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REVIEW

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Gastrointestinal and hepatic abnormalities in patients with confirmed COVID-19: A systematic review and meta-analysis

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Abstract

Although not common, gastrointestinal and liver symptoms have reportedly been the initial presentation of coronavirus disease-2019 (COVID-19) in a large group of patients. Therefore, knowing the frequency and characteristics of these manifestations of COVID-19 is important for both clinicians and health policy makers. A systematic review and meta-analysis of the available data on the gastrointestinal and liver manifestations of patients with COVID-19 was performed. PubMed and Scopus databases and Google Scholar search engine were searched for published and unpublished preprint articles up to 10 April 2020. Original studies providing information on clinical digestive symptoms or biomarkers of liver function in patients with polymerase chain reaction confirmed diagnosis of COVID-19 were included. After quality appraisal, data were extracted. Prevalence data from individual studies were pooled using a random-effects model. Overall, 67 studies were included in this systematic review and meta-analysis, comprising a pooled population of 13 251 patients with confirmed COVID-19. The most common gastrointestinal symptoms were anorexia (10.2%, 95% confidence interval [CI] = 6.2%-16.4%), diarrhea (8.4%, 95% CI = 6.2%-11.2%), and nausea (5.7%, 95% CI = 3.7%-8.6%), respectively. Decreased albumin levels (39.8%, 95% CI = 15.3%-70.8%), increased aspartate aminotransferase (22.8%, 95% CI = 18.1%-28.4%), and alanine aminotransferase (20.6%, 95% CI = 16.7%-25.1%) were common hepatic findings. After adjusting for preexisting gastrointestinal (5.9%) and liver diseases (4.2%), the most common gastrointestinal findings were diarrhea (8.7%, 95% CI = 5.4%-13.9%), anorexia (8.0%, 95% CI = 3.0%-19.8%), and nausea (5.1%, 95% CI = 2.2%-14.3%). Gastrointestinal and liver manifestations are not rare in patients with COVID-19, but their prevalence might be affected by preexisting diseases. Diarrhea and mild liver abnormalities seem to be relatively common in COVID-19, regardless of comorbidities

KEYWORDS

COVID-19, digestive symptoms, gastrointestinal symptoms, hepatic abnormalities, hepatic injury

1 | INTRODUCTION

Coronavirus disease-2019 (COVID-19) emerged in December 2019 in Wuhan, China.[1-3] As of 27 June 2020, it has infected near 10 million individuals from over 200 countries around the world with around 500 000 deaths, causing a major pandemic. The WHO considered the outbreak of COVID-19 infection as a health emergency.[4-8]

Respiratory symptoms of COVID-19 including fever, dry cough, and dyspnea are the most common manifestations of this novel infectious disease, similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).[9] Although other manifestations such as gastrointestinal symptoms are less common, the initial presentation of the disease in some patients was gastrointestinal symptoms.[9,10] Different studies have reported various prevalence rates for gastrointestinal symptoms such as diarrhea in patients with COVID-19.[11]

In the SARS epidemic, 16% to 73% of patients had diarrhea during the period of the disease usually in the first week of sickness. In the initial MERS outbreak in 2012, a quarter of patients presented gastrointestinal symptoms such as diarrhea or abdominal pain. Besides, patients with SARS and MERS have showed different degrees of liver injury.[1] Due to the phylogenetic similarities between COVID-19 and previous SARS-like coronaviruses, it is not unlikely that this novel coronavirus infection present with gastrointestinal symptoms in some patients.[10]

A growing body of evidence indicates the possibility of gastrointestinal tract and liver being target organs for COVID-19, which can be potentially linked to the fact that the main receptor-mediated entry for the novel coronavirus, angiotensin-converting enzyme 2 (ACE2), is highly expressed in the gastrointestinal tract and the liver. This potential involvement of the gastrointestinal tract can possibly justify the presence of viral RNA in the stool exams of patients, indicating a possibility for fecal-oral transmission of COVID-19.[12-16]

Recognition of clinical characteristics of COVID-19 is not only important for clinicians but also it can be helpful for health policy makers to make proper decisions.[17] Previous systematic reviews on the gastrointestinal and hepatic manifestations of COVID-19 have indicated that gastrointestinal symptoms are relatively common among the patients, with nausea or vomiting, loss of appetite, and diarrhea being the most common symptoms in this regard. However, these studies mostly included merely symptomatic patients and fail to address the effect of comorbid gastrointestinal and liver conditions on the prevalence of these symptoms.[16,18] In the present study, a systematic review and meta-analysis of the available data on the gastrointestinal and hepatic manifestations of patients with COVID-19 was performed. We also investigated the effect of comorbid gastrohepatic disorders on the rate of gastrointestinal and liver manifestations of COVID-19.

2 | METHODS

2.1 | Search strategy and data sources

Two independent inspectors (MZB and AA) searched PubMed and Scopus databases and Google Scholar search engine for published and unpublished preprint articles from 1 January 2020 to 10 April 2020. Reference list of all selected articles were searched to look for possible missing articles. This search was manually expanded to recognize additional related articles. No language limitations were imposed. Different combinations of the following search terms were used: "Gastrointestinal" OR "Digestive" AND "Liver" OR "Hepatic", AND "Coronavirus Disease 2019." For each term, all synonyms and subjects with the same heading were also searched.

2.2 | Study selection

After removing the duplicates, five investigators (MZB, MR, HG, AA, and MSG) independently screened the remaining studies for the inclusion criteria. Original studies providing information on clinical digestive symptoms or biomarkers of liver function in patients with reverse-transcriptase polymerase chain reaction confirmed diagnosis of COVID-19 were included in the review, according to current diagnostic guidelines.[19-21] Letters, comments, review articles, communications, and original articles that did not provide any reliable confirmation of COVID-19 and studies with insufficient data were excluded. To minimize the risk of bias, studies that were conducted exclusively on a specific population and were not representative of the whole range of manifestations (eg, studies only on children, severe and critical cases, fatal cases, etc) were also excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Figure 1) was followed.

2.3 | Critical appraisal

The Strengthening the Reporting of Observational studies in Epidemiology checklist was used for critical appraisal to assess the quality of studies. The checklist comprises 22 items, of which six have subitems. Twenty items can be scored a maximum of 1 point while a maximum of 2 points can be allocated to 14 other items where all the criteria regarding a certain item were reported. For each study, the final summed score out of a maximum of 48 points was converted into percentage with a maximum of 100%, to provide a clear estimation.[22] Five investigators independently appraised the papers (MZB, MR, HG, AA, and MSG) and consensus resolved the possible inconsistences.

2.4 | Data extraction

Five investigators (MZB, MR, HG, AA, and MSG) extracted the data from the included studies and possible disagreements were resolved by consensus. Extracted study characteristics were title, journal, first author, publication date, sample size, study type, and origin (country and city). Demographics of the patients including age and gender were extracted and population type (inpatient, outpatient, or both) was recorded. Main gastrointestinal symptoms including diarrhea, vomiting, nausea, anorexia, abdominal pain, and abdominal distension as well as

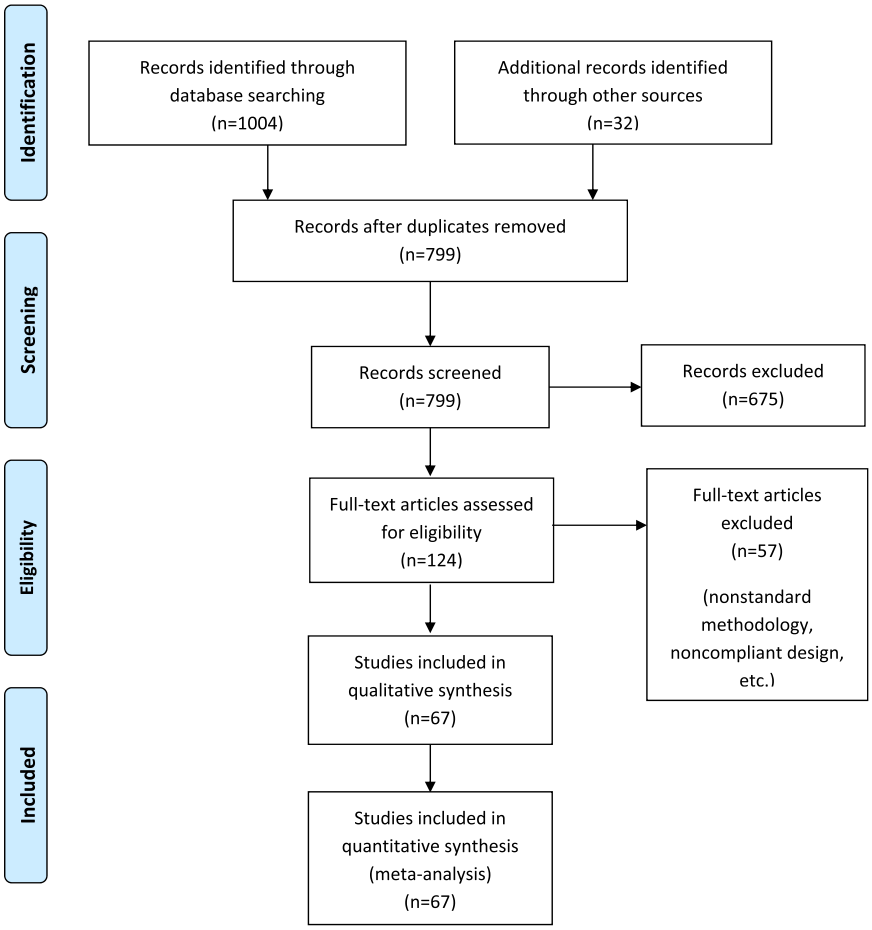

FIGURE 1 PRISMA flow diagram of the study. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

gastrointestinal comorbidities (chronic preexisting gastrointestinal or liver diseases) were extracted as main outcomes. Other main outcomes were markers of liver function, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase (ALP), and prothrombin time. Regarding the serum levels of these biomarkers, only data from studies with standard reference values and measurement methods were included.

2.5 | Publication bias

Publication bias was kept as minimum as possible by applying no language restrictions and searching different databases. However, in the existence of heterogeneity between studies, potential publication bias was evaluated using funnel plots, Egger's test, and Begg's test.[23,24]

2.6 | Statistical analysis

All data were pooled and the meta-analysis was performed using a random-effects model in Comprehensive Meta-analysis version 3.3.070. Point estimates with 95% confidence interval (95% CI) were used to present the results of meta-analysis. The heterogeneity between studies was reported with relevant indicators including I^2.[25] $P < .05$ was considered as statistically significant.

We repeated the meta-analysis, adjusting for the preexisting gastrointestinal and liver diseases, to investigate the effect of these comorbidities on the prevalence of COVID-19 findings. A subgroup analysis was performed only looking at the published studies (excluding preprint studies). Moreover, we conducted another subgroup analysis according to the severity of disease, to see whether the severity of COVID-19 affects the estimated prevalence of findings.

3 | RESULTS

3.1 | Literature selection and study characteristics

Initial search retrieved 1036 records from different sources. After removing duplicates, 675 records were screened via title and abstract review. Having excluded the irrelevant studies, the full text articles of 124 records were reviewed, of which 57 were excluded due to noncompliant design, insufficient data, or nonstandard diagnostic methods. Finally, 67 studies with a pooled population of 13 251 confirmed patients with COVID-19 were included in this systematic review and meta-analysis (Figure 1). Overall, 5079

patients (53.3%) were female and there was a relatively balanced sex distribution in the pooled population.

Characteristics of the included studies, including first author, study design, publication date, origin, sample size, and quality assessment score, as well as population type and patient demographics including sex and age are illustrated in Table 1.

3.2 | Publication bias

Regarding publication bias, funnel plots for two of the common findings are shown in Figures 2 and 3. Although funnel plots showed asymmetry for some findings, Eggers's test confirmed publication bias only for vomiting ($t = 3.47$, $P < .001$). However, the results of the Begg's test showed no notable evidence of publication bias for any of these findings (Table S1).

3.3 | Meta-analysis of gastrointestinal and liver symptoms

This meta-analysis showed that the three most prevalent gastrointestinal symptoms among patients with confirmed COVID-19 were anorexia (10.2%, 95% CI = 6.2%-16.4%), diarrhea (8.4%, 95% CI = 6.2%-11.2%), and nausea (5.7%, 95% CI = 3.7%-8.6%), respectively (Table 2; Figure 4). Common liver function abnormalities were mild decrease in albumin level (39.8%, 95% CI = 15.3%-70.8%), and mild increase in AST (22.8%, 95% CI = 18.1%-28.4%), ALT (20.6%, 95% CI = 16.7%-25.1%) (Table 2; Figure 5). Moreover, 18.0% (95% CI = 3.0%-60.8%) showed elevated prothrombin time. Total bilirubin and ALP levels were slightly elevated in 7.8% (95% CI = 5.0%-12.0%) and 4.6% (95% CI = 2.6%-7.9%), respectively. Chronic gastrointestinal and liver diseases were present in 5.9% (95% CI = 4.1%-8.5%) and 4.2% (95% CI = 3.3%-5.3%) of the patients, respectively.

3.4 | Subgroup analysis: published studies

When assessing only the published studies, we saw a change in the estimated prevalence of nearly all findings in patients with COVID-19, although the order of the most common findings remained unchanged (Table 2). Anorexia (16.2%, 95% CI = 10.3%-24.5%) and decreased albumin (39.8%, 95% CI = 15.3%-70.8%) were the most common digestive and hepatic findings, respectively. The prevalence of preexisting gastrointestinal and hepatic findings remained almost the same after exclusion of preprint articles (Table 2).

3.5 | Meta-analysis of gastrointestinal and liver symptoms after adjustment for preexisting disease

To assess the effect of comorbid gastrointestinal and hepatic conditions on the prevalence of COVID-19 findings, the meta-analysis was repeated, adjusting for these comorbid conditions. The respective results are reported in Table 3.

Overall, after adjusting for chronic preexisting illnesses, the three most common gastrointestinal findings were diarrhea (8.7%, 95% CI = 5.4%-13.9%), anorexia (8.0%, 95% CI = 3.0%-19.8%), and nausea (5.1%, 95% CI = 2.3%-11.0%). Common laboratory abnormalities in liver function were mild reduction in albumin (49.3%, 95% CI = 34.4%-64.4%) and elevations in ALT (19.4%, 95% CI = 9.9%-34.3%) and AST (15.2%, 95% CI = 9.3%-23.8%).

3.6 | Subgroup analysis: Published studies

As reported by published studies, after adjusting for preexisting illnesses, the most common gastrointestinal feature of COVID-19 was anorexia with an estimated prevalence of 20.0% (95% CI = 9.5%-37.2%), followed by diarrhea (9.9%, 95% CI = 6.5%-14.9%). Table 3 elaborates the details in this regard.

3.7 | Gastrointestinal and liver symptoms and disease severity

Results of the subgroup analysis according to disease severity are illustrated in Table 4. As is evident from the table, although anorexia was the most common gastrointestinal finding in both subgroups, its prevalence was two times higher in severe patients compared with nonsevere ones (31.4% vs 14.9%). Besides, the prevalence of diarrhea, vomiting, and abdominal pain were also markedly higher in patients with severe disease, while abdominal distension was more frequent in nonsevere cases (Table 4). The severe subgroup showed significantly higher prevalence of liver function abnormalities and preexisting illnesses, as well (Table 4).

4 | DISCUSSION

The emergence of the COVID-19 outbreak has infected millions of people worldwide and caused around 500 000 mortalities. The WHO has characterize the infection as a pandemic and called for research on all clinical aspects of COVID-19. Facing this pandemic requires a critical response and preparedness from all communities, especially health care professionals.[6-8,92,93]

A variety of symptoms has been reported in patients with COVID-19, from mild pulmonary involvement to severe bilateral pneumonia that can rapidly progress to acute respiratory distress syndrome and respiratory failure.[94] The vast majority of the symptoms associated with COVID-19 are related to respiratory tract, except for general manifestations such as fever. This is in line with the symptoms previously reported in patients with SARS and MERS, which are caused by viruses from the same phylogenic family.[95]

The focus of researchers has been on respiratory symptoms, which are thought to be the main cause of fatality in this disease, and

TABLE 1 Characteristics of the studies included in the systematic review and meta-analysis

					COVID-19 patients			
First author	Study design	Date (MM/DD)	City, country	Quality score (%)	N	Age mean ± SD/median (1st quartile-3rd quartile)	Sex (male/female)	Population type
Bai T[26]	Cross-sectional	(Preprint) 03/05	Wuhan, China	62.5	127	55.0 (44.0-67.0)	80/47	Inpatient
Cai Q[27]	Cross-sectional	04/02	Shenzhen, China	66.7	298	47.0 (33.0-61.0)	149/149	Inpatient
Chen D[28]	Cohort	06/11	Wenzhou, China	72.9	175	46 (34.0-54.0)	88/87	Inpatient
Chen G[29]	Cross-sectional	03/27	Wuhan, China	75.0	21	56.3 ± 14.3	17/4	Inpatient
Chen J[30]	Cohort	03/19	Shanghai, China	70.8	249	51.0 (36.0-64.0)	126/123	Inpatient
Chen L[31]	Cross-sectional	03/14	Wuhan, China	60.4	29	56.0 (26.0-79.0)	21/8	Inpatient
Chen N[32]	Case series	02/03	Wuhan, China	62.6	99	55·5 ± 13·1	67/32	Inpatient
Chen Z[33]	Cross-sectional	(Preprint) 03/02	Wuhan, China	64.6	89	33·3 ± 6·6	30/59	Inpatient
Cheng JL[34]	Cross-sectional	03/02	Henan province, China	50.0	1079	46.0 (IQR = 24.0)	573/505	Inpatient
Fan Z[35]	Cohort	04/10	Shanghai, China	68.7	148	50.0 (36.0-64.0)	73/75	Inpatient
Feng Z[36]	Cohort	(Preprint) 02/23	Changsha, China	75.0	141	44.0 (34.0-55.0)	72/69	Inpatient
Fu H[37]	Cross-sectional	(Preprint) 03/01	Kunming, China	47.9	36	Median: 45.0 Range, 3.0-79.0	16/20	Inpatient
Fu L[38]	Cohort	(Preprint) 03/16	Wuhan, China	64.6	200	-	99/101	Inpatient
Gong J[39]	Cohort	04/16	Guangzhou, Wuhan, China	79.2	189	49.0 (35.0-63.0)	88/101	Inpatient
Guan WJ[40]	Cohort	02/28	Guangzhou, Wuhan, China	58.3	1099	47.0 (35.0–58.0)	637/459	Inpatient and outpatient
Han R[41]	Cross-sectional	03/18	Wuhan, China	58.3	108	Mean: 45.0	38/70	Inpatient
Huang C[42]	Cohort	01/24	Wuhan, China	68.7	41	49.0 (41.0-58.0)	30/11	Inpatient
Huang M[43]	Cohort	(Preprint) 02/19	Chongqing, China	64.6	197	49.0 (41·0-58·0)	109/88	Inpatient
Jin JM[44]	Case series	04/29	Wuhan, China	54.2	43	62.0 (51.0-70.0)	22/21	Inpatient
Jin X[45]	Case-control	03/24	Zhejiang province, China	77.1	651	45.2 ± 14.4	331/320	Inpatient
Jin X[46]	Cross-sectional	03/17	Zhejiang province, China	68.7	788	45.8 ± 14.9	407/381	Inpatient
Kong I[47]	Case series	02/14	South Korea	41.7	28	42.6 (20.0-73.0)	15/13	Inpatient
Kuang Y[48]	Cross-sectional	(Preprint) 02/28	Zhejiang province, China	62.5	944	47.4 ± 22.9	476/468	N/A
Lei Z[49]	Cross-sectional	04/09	Guangzhou, China	64.6	20	43.2 ± 14·0	10/10	Inpatient
Li J[50]	Case series	(Preprint) 02/12	Dazhou, China	54.2	17	45.0 (22.0-65.0)	9/8	Inpatient
Li L[51]	Cross-sectional	(Preprint) 03/10	Beijing, China	75.0	85	49.0 (36.0-64.0)	47/38	Inpatient

TABLE 1 (Continued)

First author	Study design	Date (MM/DD)	City, country	Quality score (%)	COVID-19 patients			
					N	Age mean ± SD/median (1st quartile-3rd quartile)	Sex (male/female)	Population type
Li YY[52]	Cross-sectional	02/14	Wuhan, China	64.6	31	54.0 ± 13.0	15/16	Inpatient
Liang Y[53]	Cross-sectional	(Preprint) 02/28	Beijing, China	75.0	21	42.0 (34.5-66.0)	11/10	Outpatient
Liu C[54]	Cross-sectional	02/20	Lanzhou, Shenyang, Ankang, Lishui, Zhenjiang, Baoding, Linxiazhou, China	70.1	32	38.6 (26.3-45.8)	20/12	Inpatient
Liu F[55]	Case series	03/12	Hangzhou, China	47.8	10	42.0 (34.0-50.0)	4/6	Inpatient
Liu K[56]	Cohort	02/07	Hubei province, China	52.1	137	55.0 ± 16.0	61/76	Inpatient
Liu W[57]	Case series	(Preprint) 02/20	Wuhan, China	72.9	936	53.0 ± 14·8	296/332	Outpatient
Liu Y[58]	Case series	02/09	Shenzhen, China	58.3	12	54.0 (10.0-72.0)	8/4	Inpatient
Lo IL[15]	Case series	03/15	Macau, China	64.6	10	54.0 (27.0–64.0)	3/7	Inpatient
Luo S[59]	Case series	03/18	Wuhan, China	41.7	1141	Mean: 53.8	102/81	Inpatient
Miao C[60]	Cross-sectional	(Preprint) 03/24	Shanghai, Nanchang, Yichun, China	68.7	62	43.8 ± 13.9	32/30	Inpatient
Mo P[61]	Case series	03/16	Wuhan, China	83.3	155	54.0 (42.0-66.0)	86/69	Inpatient
Pan L[62]	Cross-sectional	04/14	Wuhan, Huanggang, China	81.2	204	52.9 ± 16.0	107/97	Inpatient
Shi H[63]	Case series	02/24	Wuhan, China	70.1	81	49·5 ± 11·0	42/39	Inpatient
Song F[64]	Cross-sectional	02/06	Shanghai, China	72.9	51	49.0 ± 16.0	25/26	Inpatient
Sun W[65]	Cross-sectional	03/15	Zhejiang province, China	54.2	148	48.0 (37.0-56.0)	73/75	N/A
Sun Y[66]	Case-control	03/25	Singapore	91.7	54	42.0 (34.0-54.0)	29/25	Inpatient and outpatient
Tang X[67]	Case-sontrol	03/26	Wuhan, China	72.9	73	67.0 (57.0-72.0)	45/28	Inpatient
Wan S[68]	Cohort	03/21	Chongqing, China	77.1	135	47.0 (36.0-55.0)	72/63	Inpatient
Wang D[69]	Case series	02/07	Wuhan, China	75.0	138	56.0 (42.0-68.0)	75/63	Inpatient
Wei XS[70]	Case series	04/18	Wuhan, China	68.7	84	37.0 (24.0-74.0)	28/56	Inpatient
Wen Y[71]	Cross-sectional	(Preprint) 03/23	Shenzhen, China	75.0	417	45.4 ± 17.7	197/220	Inpatient and outpatient
Wu J[72]	Cross-sectional	02/29	Jiangsu, China	64.6	80	46.1 ± 15.4	39/41	Inpatient

(Continues)

TABLE 1 (Continued)

First author	Study design	Date (MM/DD)	City, country	Quality score (%)	COVID-19 patients			
					N	Age mean ± SD/median (1st quartile-3rd quartile)	Sex (male/female)	Population type
Xu T[73]	Cohort	04/14	Jiangsu, China	68.7	51	-	25/26	Inpatient
Xu W[74]	Cross-sectional	(Preprint) 03/18	Suzhou, China	70.1	87	44.6 ± 14.7	46/41	Inpatient
Fang Y[75]	Case series	02/19	Zhejiang province, China	68.7	62	41.0 (32.0-52.0)	35/27	Inpatient
Xu YH[76]	Cross-sectional	02/25	Beijing, China	54.1	50	43.9 ± 16.8	29/21	Inpatient
Yang W[77]	Case series	02/26	Wenzhou, China	79.2	149	45.1 ± 13.4	81/68	Inpatient
Yao N[78]	Cross-sectional	03/10	Xi'an, China	56.3	40	53.9 ± 15.8	25/15	Inpatient
Young BE[79]	Case series	03/03	Singapore	62.5	18	47.0 (31.0-73.0)	9/9	Inpatient
Yu F[80]	Cohort	03/28	Beijing, China	70.1	76	40.0 (32.0-63.0)	38/38	Inpatient
Zhang G[81]	Case series	04/09	Wuhan, China	77.1	221	55.0 (39.0-66.5)	108/113	Inpatient
Zhang JJ[82]	Cross-sectional	02/19	Wuhan, China	68.7	140	57.0 (25.0-87.0)	71/69	Inpatient
Zhang MQ[83]	Case series	03/01	Beijing, China	41.7	9	36.0 (15.0-49.0)	5/4	Inpatient
Zhang X[84]	Cross-sectional	03/20	Zhejiang province, China	60.4	645	45.3 ± 13.9	295/278	Inpatient
Zhang Y[85]	Cohort	04/02	Wuhan, China	66.7	115	49.5 ± 17.1	49/66	Inpatient
Zhang Y[86]	Cross-sectional	(Preprint) 03/27	Wuhan, China	72.9	212	48.5 ± 13.2	119/93	Inpatient
Zhao D[87]	Case-control	03/12	Anhui province, China	62.5	19	48.0 (27.0-56.0)	11/8	Inpatient
Zhao W[88]	Cohort	03/03	Changsha, Yueyang, Changde, Xiangtan, China	60.4	101	44.4 ± 12.3	56/45	Inpatient
Zhao W[89]	Cohort	(Preprint) 03/17	Beijing, China	62.5	77	52.0 ± 20.0	34/43	Inpatient
Zhao Z[90]	Case series	(Preprint) 03/06	Hefei, China	54.1	75	47.0 (34.0-55.0)	42/33	Inpatient
Zhou F[91]	Cohort	03/11	Wuhan, China	85.4	191	56·0 (46.0–67.0)	119/72	Inpatient

Abbreviations: COVID-19, coronavirus disease-2019; IQR, interquartile range; N/A, not available; SD, standard deviation.

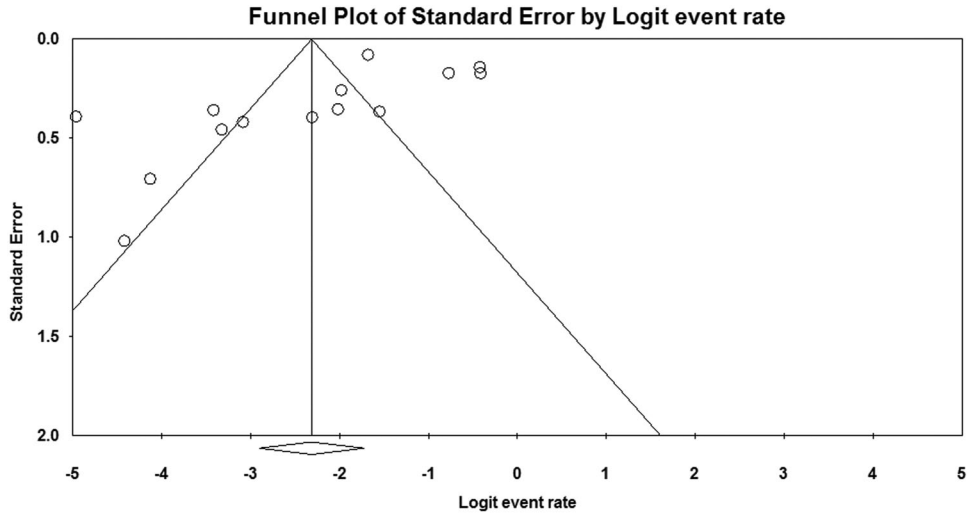

FIGURE 2 Funnel plot of studies reporting anorexia in the primary unadjusted meta-analysis

little is known about the extrapulmonary manifestations that might accompany COVID-19, especially gastrointestinal and liver abnormalities. It has been reported that presenting with gastrointestinal symptoms can delay the diagnosis and subsequently lead to worse outcomes in patients with COVID-19.[18] Therefore, this systematic review and meta-analysis was performed to provide more insight into the frequency and characteristics of gastrointestinal and liver involvements in patients with COVID-19.

The most common gastrointestinal symptoms among all patients with confirmed COVID-19 were anorexia (10.2%), diarrhea (8.4%), and nausea (5.7%). Other less common presentations were vomiting, abdominal pain, and abdominal distension. Common liver function abnormalities were mild decrease in serum albumin (39.8%) and mild increase in AST and ALT levels, which was found in 22.8% and 20.6% of the patients. Total bilirubin was mildly elevated in 7.8%, 4.6% had elevated ALP, and so was prothrombin time in 18% of patients.

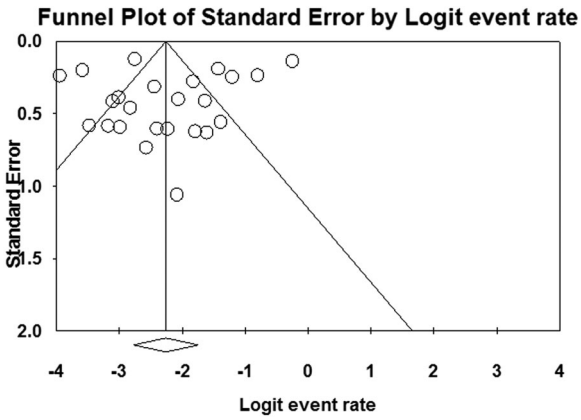

FIGURE 3 Funnel plot of studies reporting diarrhea, after adjusting for preexisting diseases

The elevation of ALP can possibly be related to the pathophysiology of COVID-19 and its main entry mechanism, which is related to ACE2 receptors. It has been reported that the biliary tree abundantly expresses ACE2, and thus it can be a potential target for the virus.[14]

Chronic gastrointestinal and liver comorbidities were found to be present in 5.9% and 4.2% of the patients, respectively. Since the prevalence of digestive findings in this study was relatively low (10% and lower), these comorbidities might have affected the actual prevalence of gastrointestinal and hepatic findings of COVID-19 in the pooled population. As reported previously, preexisting digestive disease has been reported with poorer outcomes in patients with COVID-19.[96] Therefore, in an attempt to remove the effects of these chronic preexisting conditions, the studies in which patients had preexisting diseases were excluded. The adjusted estimates revealed that common gastrointestinal findings were diarrhea (8.7%), anorexia (8.0%), and nausea (5.1%). This change in the prevalence rates after adjustment indicates the possibility of some gastrointestinal symptoms, which have been reported in several studies as common gastrointestinal features of COVID-19, being a result of comorbid preexisting conditions. In particular, anorexia and to some extent nausea were found to have a marked decrease in their frequency, after excluding preexisting illnesses.

When considering only published studies, we observed that anorexia was the most common gastrointestinal symptom with an estimated prevalence of 16.2%, which rose to 20% after adjusting for preexisting comorbidities and remained the most common gastrointestinal findings in patients with COVID-19.

It seems that diarrhea is the main gastrointestinal feature of patients with COVID-19, as was the case in patients infected with the similar pathologies of SARS and MERS.[95,97,98] However, this higher estimated prevalence of diarrhea in this study might be because some of the included studies did not assess other gastrointestinal symptoms. It is also worth noting that although rarely reported in

TABLE 2 Pooled prevalence of gastrointestinal symptoms, preexisting diseases, and liver function abnormalities in all studies reporting patients with COVID-19

	All studies (published and preprint)					Published studies				
Findings	N patients	N studies	Point estimate (%)	95% CI (%)	I^2	N patients	N studies	Point estimate (%)	95% CI (%)	I^2
Gastrointestinal symptoms										
Anorexia	3871	15	10.2	6.2-16.4	95.65	2590	11	16.2	10.3-24.5	94.83
Diarrhea	10 652	56	8.4	6.2-11.2	93.80	7101	41	8.6	6.8-10.8	83.07
Nausea	5089	23	5.7	3.7-8.6	88.08	3740	19	7.2	4.7-10.9	87.31
Vomiting	4567	20	3.8	2.5-5.9	81.80	3434	18	4.6	3.0-6.8	78.57
Abdominal pain	2342	10	3.2	2.1-4.7	44.17	2267	9	3.3	2.2-4.9	46.97
Abdominal distension	1217	3	1.1	0.2-5.6	78.76	84	1	3.6	1.2-10.5	0.00
Liver function abnormalities										
Decreased albumin	505	7	39.8	15.3-70.8	94.77	505	7	39.8	15.3-70.8	94.77
Elevated AST	2062	16	22.8	18.1-28.4	83.05	1910	14	22.4	17.2-28.5	84.31
Elevated ALT	1496	8	20.6	16.7-25.1	65.63	1282	5	20.3	15.2-26.6	78.12
Elevated PT	323	3	18.0	3.0-60.8	97.03	248	2	8.3	3.7-17.3	63.90
Elevated TBIL	1429	9	7.8	5.0-12.0	72.02	1354	7	6.8	4.1-11.0	72.64
Elevated ALP	263	2	4.6	2.6-7.9	<0.01	263	2	4.6	2.6-7.9	<0.01
Preexisting diseases										
Digestive disease	1152	9	5.9	4.1-8.5	51.73	861	6	5.9	3.7-9.2	58.31
Liver disease	5891	30	4.2	3.3-5.3	56.74	5207	24	4.3	3.3-5.6	61.84

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease-2019; PT, prothrombin time; TBIL, total bilirubin.

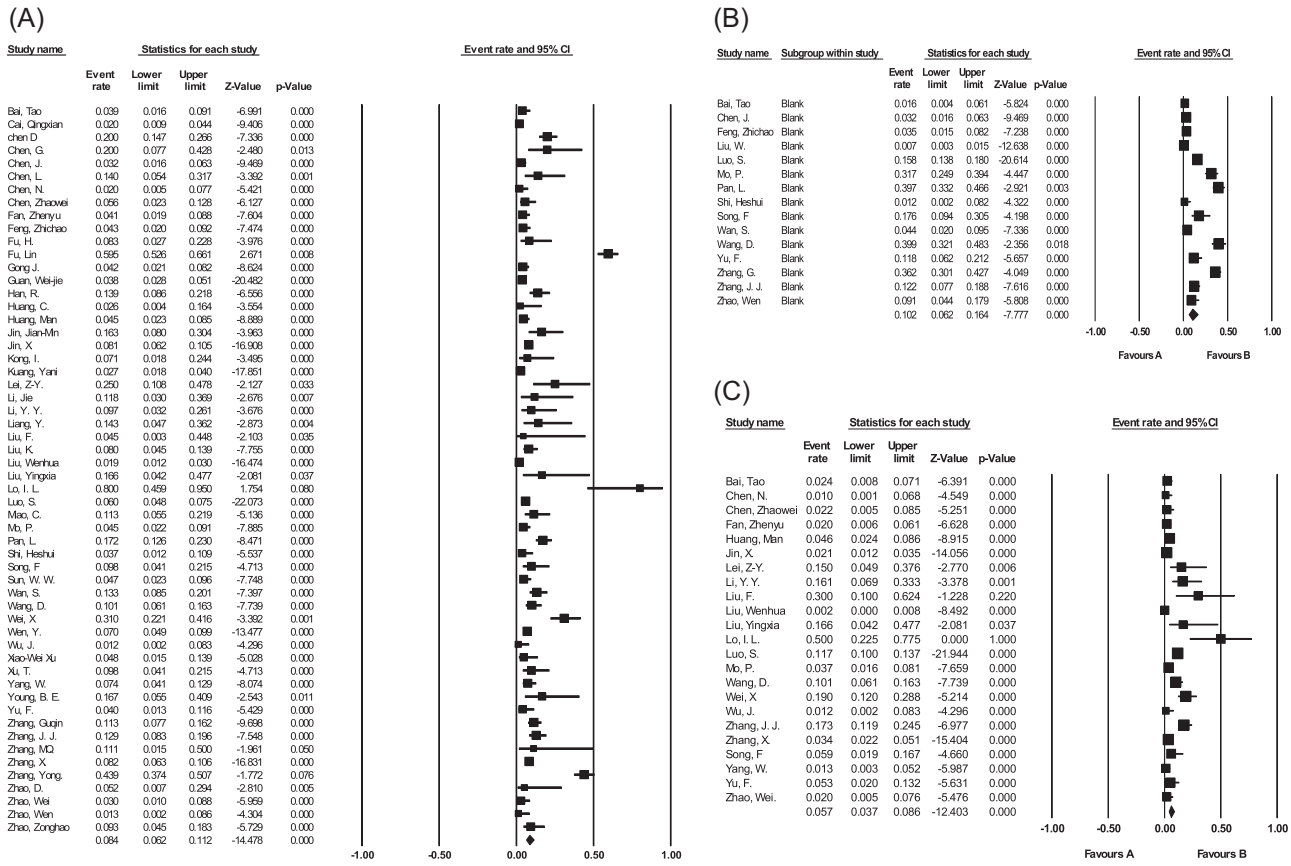

FIGURE 4 Forest plots for the prevalence of major gastrointestinal findings in meta-analysis of all studies. A, Diarrhea. B, Anorexia. C, Nausea. CI, confidence interval

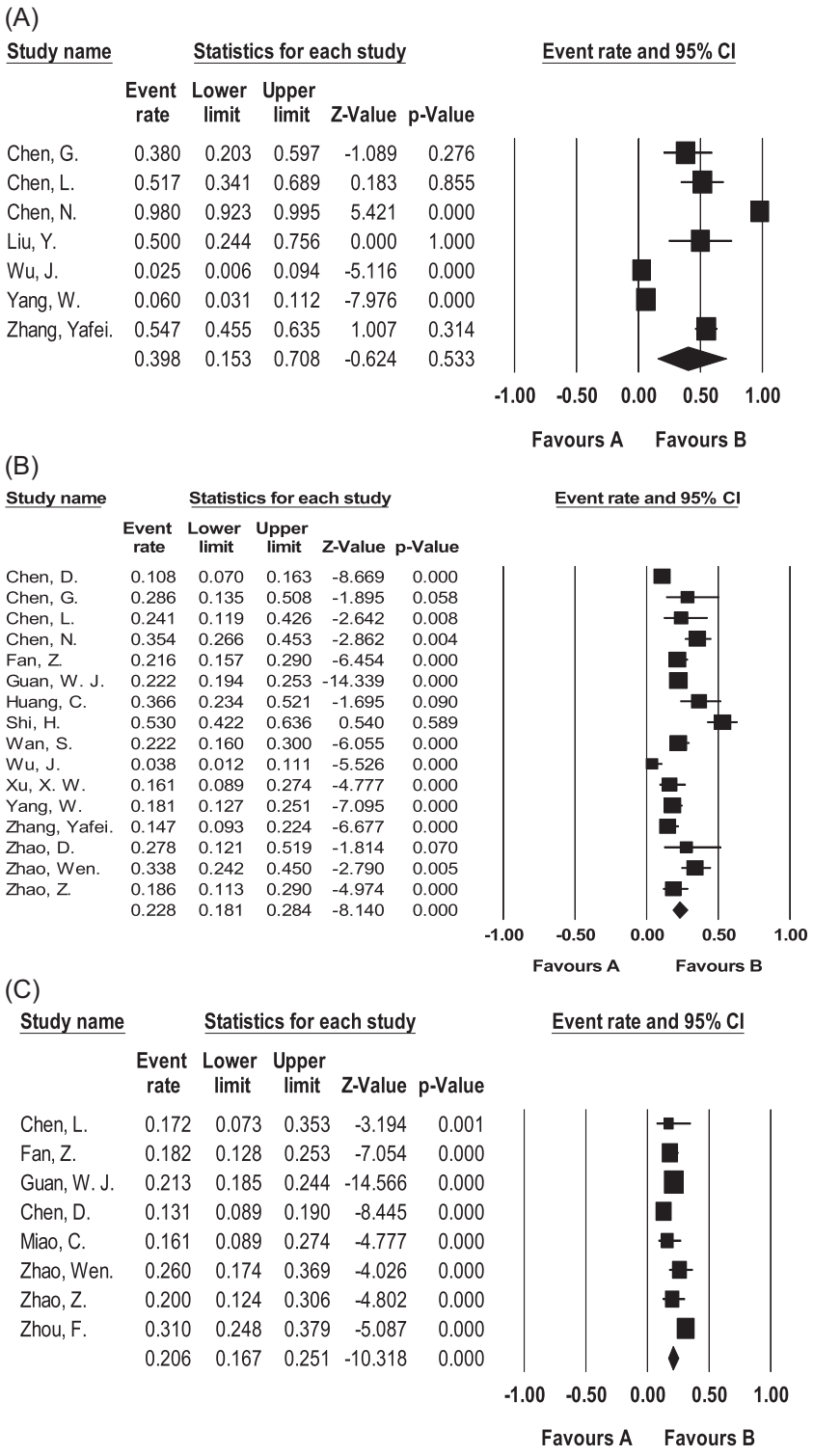

FIGURE 5 Forest plots for the prevalence of major hepatic findings in meta-analysis of all studies. A, Decreased albumin. B, Increased AST. C, Increased ALT. ALT, aminotransferase; AST, aspartate aminotransferase; CI, confidence interval

previous studies, COVID-19 can present with constipation or other uncommon gastrointestinal symptoms.[99] For instance, few sparse studies reported gastrointestinal bleeding and this finding was not incorporated into meta-analysis.[26,68] It should be studied further by large-scale studies.

The exact pathologic mechanisms behind the gastrointestinal involvement of COVID-19 is yet to be known. However, as the virus targets ACE2 to infect human cells, it seems likely that intestinal cells, which largely express the ACE2 cell receptors, are infected in the same way. Moreover, viral particles have been detected in stool samples of a large number of patients with COVID-19, even longer than what detected in respiratory samples. Interestingly, patients with diarrhea reportedly have higher frequency of virus being detected in their feces.[16]

TABLE 3 Pooled prevalence of gastrointestinal and liver symptoms in patients with COVID-19, after adjustment for preexisting diseases

	All studies (published and preprint)					Published studies				
Findings	N patients	N studies	Point estimate (%)	95% CI (%)	I^2	N patients	N studies	Point estimate (%)	95% CI (%)	I^2
Gastrointestinal symptoms										
Diarrhea	5104	23	8.7	5.4-13.9	94.62	2308	15	9.9	6.5-14.9	85.90
Anorexia	2515	5	8.0	3.0-19.8	97.21	1438	3	20.0	9.5-37.2	95.97
Nausea	2458	7	5.1	2.3-11.0	88.63	1349	4	8.1	4.0-15.6	70.30
Vomiting	2513	6	3.7	1.6-8.3	85.29	1577	5	5.8	3.3-10.2	71.67
Abdominal pain	1400	3	3.7	2.8-4.8	<0.01	1400	3	3.7	2.8-4.8	<0.01
Abdominal distension	1020	2	0.7	0.0-18.9	89.22	84	1	3.6	1.2-10.5	0.00
Liver function abnormalities										
Decreased albumin	136	2	49.3	34.4-64.4	48.41	136	2	49.3	34.4-64.4	48.41
Elevated ALT	426	3	19.4	9.9-34.3	88.68	364	2	20.8	8.3-43.4	93.71
Elevated AST	311	3	15.2	9.3-23.8	59.98	311	3	15.2	9.3-23.8	59.98

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease-2019.

In a subgroup analysis, we found that anorexia was the most common gastrointestinal finding in both severe and nonsevere groups. However, the prevalence of almost all gastrointestinal and liver symptoms were markedly higher in severe patients compared with nonsevere ones, with the exception of nausea and abdominal distension. The severe subgroup showed significantly higher prevalence of liver function abnormalities, as well. Decreased albumin was seen in about 80% of the severe cases. As expected, the prevalence of digestive and hepatic comorbidities were also higher in severe patients, which is in line with the previous reports indicating the higher risk of severe COVID-19 in patients with comorbidities.[96]

The higher prevalence of gastrointestinal and liver symptoms among severe cases has been reported in two previous meta-analysis study.[16,18] Several studies have suggested a relationship between gastrointestinal and hepatic manifestations of COVID-19 and the disease severity in these patients.[32,100,101]

The results from the meta-analysis by Mao et al[18] are relatively similar to the findings of our main meta-analysis in this study. They reported diarrhea, nausea, or vomiting, and abdominal pain to be present in about 9%, 6%, and 3% of patients, respectively, which is in line with our findings. They also found the prevalence of digestive and hepatic comorbidities to be 4% and 3%, respectively, which is

TABLE 4 Pooled prevalence of gastrointestinal symptoms, preexisting diseases, and liver function abnormalities in patients with different severities of COVID-19

	Nonsevere					Severe				
Findings	N patients	N studies	Point estimate (%)	95% CI (%)	I^2	N patients	N studies	Point estimate (%)	95% CI (%)	I^2
Gastrointestinal symptoms										
Anorexia	502	5	14.9	7.6-27.2	84.92	208	5	31.4	12.4-59.7	91.49
Diarrhea	2006	11	5.5	3.5-8.4	71.67	535	10	11.1	6.7-18.0	69.02
Nausea	326	3	9.5	3.0-26.2	89.24	148	3	9.5	5.7-15.4	<0.01
Vomiting	326	3	2.5	0.7-9.2	59.59	148	3	5.1	2.4-10.3	<0.01
Abdominal pain	350	3	1.8	0.8-4.0	<0.01	148	3	8.1	4.5-14.0	<0.01
Abdominal distension	142	1	2.1	0.7-6.3	<0.01	55	1	1.8	0.3-11.8	<0.01
Liver function abnormalities										
Decreased albumin	94	2	27.2	6.2-67.9	66.39	42	2	80.2	44.1-95.4	72.81
Elevated AST	1265	8	11.6	7.2-18.0	81.77	355	8	36.7	30.0-43.9	34.97
Elevated ALT	1039	4	15.0	8.5-25.2	89.27	253	4	30.8	25.0-37.3	8.81
Elevated TBIL	918	3	7.5	4.7-11.7	59.33	217	3	17.3	11.4-25.4	39.20
Elevated ALP	324	2	0.1	0.01-8.7	56.97	89	2	5.7	0.7-32.4	71.40
Preexisting diseases										
Digestive disease	281	3	5.2	3.1-8.6	<0.01	133	3	6.9	1.9-22.3	69.18
Liver disease	1781	8	3.2	1.8-5.7	69.94	488	8	4.9	2.4-9.5	50.32

slightly lower the rates we found. Although our results regarding the frequency of elevated AST, ALT, and bilirubin were consistent with those reported by Mao et al,[18] they reported a far lower rate for decreased albumin (6%). These inconsistencies might be attributed to different eligibility criteria, lower number of included studies, and different analytic methodology.

A recent meta-analysis on the gastrointestinal symptoms of COVID-19 by Cheung et al[16] indicated relatively higher prevalence for virtually every symptom, compared with these findings. They found anorexia to be the most prevalent gastrointestinal presentation of COVID-19, which is in line with these findings in patients with any preexisting conditions. However, they found it in about 26.8% of patients, which is by far higher than what were found in this study. Besides, after comorbid chronic conditions were adjusted, diarrhea overtook anorexia to become the most prevalent symptom in patients with COVID-19. Nevertheless, it did not happen when assessing only the published studies, where anorexia remained the most prevalent symptom after adjustment. Also in contrast with these findings, Cheung et al[16] found diarrhea and nausea/vomiting in 12.5% and 10.2% of patients, respectively, which is also relatively higher than these findings. This inconsistency can be ascribed to different reasons. First, there are several differences between the eligibility criteria and those used in the study by Cheung et al.[16] They excluded the asymptomatic cases of COVID-19, while the patients with a variety of manifestations from asymptomatic to severely symptomatic were included in this study, to reduce the risk of bias. Moreover, to reduce the chance of bias, the studies that were conducted exclusively on specific populations, for example, studies that only included critically ill patients or fatal cases were excluded. As reported by Cheung et al,[16] patients with severe COVID-19 are more likely to present with gastrointestinal symptoms and show higher prevalence of these symptoms compared with nonsevere cases. Therefore, excluding the studies that only reported severe cases might be the reason behind these lower prevalence estimations. Second, the data regarding preexisting conditions were reported and calculated the prevalence of different findings in absence of these comorbidities, while Cheung et al[16] did not consider preexisting diseases that can affect the prevalence of gastrointestinal symptoms. Finally, it could be due to the difference in the methodology of studies; for instance, nausea and vomiting separately were reported, while Cheung et al[16] merged them into one single symptom. In contrast with the study by Cheung et al,[16] a recent review of the literature on the prevalence of diarrhea in about 2500 patients with COVID-19 showed an overall prevalence of 5.8%, which is more comparable with the findings of the present study.[102]

Different studies have reported varying rates regarding the prevalence of liver injury in COVID-19, between 15% and 78%. However, similar to these findings, most studies have reported slight elevation of AST, ALT, and bilirubin levels as common findings in COVID-19.[103] The inconsistency in the prevalence of hepatic findings between this review and the previous ones can be attributed to different inclusion and exclusion criteria, as stated before regarding the gastrointestinal findings. The studies that reported high frequency of abnormal liver function are mainly conducted only on severe or fatal cases of COVID-19.[104] As reported in a recent meta-analysis, liver injury is associated with high severity of disease in patients with COVID-19,[105] which was the case in the results of our subgroup analysis according to disease severity. The results regarding the prevalence of abnormal liver function are comparable to a previous meta-analysis in terms of elevations in ALT, AST, and bilirubin levels. However, Rodriguez-Morales et al[106] reported a prevalence of 75.8% for decreased albumin that is in contrast with the findings of current review. The reason behind this inconsistency probably lies in the limited number of studies that reported this finding in patients with COVID-19. Seven studies reporting decreased albumin were included in this meta-analysis, only two of which were reported in the above mentioned study. Of course, further studies with large sample sizes would provide more accurate estimates. Furthermore, other hepatic biomarkers including gamma glutamyl transferase, international normalized ratio, and direct bilirubin levels were reported in few studies and thus they were not incorporated in the analyses. Further studies are recommended to assess these markers as well, to provide more insight into the extent of liver injury in COVID-19.

The present study provides several important insights into gastrointestinal and hepatic manifestations of COVID-19, which can be of interest especially for clinicians and epidemiologists to obtain a clear overview of the prevalence and characteristics of these findings. As reported previously, gastrointestinal symptoms can precede other commonly reported symptoms of fever and respiratory abnormalities,[107] which can delay the diagnosis.[18] Therefore, every clinician should be vigilant when facing a patient presenting these symptoms, particularly in the highly infected regions. Precautionary measures and possible evaluation of such patients for COVID-19 is recommended.

This study had some limitations. For one thing, there are currently limited large-scale studies available on patients with COVID-19 outside of China and most of the included studies are from a limited geographical area. Moreover, gastrointestinal symptoms might have been underreported in some of the included studies, which can affect the prevalence of some findings. Although disease severity was incorporated into this meta-analysis, the results can be subject to bias as the literature is too heterogeneous in this regard and studies have used different criteria for severity.

In conclusion, gastrointestinal and hepatic presentations are not rare in COVID-19. The prevalence of these manifestations in patients with COVID-19 might be affected by preexisting comorbidities. However, diarrhea and mild elevation of liver enzymes are ostensibly the most common gastrointestinal and hepatic features of COVID-19, in the absence of preexisting diseases.

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AUTHOR CONTRIBUTIONS

MZB, AZ, MK, MA, and AG contributed to the design and conceptualization of the study. MZB, AA, AZ, SA, and AG contributed in designing the search strategy and literature search. Data extraction was conducted by MZB, MR, HG, AA, and MSG. Data entry and statistical analysis were performed by SA and MZB. Critical appraisal was done by MZB, MR, HG, AA, MK, and MSG. AZ and MR contributed to drafting and writing the manuscript. All the authors reviewed and contributed in editing the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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