early in the COVID-19 outbreak showed that the mortality rate of COVID-19 was 15%. However, in the study of Guan et al70 which included 1099 cases from 552 hospitals in 30 provinces, autonomous regions in China, the mortality rate is 1.4%. The variation might because of the emergence of more mild-moderate patients.

Compared with general/non-ICU group, the patients in severe/ICU group were more likely to have diarrhea, anorexia, abdominal pain, increased AST, and increased ALT in this meta-analysis. However, there were no significant differences between severe/ICU group and general/non-ICU group for the prevalence of nausea and vomiting and liver disease. The study of Wang and colleagues reported 5% of the patients had vomiting, 14% of the patients had diarrhea or nausea, and there was no significant difference between ICU patients and non-ICU patients. However, patients in ICU were more likely to have abdominal pain, anorexia, and abnormal liver function.9 The study of Liu et al39 showed 29% of the ICU patients had liver dysfunction. The patients with hepatic insufficiency usually had multiple complications such as acute respiratory distress syndrome, respiratory failure, and renal insufficiency, therefore, the liver damage might be the reflection of disease severity and be induced by cytokine release syndrome (CRS). CRS was a systemic inflammatory response caused by a variety of factors such as infection and drugs which could lead to multiorgan system failure, hepatomegaly, hypofibrinogenemia, liver failure, and abnormal liver enzymes were common in CRS.67 Besides, the severe patients usually received combination therapy of antivirals agents and antibiotics which could increase the burden of liver.

There were limitations in this meta-analysis. First, classification of digestive system disease and liver disease was unclear in most studies. Second, few studies have performed colonoscopy to observe colon directly, or biopsy of liver and colon to identified the pathologic features. Third, quite a part of included studies had small samples. Most studies were published in China, studies from other countries outside China were needed for further analysis. Besides, the heterogeneity between several studies were high because of varies sample size and different severity among the cases.
In conclusion, we have analyzed the prevalence of GI symptoms, abnormal liver function, digestive system disease, and liver disease using different set of studies and patients. Diarrhea and anorexia were the most common GI symptoms in patients with COVID-19. COVID-19 could cause liver damage in different extent, the most significant abnormal liver function was increased ALT. The prevalence of digestive system disease and liver disease was 5% and 3%, respectively. The prevalence of nausea and vomiting, diarrhea, abnormal liver function, digestive system disease, and liver disease was higher in Wuhan group. Severe patients were more likely to have GI symptoms and abnormal liver function. More researches were needed to explore the relevant mechanism of the outcomes.

REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J Med Virol. 2020;94:401–402.
2. Hui DS, I Azhar E, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264–266.
3. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [World Health Organization]. Available at: www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-19)-and-the-virus-that-causes-it. Accessed April 6 2020.
4. World Health Organization, WHO Director-General’s opening remarks at the media briefing on COVID-19 - 3 April 2020 [World Health Organization]. 2020. Available at: www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-3-april-2020. Accessed April 6 2020.
5. World Health Organization. WHO Director-General’s opening remarks at the media briefing on COVID-19 - 11 March 2020 [World Health Organization]. 2020. Available at: www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19-11-march-2020. Accessed April 6 2020.
6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
7. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–513.
8. Guan W, Ni Z, Hu Y, et al. China medical treatment expert group for C. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708–1720.
9. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–1069.
10. Liu C, Jiang ZC, Shao CX, et al. Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study [Chinese]. Zhonghua Gan Zang Bing Za Zhi. 2020;28:148–152.
11. Bai HX, Hsieh B, Xiong Z, et al. Performance of radiologists in differentiating COVID-19 from viral pneumonia on chest CT. Radiology. 2020;206:E40–E54.
12. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1091.
13. Chu J, Yang N, Wei Y, et al. Clinical characteristics of 54 medical staff with COVID-19: a retrospective study in a single center in Wuhan, China. J Med Virol. 2020;92:807–813.
14. Chung M, Bu Y, Chen A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology. 2020;295:202–207.
15. Dong X, Cao YY, Lu XX, et al. Eleven faces of coronavirus disease 2019. Allergy. 2020;75:1699–1709.
16. Easom N, Moss P, Barlow G, et al. 68 consecutive patients assessed for COVID-19 infection; experience from a UK regional infectious disease unit. Influenza And Other Respiratory Viruses. 2020;14:374–379.
17. Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. Clin Infect Dis. 2020;71:740–747.
18. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69:997–1001.
19. Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin J Radiol. 2020;13:101.
20. Liu Y, Yang Y, Zhang C, et al. Clinical and biochemical indexes from 2019-nCoV-infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020;63:364–374.
21. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Clin Infect Dis. 2020. [Epub ahead of print].
22. Peng YD, Meng K, Guan HQ, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV [Chinese]. Zhonghua Xin Xue Guan Bing Za Zhi. 2020;48:450–455.
23. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20:425–434.
24. Wang Z, Chen X, Lu Y, et al. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biociens. 2020;14:64–68.
25. Wu J, Liu J, Zhao X, et al. Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study. Clin Infect Dis. 2020;71:706–712.
26. Xu X, Yu C, Qu J, et al. Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2. Eur J Nucl Med Mol Imaging. 2020;47:1275–1280.
27. Xu X, Wu X, Jiang X, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. BMJ. 2020;368:m606.
28. Yang W, Cao Q, Qin L, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80:388–393.
29. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475–481.
30. Zhang G, Zhang J, Wang B, et al. Analysis of clinical characteristics and radiological findings for 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respir Res. 2020;21:74.
31. Zhang J, Dong X, Cao Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75:1730–1741.
32. Zhang MQ, Wang XH, Chen YL, et al. Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing. Zhonghua Jie He He Hu Xi Za Zhi. 2020;43:215–218.
33. Zhao D, Yao F, Wang L, et al. A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias. Clin Infect Dis. 2020;71:756–761.
34. Zhao W, Zhang Z, Xie X, et al. Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) Pneumonia: A Multicenter Study. AJR. 2020;214:1072–1077.
35. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054–1062.
36. Zhou Z, Zhao N, Shu Y, et al. Effect of gastrointestinal symptoms on patients infected with COVID-19. Gastroenterol Mol Biol. 2020;14:1033–1034.
37. de Wit E, van Doremalen N, Dyarly F, et al. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14:523–534.
38. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med. 2020;382:727–733.
39. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395:565–574.
40. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. Gastroenterology. 2020;158:1518–1519.
41. Young BE, Ong SWX, Kalimuddin S, et al. Singapore novel coronavirus infection: a single case report and review of the literature. Med J Singapore. 2020;50:32–37.
42. Perlot T, Penninger JM. ACE2 - from the renin-angiotensin system to gut microbiota and malnutrition. Microbes Infect. 2013;15:866–873.
43. Hui DSC, Zumla A. Severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. Lancet. 2004;363:1377–1386.
44. Neuman H, Forsythe P, Uzan A, et al. Antibiotics in early life: risk of antibiotic-associated diarrhea in adults (18–64 years) but not the elderly (> 65 years); a meta-analysis. Nutr Clin Pract. 2016;31:502–513.
45. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270–273.
46. Boonacker E, Van Noorden CJ. The multifunctional or moonlighting protein CD26/DPP4. Eur J Cell Biol. 2003;82:53–73.
47. Cen L, Pan J, Zhou B, et al. Specific ACE2 expression in the gallbladder and the risk of chronic cholecystitis and cholelithiasis: a systematic review and meta-analysis. Gastroenterology. 2013;145:630–640.
48. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immuno ther Cancer. 2018;6:56.