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REVIEW ARTICLE

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

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

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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 = 97.6%) 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 1.66–3.14, $P < 0.00001$, I^2 = 31%), myalgia (OR 1.96, 95 CI 1.06–3.65, P = 0.03, I^2 = 69%), 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 3.53, 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.[1-3] 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 .[4] 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,[5] and six patients only suffering digestive symptoms but no respiratory symptoms as clinical

manifestation were reported.[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.[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%,[7,8] and liver injury was identified in 2.5–55.0%[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.[1] In addition, the prevalence of diarrhea and abdomen pain was significantly higher in severe patients than that in mild patients.[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.[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,

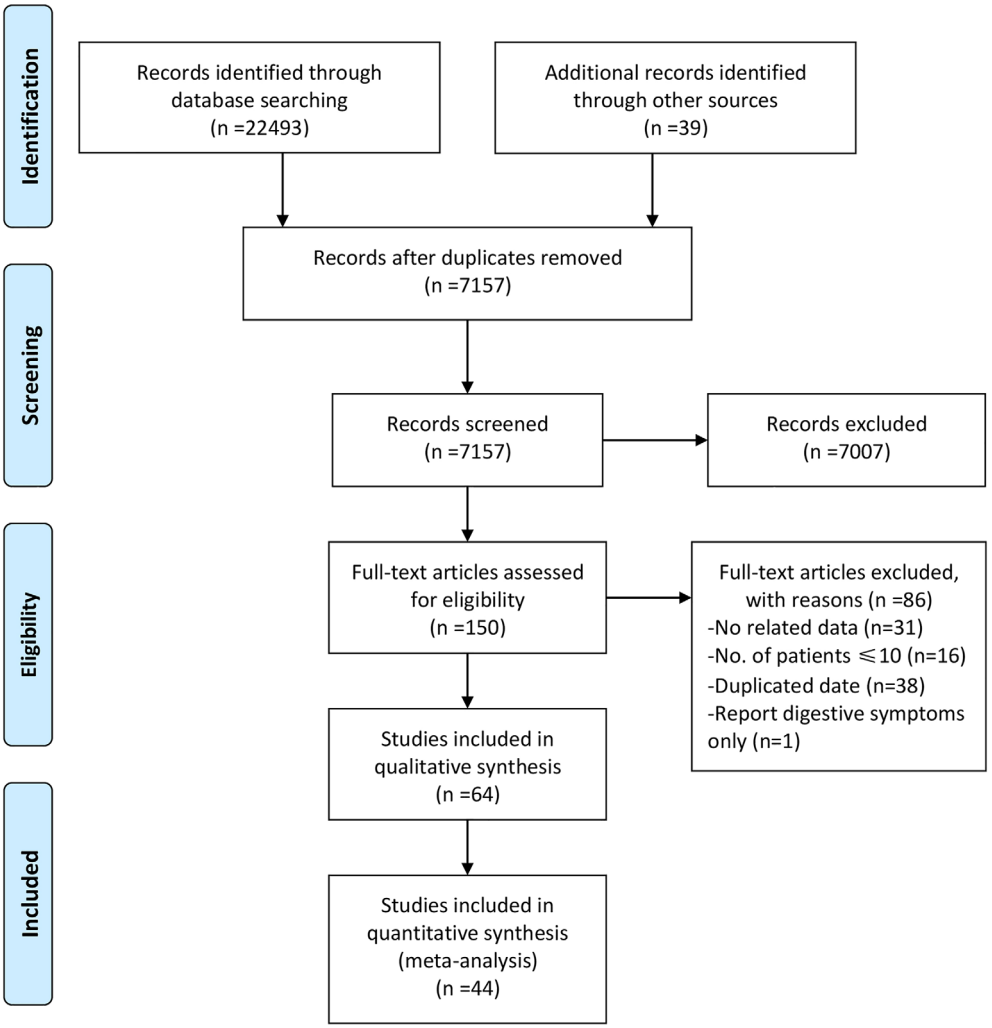

Figure 1 Flow diagram of the search results and study selection.

Table 1 Characteristics of studies

Author	Published language	Areas, center	Cases (severe)	Female	Age	Digestive comorbidities†	Liver comorbidities	Quality score
Min Liu[35]	Chinese	Hubei, 1	30 (4)	20	35 ± 8	—	—	6
Hansheng Xie[56]	English	Hubei, 1	79 (28)	35	60 (range 48–66)	—	—	6
Fei Zhou[69]	English	Hubei, 2	191 (119)	72	56 (IQR 46–67)	—	—	9
Xiaobo Yang[60]	English	Hubei, 1	52 (52)	17	59.7 ± 13.3	—	—	8
Heshui Shi[45]	English	Hubei, 2	81	39	49.5 ± 11.0	—	7	8
Chaomin Wu[54]	English	Hubei, 1	201	73	51 (IQR 43–60)	—	7	8
Tao Chen[21]	English	Hubei, 1	274	103	62 (IQR 44–70)	14	11	9
Ling Mao[37]	English	Hubei, 3	214 (88)	127	52.7 ± 15.5	—	—	7
Qian Li[32]	Chinese	Hubei, 2	30 (1)	12	6 (range 0–14)	—	—	7
Kui Liu[34]	English	Hubei, 9	137	76	57 (range 20–83)	—	—	7
Dan Fang[25]	Chinese	Hubei, 1	305 (46)	159	57(range 18–95)	—	—	6
Lei Pan[1]	English	Hubei, 3	204	97	52.91 ± 15.98	7	—	8
Yuanmei Guo[27]	Chinese	Hubei, 1	663 (409)	342	58 (IQR 44–69)	31	—	7
Jin-jin Zhang[64]	English	Hubei, 1	140 (58)	69	57 (range 25–87)	21	14	7
Xiaoxia Lu[36]	English	Hubei, 1	171	67	6.7 (range 1 day–15)	—	—	6
Min Bai[17]	Chinese	Hubei, 1	472	257	50.7 ± 11.6	—	—	6
Shi Chen[20]	Chinese	Hubei, 1	109 (44)	61	52.5 ± 10.8	—	—	7
Gemin Zhang[63]	English	Hubei, 1	95 (32)	42	49 (range 39–58)	—	—	8
Zili Zhou[70]	English	Hubei, 1	254	139	50.6 (range 15–87)	—	3	7
K. Wang[51]	English	Hubei, 1	114	56	53 (range 23–78)	5	—	6
Zhongliang Wang[52]	English	Hubei, 1	69	37	42 (IQR 35–62)	—	1	6
Fenghua Xu[57]	Chinese	Hubei, 1	251 (175)	119	59.9 ± 15.7	—	4	6
Rong Wang[44]	Chinese	Hubei, 1	96 (54)	50	NA	7	2	5
Pingzheng Mo[38]	English	Hubei, 1	155 (92)	69	54 (IQR 42–66)	—	7	7
Dawei Wang[5]	English	Hubei, 1	138	63	56 (IQR 42–68)	—	4	8
Wei-jie Guan[2]	English	China, 522	1099 (173)	459	47 (IQR 35–58)	—	23	9
Dahai Zhao[66]	English	Anhui, 2	19	8	48 (IQR 27 ∼ 56)	—	1	7
Yalin Li[14]	Chinese	Anhui, 1	49 (27)	21	45 (range 14 ∼ 82)	—	3	5
De Chang[18]	English	Beijing, 3	13	3	34 (IQR 34–48)	—	—	6
Ke Wen[53]	Chinese	Beijing, 1	46 (11)	19	41.8 ± 16.3	—	—	6
Xi Xu[59]	English	Guangdong, 1	90	51	50 (range 18–86)	—	—	7
Jing Yuan[62]	English	Guangdong, 1	94 (11)	52	40 (range 1–78)	—	—	8
Lu Lin[7]	English	Guangdong, 1	95 (20)	50	45.3 ± 18.3	—	—	8
Rui Zhao[67]	Chinese	Guangxi, 1	28(2)	17	44.5 (range 11–68)	—	—	5
Chan Sun[46]	Chinese	Henan, 16	150 (39)	83	45 ± 16	—	1	6
Ye Zhao[8]	Chinese	Henan, 1	106 (15)	40	48.9 ± 13.1	—	2	8
Fang Zheng[68]	English	Hunan, 1	161 (30)	81	45 (range 33.5–57)	—	4	6
Xin Tan[47]	Chinese	Hunan, 1	13 (1)	9	8 (range 1–17)	—	—	6
Dan Li[31]	Chinese	Hunan, NA	80 (17)	40	47.5 (range 3–90)	—	3	6
Tianmin Xu[58]	English	Jiangsu, 1	51	26	35 (IQR 29–51) (n = 15) 37(IQR24–47.5) (n = 17) 53 (IQR35–65) (n = 19)	—	1	6
Miao Zhu[15]	Chinese	Jiangsu, 1	23	13	50.0 ± 13.0	—	—	5
Jian Wu[10]	English	Jiangsu and Anhui, 4	280 (83)	129	43.12 ± 19.02	16	7	7
Tianxin Xiang[55]	Chinese	Jiangxi, 1	49 (9)	16	42.9 (range 18–78)	—	6	6
Shuxiang Zhang[65]	Chinese	Ningxia, 1	34 (5)	14	41 ± 17	—	—	7
Na Yao[9]	Chinese	Shaanxi, 1	40 (22)	15	53.9 ± 15.8	—	—	6
Jun Chen[19]	English	Shanghai, 1	249	123	51(IQR 36–64)	—	2	6
Dan Li 2[30]	Chinese	Liaoning, 1	30 (9)	12	43 (range 21–72)	—	—	6
Xiaochun Dong[23]	Chinese	Tianjin, NA	135 (62)	63	48.6 ± 16.8	—	—	5
Kelvin Kai-Wang[29]	English	Hongkong, 2	23 (10)	10	62 (range 37–75)	—	—	8
Xi Jin[28]	English	Zhejiang, NA	651	320	46.1 ± 14.2 (n = 74) 45.1 ± 14.5 (n = 577)	—	25	9
Xiaolong Qi[41]	English	China, 9	70 (3)	31	41 (IQR 27.5–50) (n = 32) 38.5 (IQR 26–47.3) (n = 38)	—	—	6
Duan Wang[50]	Chinese	China, 21	31 (0)	NA	7.1 (range 0.5–17)	—	—	5

(*Continues*)

Table 1 (Continued)

Author	Published language	Areas, center	Cases (severe)	Female	Age	Digestive comorbidities†	Liver comorbidities	Quality score
Chuan Liu[33]	Chinese	China, 7	32 (4)	12	38.5 (IQR 26.3–45.8)	—	1	7
Suxin Wan[49]	Chinese	Chongqing, 1	135 (40)	63	47 (IQR 36–55)	—	2	6
Jing Yuan[16]	Chinese	Chongqing, 1	223 (31)	117	46.5 ± 16.1	—	8	5
Maria Effenberger[24]	English	Austria,1	40	16	58.4 ± 17.1 (n = 18) 66.3 (±13.1) (n = 13) 78.3 (±13.8) (n = 9)	—	—	5
The COVID-19 Investigation Team[48]	English	America, 6	12	4	53 (range 21–68)	—	2	5
Safiya Richardson[43]	English	America, 12	5700	2263	63 (IQR 52–75)	—	30	6
George Cholankeril[22]	English	America, 1	116	54	50 (IQR 35–67)	—	3	5
Walker D. Redd[42]	English	America, 9	318	144	63.4 ± 16.6	122	—	5
Yael R. Nobel[39]	English	America, 1	278	133	Range 18–30 (n = 31); 31–50 (n = 69); 51–70 (n = 103); >70 (n = 75)	—	—	5
Mario Fernández-Ruiz[26]	English	Spain, 1	18	4	72 (range 39–80)	7	7	5
Rachael Pung[40]	English	Singapore, 1	17	10	40 (IQR 36–51)	—	—	6
BE Young[61]	English	Singapore, 4	18	9	47 (range 31–73)	—	—	7

†Including 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 I^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. I^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 Q test and $I^2 > 50\%$ for the I^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 studies[1,2,5,7-10,14-70] 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[35]	30	—	—	—	—	9/30	—	—	—	7/30
Hansheng Xie[56]	79	7	—	—	—	—	25/79	28/79	4/79	—
Fei Zhou[69]	191	9	7	—	—	—	59/189	—	—	—
Xiaobo Yang[60]	52	—	2	—	—	—	—	—	—	15/52
Heshui Shi[45]	81	3	4	—	1	—	—	43/81	—	—
Chaomin Wu[54]	201	—	—	—	—	—	43/198	59/198	10/198	—
Tao Chen[21]	274	77	24,16[†]	19	66	—	60/274	84/274	—	—
Ling Mao[37]	214	41	—	10	68	—	—	—	—	—
Qian Li[32]	30	2	2	—	—	—	—	—	—	—
Kui Liu[34]	137	11	—	—	—	—	—	—	—	—
Dan Fang[25]	201	146/295[‡]	59,32	12	101	159/201[‡]	76/304	97/304	6/304	119/304
Lei Pan[1]	204	35	4	2	81	103/204	27/204	22/204		
Yuanmei Guo[27]	663	70	—	—	—	—	151/617	171/617	—	—
Jin-jin Zhang[64]	139	18	24,7	8	17	55/139	—	—	—	—
Xiaoxia Lu[36]	171	15	11	—	—	—	—	—	—	—
Min Bai[17]	472	38	10	—	—	—	—	—	—	—
Shi Chen[20]	109	23	—	—	—	—	25/109	23/109	—	—
Gemin Zhang[63]	95	—	—	—	—	—	52/95	45/95	—	—
Zili Zhou[70]	254	46	21,15	3	—	66/254	—	—	—	—
K. Wang[51]	114	3	—	—	—	—	—	—	—	—
Zhongliang Wang[52]	69	10	3	—	7		23/69	19/69	—	—
Fenghua Xu[57]	251	30	19	3	85	116/251	106/251	110/251	31/251	143/251
Rong Wang[44]	96	11	—	—	—	—	—	—	—	—
Pingzheng Mo[38]	155	7	3,3	3	26	—	—	—	—	—
Dawei Wang[5]	138	14	14,5	3	55	—	—	—	—	—
Wei-jie Guan[2]	1099	42	55	—	—	—	158/741	168/757	76/722	—
Dahai Zhao[66]	19	1	—	—	—	—	5/18	5/18	—	—
Yalin Li[14]	49	31	—	—	—	—	13/49	11/49	—	—
De Chang[18]	13	1	—	—	—	—	—	—	—	—
Ke Wen[53]	46	1	—	—	—	—	8/46	5/46	—	—
Xi Xu[59]	90	5	5,2	—	—	—	—	—	—	—
Jing Yuan[62]	94	8	—	—	—	—	—	—	—	—
Lu Lin[7]	95	23	17,4	—	17	58/95	—	—	—	—
Rui Zhao[67]	28	—	—	—	—	—	6/28	3/28	—	—
Chan Sun[46]	150	2	—	—	20	—	24/150	15/150	3/150	—
Ye Zhao[8]	106	7	1	0	—	8/106	—	—	—	—
Fang Zheng[68]	161	17	6	—	—	—	13/161	22/161	9/161	—
Xin Tan[47]	13	2	1	1	—	—	—	—	—	—
Dan Li[31]	80	13	—	—	—	—	—	—	—	—
Tianmin Xu[58]	51	5	—	—	—	—	—	—	—	—
Miao Zhu[15]	23	—	—	—	—	2/23	—	—	—	2/23
Jian Wu[10]	280	7	3	—	—	—	—	—	—	7/280
Tianxin Xiang[55]	49	2	—	—	—	—	—	—	—	—
Shuxiang Zhang[65]	34	1	—	1	—	—	—	—	—	—
Na Yao[9]	40	—	—	1	—	7/40	21/40	—	10/40	22/40
Jun Chen[19]	249	8	—	—	—	—	—	—	—	—
Dan Li 2[30]	30	—	—	—	—	5/30	—	—	—	6/30
Xiaochun Dong[23]	135	7	—	—	—	—	—	—	—	—
Kelvin Kai-Wang[29]	23	2	1	—	—	—	4/23	—	—	—
Xi Jin[28]	651	53	10,11	—	—	74/651	—	—	—	64/651
Xiaolong Qi[41]	70	7	—	—	—	—	15/70	5/70	25/70	32/70
Duan Wang[50]	31	3	2	—	—	—	—	—	—	6/27
Chuan Liu[33]	32	—	—	—	—	—	9/32	2/32	—	—
Suxin Wan[49]	135	18	4	—	6	—	—	30/135	—	—
Jing Yuan[16]	223	12	—	—	—	—	42/223	32/223	—	—

(*Continues*)

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 Effenberger[24]	40	22	11,5	—	—	—	—	—	—	—
The COVID-19 Investigation Team[48]	12	1	1	—	—	—	—	—	—	—
Safiya Richardson[43]	5700	—	—	—	—	—	—	3263/5700	—	—
George Cholankeril[22]	116	12	12	10	22	37/116	—	—	—	26/65
Walker D. Redd[42]	318	107	84,49	46	110	195/318	—	—	—	—
Yael R. Nobel[39]	278	56	63	—	—	97/278	—	—	—	—
Mario Fernández-Ruiz[26]	18	4	1	—	—	—	—	—	—	—
Rachael Pung[40]	17	4	1	—	—	—	—	—	—	—
BE Young[61]	18	3	—	—	—	—	—	—	—	—

[†]No. of patients with nausea, No. of patients with vomiting.
[‡]Excluded from the meta-analysis (many patients presented with diarrhea after using oseltamivir and/or abidor).
AST, aspartate aminotransferase; ALT, alanine aminotransaminase; TBil, total bilirubin;

Table 3 Results of meta-analysis (random-effect model)

Characteristics	Studies	Patients	I^2 (%)	Heterogeneity *P*	Pooled rate (%)	95% CI (%)
Digestive symptoms	14	2535	97.6	0.000	31.8	21.0–42.5
Diarrhea	53	8604	90.7	0.000	11.2	9.3–13.1
Nausea and/or vomiting	33	6165	94.4	0.000	10.0	7.6–12.3
Loss of appetite	15	2540	97	0.000	21.3	14.0–28.7
Abdominal pain	14	2203	82.5	0.000	4.6	2.7–6.5
Digestive diseases	9	2107	95.2	0.000	11.2	6.1–16.3
Abnormal liver function	12	1878	97.9	0.000	27.4	16.9–37.9
ALT	23	3973	87.8	0.000	25.3	21.3–29.2
AST	23	9650	98.8	0.000	25.4	16.1–34.6
TBil	9	1975	91.5	0.000	8.8	5.1–12.5
Liver diseases	29	10 839	75	0.000	2.5	1.8–3.3

ALT, alanine aminotransaminase; AST, aspartate aminotransferase; CI, confidence level; 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%, I^2 = 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%, I^2 = 90.7%, heterogeneity P = 0.000) (Fig. S1c), nausea and/or vomiting (33 studies, 6165 patients: 10.0%, 95 CI 7.6–12.3%, I^2 = 94.4%, heterogeneity P = 0.000) (Fig. S1f), loss of appetite (15 studies, 2540 patients: 21.3%, 95 CI 14.0–28.7%, I^2 = 97%, heterogeneity P = 0.000) (Fig. S1d), and abdominal pain (14 studies, 2203 patients: 4.6%, 95 CI 2.7–6.5%, I^2 = 82.5%, heterogeneity P = 0.000) (Fig. S1e). The pooled estimate of digestive disease comorbidities was 11.2% (95 CI 6.1–16.3%, I^2 = 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%, I^2 = 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%, I^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%, I^2 = 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%, I^2 = 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%, I^2 = 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 studies[1,7,8,27,28,42,57,70] 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, I^2 = 31%, heterogeneity P = 0.21, 5 studies, 1992

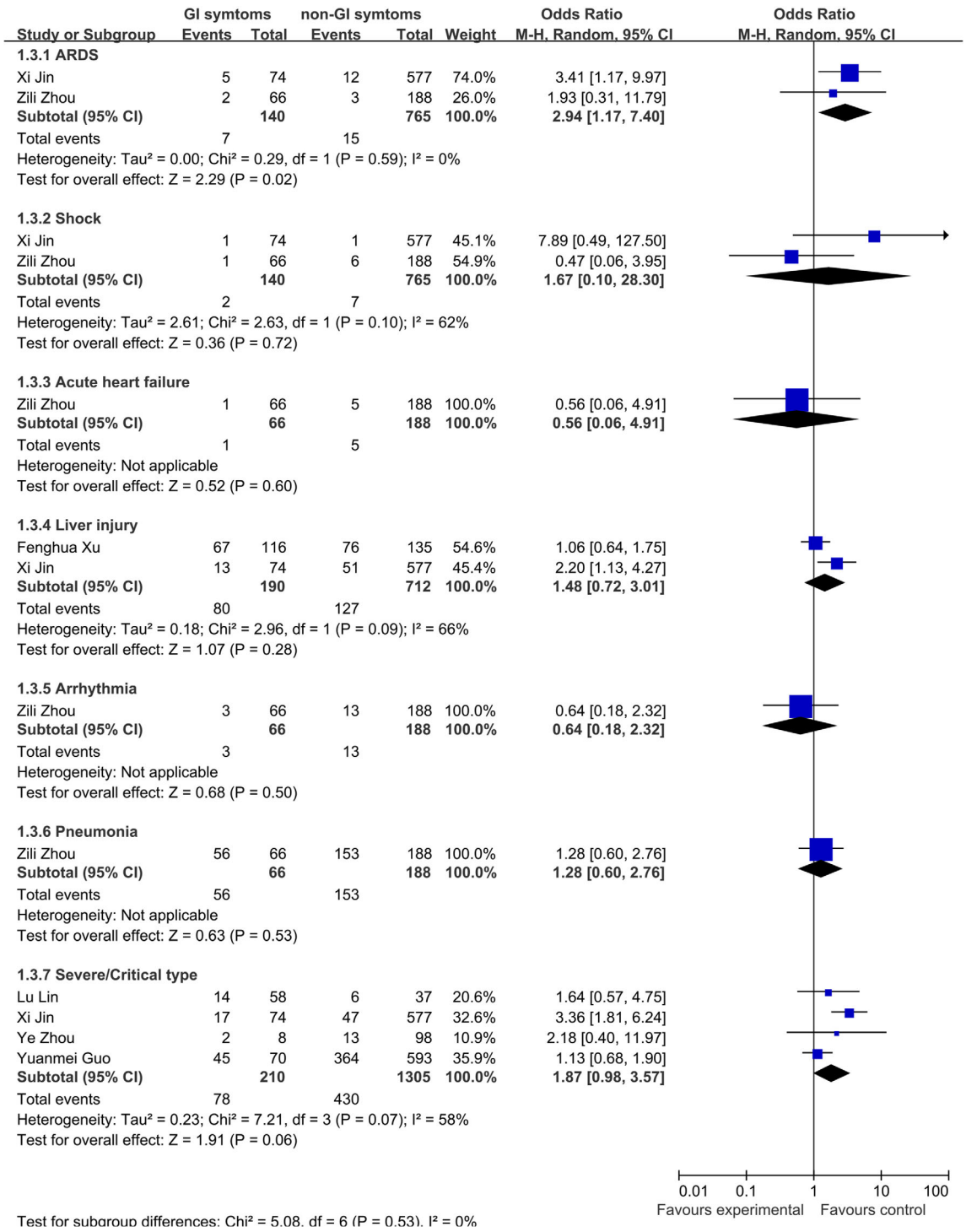

Figure 2 Comparison of complications between COVID-19 patients with and without digestive symptoms.

patients) and myalgia (OR 1.96, 95 CI 1.06–3.65, P = 0.03, I^2 = 69%, heterogeneity P = 0.04, 3 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 studies, 905 patients) (Fig. 2). No difference was found in shock, acute heart

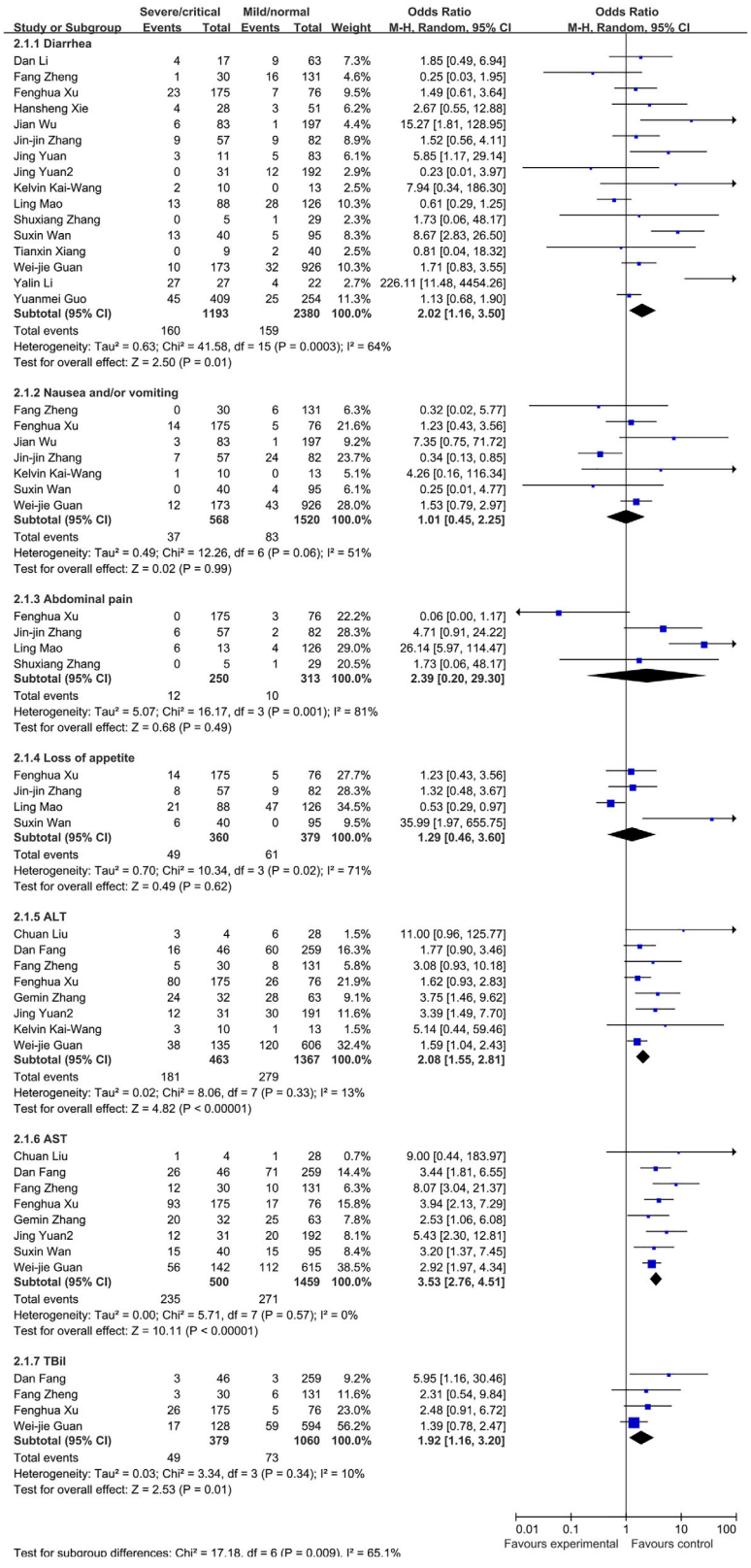

Figure 3 Comparison of normal/mild and severe/critical patients with COVID-19.

failure, arrhythmia, 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, $P = 0.06$, $I^2 = 58\%$, 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, $P = 0.0001$, $I^2 = 0$, 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, $P = 0.01$, $I^2 = 64$, heterogeneity $P = 0.0003$, 16 studies, 3849 patients) and have high ALT (OR 2.08, 95 CI 1.55–2.81, $P < 0.00001$, $I^2 = 13\%$, heterogeneity $P = 0.33$, 8 studies, 1830 patients) and AST (OR 3.53, 95 CI 2.76–4.51, $P < 0.00001$, $I^2 = 0$, 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. 3).

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[71] 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.[72] 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[73] and Huang *et al.*'s study[74] were also included in Zhou *et al.*'s study[69] and Wu *et al.*'s study.[54] We excluded Chen *et al.*'s study[73] and Huang *et al.*'s study[73,74] 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%).[72]

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,[1] 6 patients presented with only digestive symptoms in the absence of respiratory symptoms (one patient even without fever). Luo *et al.*'s[75] study reported that 183 (16%) patients only presented with GI symptoms of the 1141 confirmed COVID-19 cases. Jin *et al.*'s study[28] 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

injury, and ARDS. This might be of great significance to the treatment of COVID-19. Currently, few studies focused on the difference between COVIP-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).[1] 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[74] demonstrated that the rate of elevated AST was 37%, and the rate was up to 62% in severe patients. In a national multicenter study,[2] 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.[2] 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 follow: 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 2008 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.

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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