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Gastrointestinal predictors of severe COVID-19: systematic review and meta-analysis

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Abstract

Background COVID-19 pandemic has created a need to identify potential predictors of severe disease. We performed a systematic review and meta-analysis of gastrointestinal predictors of severe COVID-19.

Methods An extensive literature search was performed using PubMed, Embase, Web of Science and Cochrane. Odds ratio (OR) and mean difference (MD) were calculated for proportional and continuous outcomes using a random-effect model. For each outcome, a 95% confidence interval (CI) and P-value were generated.

Results A total of 83 studies (26912 patients, mean age 43.5±16.4 years, 48.2% female) were included. Gastrointestinal predictors of severe COVID-19 included the presence of diarrhea (OR 1.50, 95%CI 1.10-2.03; P=0.01), elevated serum aspartate aminotransferase (AST) (OR 4.00, 95%CI 3.02-5.28; P<0.001), and elevated serum alanine aminotransferase (ALT) (OR 2.54, 95%CI 1.91-3.37; P<0.001). Significantly higher levels of mean AST (MD 14.78 U/L, 95%CI 11.70-17.86 U/L; P<0.001), ALT (MD 11.87 U/L, 95%CI 9.23-14.52 U/L; P<0.001), and total bilirubin (MD 2.08 mmol/L, 95%CI 1.36-2.80 mmol/L; P<0.001) were observed in the severe COVID-19 group compared to non-severe COVID-19 group.

Conclusion Gastrointestinal symptoms and biomarkers should be assessed early to recognize severe COVID-19.

Keywords SARS-CoV-2, COVID-19, diarrhea, severe COVID-19, predictors

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Introduction

COVID-19, caused by SARS-CoV-2, has become a worldwide pandemic imposing a significant burden on healthcare systems around the globe. The virus causes a variety of manifestations, including pneumonia, acute respiratory distress syndrome, shock, sepsis, and death [1]. Currently, no specific therapy (preventive or therapeutic) is available for this disease [2].

Symptomatically, the virus leads to fever, fatigue, cough, shortness of breath, myalgias, arthralgias, nasal congestion, runny nose, sore throat, nausea/vomiting, and diarrhea [1]. The virus further causes laboratory abnormalities, including derangements of white cell count, platelet count, C-reactive protein, procalcitonin, lactate dehydrogenase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), creatinine, and D-dimer [1]. The pandemic nature of this disease necessitates emergent and early recognition of symptomatic patients to identify those at most severe risk and to provide supportive measures as needed, up to and including mechanical ventilation.

Gastrointestinal parameters (symptoms and laboratory findings) have been reported in the literature among patients with COVID-19 [3], but there is little comprehensive information regarding gastrointestinal symptoms in these patients. We performed a systematic review and meta-analysis

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Conflict of Interest: None

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to evaluate whether gastrointestinal symptoms and abnormal laboratory findings predict disease severity.

Materials and methods

A comprehensive literature search was performed from January 1st, 2020, to May 31st, 2020, using the following databases: PubMed/Medline, Embase, Cochrane, Web of Science. The search strategy, using a predeveloped vocabulary for COVID-19 [4], was created by an experienced librarian (WLS) and crosschecked by another reviewer (MA). An example search strategy using EMBASE is highlighted in Supplementary Table 1. Article screening and data extraction was performed by 2 independent reviewers (MA and HH) and any discrepancies in screening/extraction were resolved through mutual discussion. Interobserver agreement was evaluated using % of agreement and Cohen's Kappa (K) statistic. Articles were selected if they reported data on COVID-19 patients with respect to gastrointestinal symptoms (diarrhea, abdominal pain, and nausea/vomiting) or laboratory findings (serum AST, ALT, or TB). We excluded articles if the data of interest were not reported or the article had not undergone a peer-review process. We further excluded case reports and retrospective studies/case series reporting <10 cases. We used the bibliography of the finalized articles to further broaden our literature search. We did not restrict our search according to language.

Severe COVID-19 was defined as respiratory distress (rate ≥30 /min, oxygen saturation ≤93% at rest and/or PaO_2/FiO_2 ≤300 mmHg) [1], intensive care unit (ICU) admission, and/or death. Laboratory data (mean serum AST, ALT and TB) were reported based on the local laboratory's reference parameters for each study. Symptoms (diarrhea and nausea/vomiting) were reported based on initial presentation.

Statistical analysis

Data extraction was performed using Microsoft Excel (Microsoft, Redmond, Wash, USA). Continuous variables (using mean and standard deviation [SD]) and proportional variables (using event and total patients) were compared using the DerSimonian-Laird approach or a random-effects model. The fixed effect model was used as a sensitivity tool; however, given the presumed heterogeneity of study data from diverse sources and clinical settings, the random-effects model was considered more appropriate and results were reported using that approach [5,6]. The mean and SD were calculated from median and interquartile range where applicable. Results are displayed using forest plots for each summary estimate, i.e., mean difference (MD) and odds ratio (OR) for continuous and proportional variables, respectively. A 95% confidence interval (CI), P-value (<0.05 was considered statistically significant), and study heterogeneity using I^2 statistic (>50% was considered as substantial heterogeneity) were calculated for each outcome [7]. Subgroup analysis was performed based on the definition of severe COVID-19 (respiratory distress, ICU admission, and death) if at least 3 studies reported the outcome. Sensitivity analysis using leave-one-out meta-analysis was performed and point estimates were generated. Meta-regression was attempted to assess the impact of moderator variables on study outcomes. The moderator variables assessed included female proportions in each study, region of study (Asia, Europe, North America, South America), and number of centers in each study (single center, dual center, multicenter). The statistical analysis was performed using Open Meta Analyst (CEBM, University of Oxford, Oxford, United Kingdom) and Comprehensive Meta-Analysis (BioStat, Englewood, NJ, USA).

We utilized the Quality in Prognostic Studies (QUIPS) tool for assessing the risk of bias in the observational studies [8]. Publication bias was assessed qualitatively by visualizing the funnel plot and quantitatively using Egger's regression analysis. We adhered to "preferred reporting items for systematic reviews and meta-analyses (PRISMA)" guidelines for the purposes of this manuscript.

Results

Literature search

Using the search strategy defined above, a total of 1525 records were generated. After the inclusion/exclusion criteria had been applied, a total of 83 published studies (all observational) remained that reported data on gastrointestinal symptoms and/or laboratory findings (Fig. 1) [1,3,9-89]. All studies included laboratory-confirmed COVID-19 patients. The percentage of agreement was >90% for both screening and data extraction and corresponding K values of 0.72 and 0.69 (substantial agreement), respectively, were noted. Of the 83 included studies, 42 reported data on disease severity with respect to symptoms and/or lab findings.

Characteristics of the included studies

Study details and demographics of included patients are highlighted in Table 1. Based on region, 70 studies originated from Asia, 8 from North America, 1 from South America, and 4 from Europe. The study duration was from December 11th through May 5th, 2020. Based on the number of centers reporting data, 17 studies were multicenter, 6 were dual-center, 57 were single-center, and 3 studies failed to mention the center from where the data originated. A total of 26,912 patients were included across these 83 studies. The patients' mean age was 43.5±16.4 years and the female proportion was 48.2%.

Table 1 Study characteristics and baseline demographic data for included patients

Study, year	Hospital (single, dual, multicenter)	Region	Language	Study period	Total patients, N	Mean/ Median age, n	Female sex, N (%)	Severe disease[a], N
Guan, 2020 [1]	Multi	Asia	English	Dec 11 - Jan 29	1099	47	459 (41.9%)	173
Wang, 2020 [9]	Single	Asia	English	Jan 1 - Feb 3	138	56	63 (45.7%)	36
Huang, 2020 [10]	Single	Asia	English	Dec 16 - Jan 2	41	49	11 (26.8%)	13
Chen, 2020 [11]	Single	Asia	English	Jan 1 - Jan 20	99	55.5	32 (32.3%)	23
Chen, 2020 [3]	Single	Asia	English	Jan 13 - Feb 28	799	-	-	113
Liu, 2020 [12]	Single	Asia	English	Jan 11 - Jan 21	12	58.9	4 (33.3%)	6
Liu, 2020 [13]	Multi	Asia	English	Dec 30 - Jan 24	137	57	76 (55.5%)	34
Wu, 2020 [14]	Multi	Asia	English	Jan 22 - Feb 14	80	46.1	41 (51.3%)	3
Wu, 2020 [15]	-	Asia	Chinese	Jan 19 - Jan 25	40	-	27 (67.5%)	13
Xu, 2020 [16]	Multi	Asia	English	Jan 10 - Jan 26	62	41	27 (43.5%)	2
Luo, 2020 [17]	Single	Asia	English	Jan 1 - Feb 20	1141	-	-	-
Chen, 2020 [18]	Single	Asia	English	Dec - Jan 27	21	56	4 (19.0%)	11
Lei, 2020 [19]	Single	Asia	Chinese	Jan 14 - Jan 29	29	56	8 (27.6%)	-
Jin, 2020 [20]	Multi	Asia	English	Jan 17 - Feb 8	651	45.2	320 (49.2%)	64
Mo, 2020 [21]	Single	Asia	English	Jan 1 - Feb 5	155	54	69 (44.5%)	92
Wan, 2020 [22]	Single	Asia	English	Jan 23 - Feb 8	135	47	63 (46.7%)	40
Xiao, 2020 [23]	Single	Asia	English	Feb 1 - Feb 14	73	43	32 (43.8%)	-
Yao, 2020 [24]	Single	Asia	Chinese	Jan 21 - Feb 21	40	-	15 (37.5%)	17
Young, 2020 [25]	Multi	Asia	English	Jan 23 - Feb 3	18	47	9 (50.0%)	2
Zhang, 2020 [26]	Single	Asia	English	Jan 16 - Feb 25	95	49	42 (44.2%)	32
Zhang, 2020 [27]	Single	Asia	English	Jan 16 - Feb 3	140	57	69 (49.3%)	58
Zhang, 2020 [28]	Multi	Asia	English	Jan 17 - Feb 8	645	45.3	317 (49.1%)	-
Zhou, 2020 [29]	-	Asia	English	Dec 20 - Feb 9	254	50.6	139 (54.7%)	-
Zhao, 2020 [30]	Dual	Asia	English	Jan 23 - Feb 5	19	48	8 (42.1%)	2
Shi, 2020 [31]	Single	Asia	English	Dec 20 - Jan 23	81	49.5	39 (48.1%)	-
Liu. 2020 [32]	Multi	Asia	Chinese	Jan 23 - Feb 8	32	38.5	12 (37.5%)	4
Liu. 2020 [33]	Single	Asia	Chinese	Jan 10 - Jan 31	30	35	20 (66.7%)	4
Liu. 2020 [34]	Multi	Asia	English	Dec 30 - Jan 15	78	38	39 (50.0%)	11
Zhang, 2020 [35]	Single	Asia	English	Jan 18 - Feb 22	115	49.52	66 (57.4%)	31
Zhou, 2020 [36]	Single	Asia	English	Jan 28 - Feb 6	17	41.7	11 (64.7%)	5
Han, 2020 [37]	Single	Asia	English	Jan 4 - Feb 3	108	45	70 (64.8%)	-
Peng, 2020 [38]	Single	Asia	English	Jan 20 - Feb 15	112	62	59 (52.7%)	16
Shi, 2020 [39]	Single	Asia	English	Jan 20 - Feb 10	416	64	211 (50.7%)	-
Wang, 2020 [40]	Single	Asia	English	Jan 16 - Jan 29	69	42	37 (53.6%)	14
Xie, 2020 [41]	Single	Asia	English	Feb 2 - Feb 23	79	60	44 (55.7%)	28
Cai, 2020 [42]	Single	Asia	English	Jan 11 - Feb 6	298	47.5	153 (51.3%)	58
Gao, 2020 [43]	Single	Asia	English	Jan 23 - Feb 2	43	43.74	17 (39.5%)	15
Zhou, 2020 [44]	Dual	Asia	English	Dec 29 - Jan 31	191	56	72 (37.7%)	54
Bonetti, 2020 [45]	Single	Europe	English	Mar 1 - Mar 30	144	69.8	49 (34.0%)	70
Buscarini, 2020 [46]	Single	Europe	English	Feb 21 - Mar 13	411	-	-	112
Cai, 2020 [47]	Single	Asia	English	Jan 11 - Feb 21	318	-	-	85
Chen, 2020 [48]	Single	Asia	English	Jan 1 - Mar 11	145	47.5	66 (45.5%)	43

(*Contd...*)

Table 1 (*Continued*)

Study, year	Hospital (single, dual, multicenter)	Region	Language	Study period	Total patients, N	Mean/ Median age, n	Female sex, N (%)	Severe disease[a], N
Chen, 2020 [49]	Single	N. America	English	Mar 9 - Apr 15	101	48.3	60 (59.4%)	3
Cholankeril, 2020 [50]	Single	N. America	English	Mar 4 - Mar 24	116	50	54 (46.6%)	-
Diaz, 2020 [51]	Dual	S. America	English	Through Apr 11	7016	40	3508 (50.0%)	439
Duan, 2020 [52]	Dual	Asia	English	Jan 1 - Feb 29	348	44.8	164 (47.1%)	20
Fan, 2020 [53]	Single	Asia	English	Jan 20 - Jan 31	148	50	75 (50.7%)	10
Hajifathalian, 2020 [54]	Dual	N. America	English	Mar 4 - Apr 9	1059	61	448 (42.3%)	-
Han, 2020 [55]	Single	Asia	English	Feb 13 - Feb 29	206	62.5	115 (55.8%)	-
He, 2020 [56]	Single	Asia	English	Jan 10 - Feb 13	204	49	125 (61.3%)	69
Hong, 2020 [57]	Single	Asia	English	Through Mar 29	98	55.4	60 (61.2%)	13
Kaafarani, 2020 [58]	Single	N. America	English	Mar 13 - Apr 12	141	57	49 (34.8%)	141
Kim, 2020 [59]	Multi	Asia	English	Through Feb 17	28	42.6	13 (46.4%)	-
Klopfenstein, 2020 [60]	Single	Europe	English	Mar 1 - Mar 17	114	-	-	-
Kluytmans-van den Bergh, 2020 [61]	Dual	Europe	English	Mar 7 - Mar 12	86	49	71 (82.6%)	-
Lian, 2020 [62]	Multi	Asia	English	Jan 17 - Jan 31	465	45	222 (47.7%)	49
Lin, 2020 [63]	Single	Asia	English	Jan 17 - Feb 15	95	45.3	50 (52.6%)	20
Liu, 2020 [64]	Multi	Asia	English	Jan 21 - Apr 6	373	-	198 (53.1%)	-
Liu, 2020 [65]	Single	Asia	English	Jan 17 - Feb 11	85	43	48 (56.5%)	7
Meng, 2020 [66]	Single	Asia	English	Jan 16 - Feb 4	168	56.7	82 (48.8%)	168
Nobel, 2020 [67]	Multi	N. America	English	Mar 10 - Mar 21	278	55.6	133 (47.8%)	44
Palaiodimos, 2020 [68]	Single	N. America	English	Mar 9 - Apr 12	200	62.8	102 (51.0%)	-
Pan, 2020 [69]	Multi	Asia	English	Jan 18 - Feb 28	204	52.9	97 (47.5%)	37
Phipps, 2020 [70]	Multi	N. America	English	Mar 8 - Apr 14	2273	64.5	976 (42.9%)	-
Redd, 2020 [71]	Multi	N. America	English	Through Apr 2	318	63.4	144 (45.3%)	-
Remes-Troche, 2020 [72]	Single	N. America	English	Apr 1 - May 5	112	43.7	31 (27.7%)	5
Shang, 2020 [73]		Asia	English	Jan 10 - Mar 3	307	45	143 (46.6%)	0
Sun, 2020 [74]	Single	Asia	English	Through Apr 11	63	47	26 (41.3%)	19
Wan, 2020 [75]	Multi	Asia	English	Jan 19 - Mar 6	230	48	101 (43.9%)	61
Wang, 2020 [76]	Single	Asia	English	Jan 10 - Feb 28	85	59.4	40 (47.1%)	39
Wang, 2020 [77]	Single	Asia	English	Jan 29 - Feb 22	28	68.6	7 (25.0%)	14
Wang, 2020 [78]	Single	Asia	English	Jan 7 - Feb 11	296	47.3	156 (52.7%)	19
Wang, 2020 [79]	Single	Asia	English	Jan 20 - Feb 18	125	38.7	54 (43.2%)	25
Wang, 2020 [80]	Single	Asia	English	Feb 7 - Feb 12	1012	49.2	488 (48.2%)	100
Wei, 2020 [81]	Single	Asia	English	Jan 19 - Feb 7	84	43	56 (66.7%)	-
Yan, 2020 [82]	Single	Asia	English	Jan 10 - Feb 24	193	62.5	79 (40.9%)	193
Yang, 2020 [83]	Single	Asia	English	Jan 30 - Feb 8	200	55	102 (51.0%)	29
Zhang, 2020 [84]	Single	Asia	English	Jan 2 - Feb 10	221	43.5	113 (51.1%)	55
Zhang, 2020 [85]	Single	Asia	English	Jan 11 - Feb 6	663	56	342 (51.6%)	409
Zhang, 2020 [86]	Single	Asia	English	Jan 18 - Feb 22	115	49.5	66 (57.4%)	31
Zhao, 2020 [87]	Single	Asia	English	Jan 16 - Feb 10	91	46	42 (46.2%)	30
Zheng, 2020 [88]	Single	Asia	English	Jan 16 - Feb 20	99	49.4	48 (48.5%)	32
Zhou, 2020 [89]	Single	Asia	English	Dec 20 - Feb 9	254	50	139 (54.7%)	-

[a]Severe disease was defined as respiratory distress (rate ≥30/min, oxygen saturation ≤93% at rest and/or PaO_2/FiO_2 ≤300 mmHg), intensive care unit admission and/or death

N, total patients; n, mean/median

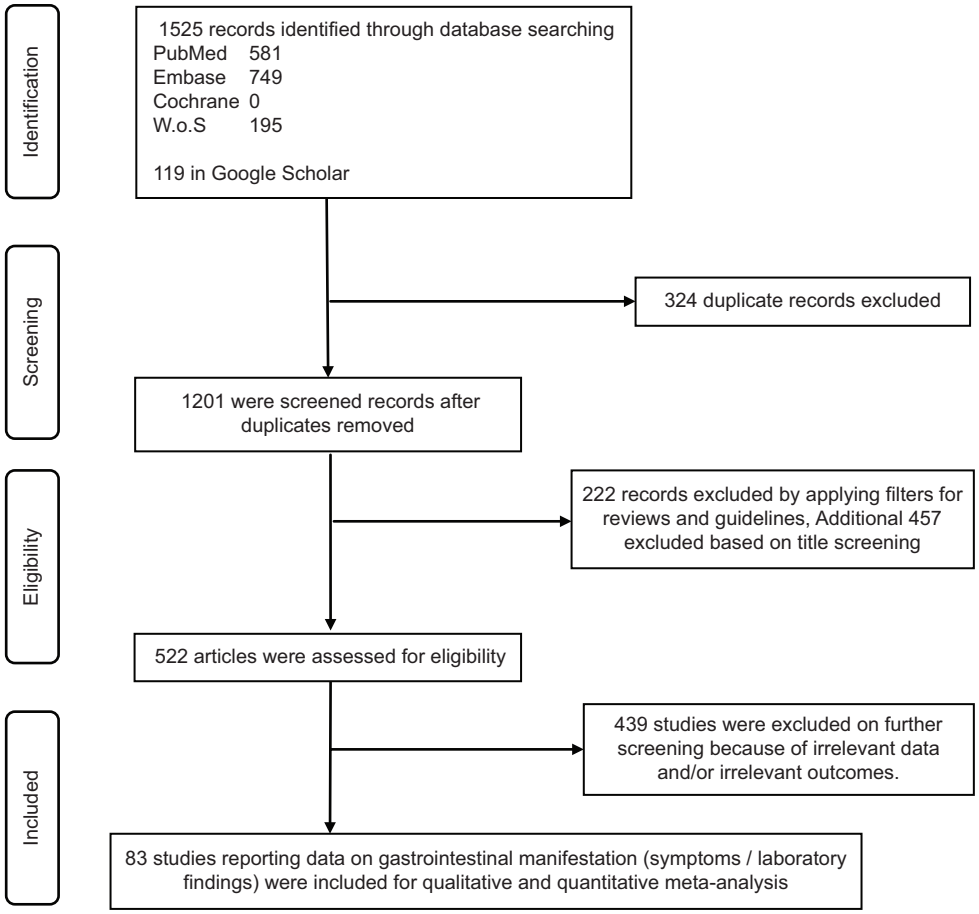

Figure 1 PRISMA diagram

Prevalence of gastrointestinal parameters on admission

Symptoms

The overall prevalence of diarrhea on admission among the study population was 13.0% (95%CI 10.8-15.5%; I^2=95.1%). Based on region, the following prevalences were noted: Europe 16.8% (95%CI 2.9-57.8%; I^2=98.0%), North America 26.2% (95%CI 20.1-33.3%; I^2=90.6%), and Asia 11.5% (95%CI 9.5-13.9%; I^2=91.8%). The overall prevalence of nausea/vomiting on admission among the study population was 9.5% (95%CI 7.9-11.4%; I^2=92.6%). Based on region, the following prevalences were noted: Europe 8.9% (95%CI 2.1-30.4%; I^2=94.1%), North America 18.7% (95%CI 14.6-23.6%; I^2=83.9%), and Asia 7.7% (95%CI 5.9-9.9%; I^2=91.6%).

Laboratory abnormalities

The prevalence of abnormal AST findings on admission was 27.1% (95%CI 21.7-33.2%; I^2=95.9%). Based on region, the following prevalences were noted: North America 46.3% (95%CI 27.7-66.0%; I^2=96.6%), and Asia 26.3% (95%CI 22.1-31.0%; I^2=89.3%). The prevalence of abnormal ALT findings on admission was 22.3% (95%CI 18.4-26.7%; I^2=92.3%). Based on region, the following prevalences were noted: North America 21.4% (95%CI 16.5-27.4%; I^2=69.1%), and Asia 22.1% (95%CI 17.4-27.6%; I^2=92.7%). The prevalence of abnormal TB levels on admission was 10.6% (95%CI 5.0-21.0%; I^2= 97.1%). All studies that reported abnormal TB were from Asia.

Gastrointestinal predictors of severe COVID-19

Symptoms

The odds of patients with diarrhea having severe disease were significantly greater compared to those without diarrhea (26 studies, OR 1.50, 95%CI 1.10-2.03; P=0.01; I^2=54.1%) (Fig. 2A). Leave-one-out meta-analysis demonstrated consistent results, with a point estimate (OR) ranging between 1.46-1.74. A subgroup analysis of 17 studies that defined disease severity in terms of respiratory distress also showed consistent results (OR 1.62, 95%CI 1.11-2.37; P=0.01; I^2=54.1%). Subgroup analysis based on ICU admission (5 studies) did not demonstrate increased odds of severe disease (OR 1.39, 95%CI 0.70-2.73; P=0.35; I^2=27.1%). Meta-regression did not demonstrate any significant moderating impact of female proportion (P=0.39) or the number of centers involved in the study (P=0.89).

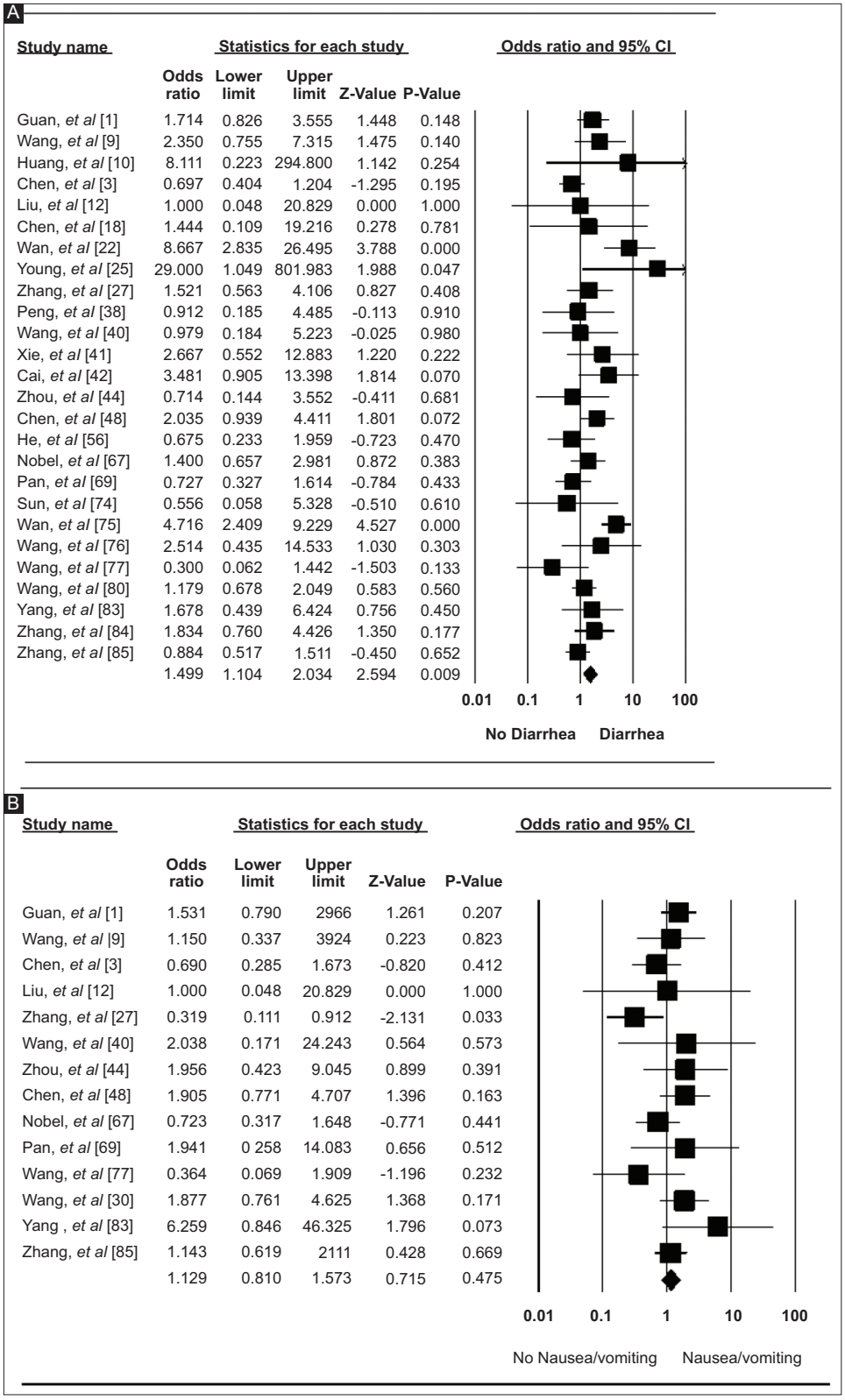

Figure 2 Forest plot demonstrating (A) severe disease in diarrhea vs. no diarrhea, and (B) severe disease in nausea/vomiting vs. no nausea/vomiting

Fourteen studies evaluated nausea/vomiting and disease severity and no significant association was found (OR 1.13, 95%CI 0.81-1.57; P=0.48; I^2=22.6%) (Fig. 2B). Consistent results were obtained on leave-one-out meta-analysis

(OR 1.07-1.24). The subgroup analysis also did not demonstrate a significant association when severity was classified on the basis of respiratory distress (8 studies, OR 1.27, 95%CI 0.84-1.90; P=0.26; I^2=21.2%) or ICU admission (4 studies, OR 0.98, 95%CI 0.41-2.35; P=0.97; I^2=42.1%). Meta-regression did not reveal any moderating impact of variables on outcomes, i.e., female proportion (P=0.20), region of study (P=0.19), or number of centers (P=0.33).

Laboratory abnormalities

Elevated serum AST levels in patients were evaluated in 16 studies and greater odds of disease severity were noted compared to patients without elevated AST (OR 4.00, 95%CI 3.02-5.28; P<0.001; I^2=40.4%) (Fig. 3A). The results were consistent on leave-one-out meta-analysis (OR 3.64-4.14) as well as subgroup analysis for disease severity defined based on respiratory distress (11 studies, OR 3.80, 95%CI 2.77-5.22; P<0.001; I^2=38.7%), and ICU admission (3 studies, OR 5.69, 95%CI 2.01-16.09; P=0.001; I^2=45.8%). On meta-regression, the proportion of females in the study inversely correlated with the odds of having greater disease severity (P=0.04).

Elevated serum ALT levels on admission were evaluated in 14 studies and greater odds of disease severity were noted compared to patients with normal ALT (OR 2.54, 95%CI 1.91-3.37; P<0.001; I^2=39.3%) (Fig. 3B). Similar results were obtained using leave-one-out meta-analysis (OR 2.28-2.73) and subgroup analysis for disease severity based on respiratory distress (9 studies, OR 2.93, 95%CI 1.92-4.48; P<0.001; I^2=55.9%). No significant moderating impact of female proportion (P=0.35) or number of centers (P=0.24) was noted.

Only 5 studies evaluated elevated serum TB levels in association with disease severity, and elevated TB was associated with severe disease (OR 2.09, 95%CI 1.36-3.21; P=0.001; I^2=17.5%) (Fig. 3C). Leave-one-out meta-analysis demonstrated a consistent association (OR 1.89-2.51). A subgroup analysis and meta-regression were not possible because of the low number of studies.

Mean laboratory findings and severe COVID-19

The mean serum AST level was significantly higher in the severe group compared to the non-severe group (32 studies, MD 14.78 U/L, 95%CI 11.70-17.86 U/L; P<0.001; I^2=97.5%) (Fig. 4A). The leave-one-out meta-analysis was consistent with a point estimate (MD) ranging from 13.70-15.32 U/L. Subgroup analysis was performed on the basis of severity and significantly higher mean AST levels were noted for the severe group, defined in terms of ICU admission (5 studies, MD 20.49 U/L, 95%CI 7.60-33.39 U/L; P=0.002; I^2=98.03%), death (4 studies, MD 18.01 U/L; 95%CI 13.62-22.41 U/L; P<0.001; I^2=93.7%), and respiratory distress (20 studies, MD 13.60 U/L, 95%CI 9.95-17.24 U/L; P<0.001; I^2=96.9%). Meta-regression did not reveal any moderating impact of region of study (P=0.89) or number of centers (P=0.94).

The mean serum ALT level was also significantly higher for the severe group compared to the non-severe group (31 studies, MD 11.87 U/L, 95%CI 9.23-14.51 U/L; P<0.001; I^2=95.5%) (Fig. 4B). The results were consistent on leave-one-out meta-analysis (MD 11.14-12.61 U/L) and subgroup analysis for severity based on respiratory distress (20 studies, MD 13.01 U/L, 95%CI 8.84-17.17 U/L; P<0.001; I^2=96.7%), ICU admission (5 studies, MD 14.78 U/L, 95%CI 9.20-20.37 U/L; P<0.001; I^2 = 83.7%), and death (3 studies, MD 6.56 U/L, 95%CI 3.00-10.13 U/L; P<0.001; I^2=89.3%). On meta-regression, female proportions were inversely correlated with disease severity on the basis of mean ALT level (P=0.04).

The mean serum TB level was evaluated in 26 studies and a significantly higher level was found in severe COVID-19 patients compared to the non-severe group (MD 2.08 mmol/L, 95%CI 1.36-2.80 mmol/L; P<0.001; I^2=94.2%) (Fig. 4C). Consistent results were obtained using leave-one-out meta-analysis (MD 1.89-2.15 mmol/L) and subgroup analysis based on the severity criteria of ICU admission (5 studies, MD 2.91 mmol/L, 95%CI 1.24-4.58 mmol/L; P=0.001; I^2=95.7%), death (3 studies, MD 2.92 mmol/L, 95%CI 1.20-4.64 mmol/L; P<0.001; I^2=94.6%), and respiratory distress (14 studies, MD 1.62 mmol/L, 95%CI 0.92-2.33 mmol/L; P<0.001; I^2=80.7%). On meta-regression, female proportions were inversely correlated with disease severity on the basis of mean TB level (P=0.03).

Risk of bias

Based on QUIPS tools, most of the studies (n=63) were at risk of bias for failing to account for confounders, while the remaining (n=20) accounted for some confounders. Twenty studies lacked details of the statistical design (Supplementary Table 2). Visible asymmetry was observed on a funnel plot based on the symptom of diarrhea; however, Egger's regression did not reveal a significant publication bias (P=0.76) (Supplementary Fig. 1).

Discussion

Our meta-analysis demonstrated significant correlations between gastrointestinal parameters (diarrhea, elevated serum ALT, AST and TB) and severe disease outcomes, i.e., respiratory distress, ICU admission, and/or death. Although the most frequent manifestation of COVID-19 is pneumonia, gastrointestinal signs/symptoms are seen in a significant number of patients and can be the presenting manifestations of the disease [90]. A systematic review by Cheung *et al* reported diarrhea and nausea/vomiting in 13% and 10% of COVID-19 patients, respectively [91]. We demonstrated a similar prevalence of diarrhea (13%) and nausea/vomiting (9.5%). We believe that the reported prevalence of diarrhea and nausea/vomiting is somewhat lower than in reality, as some of these patients only present with these symptoms and may not

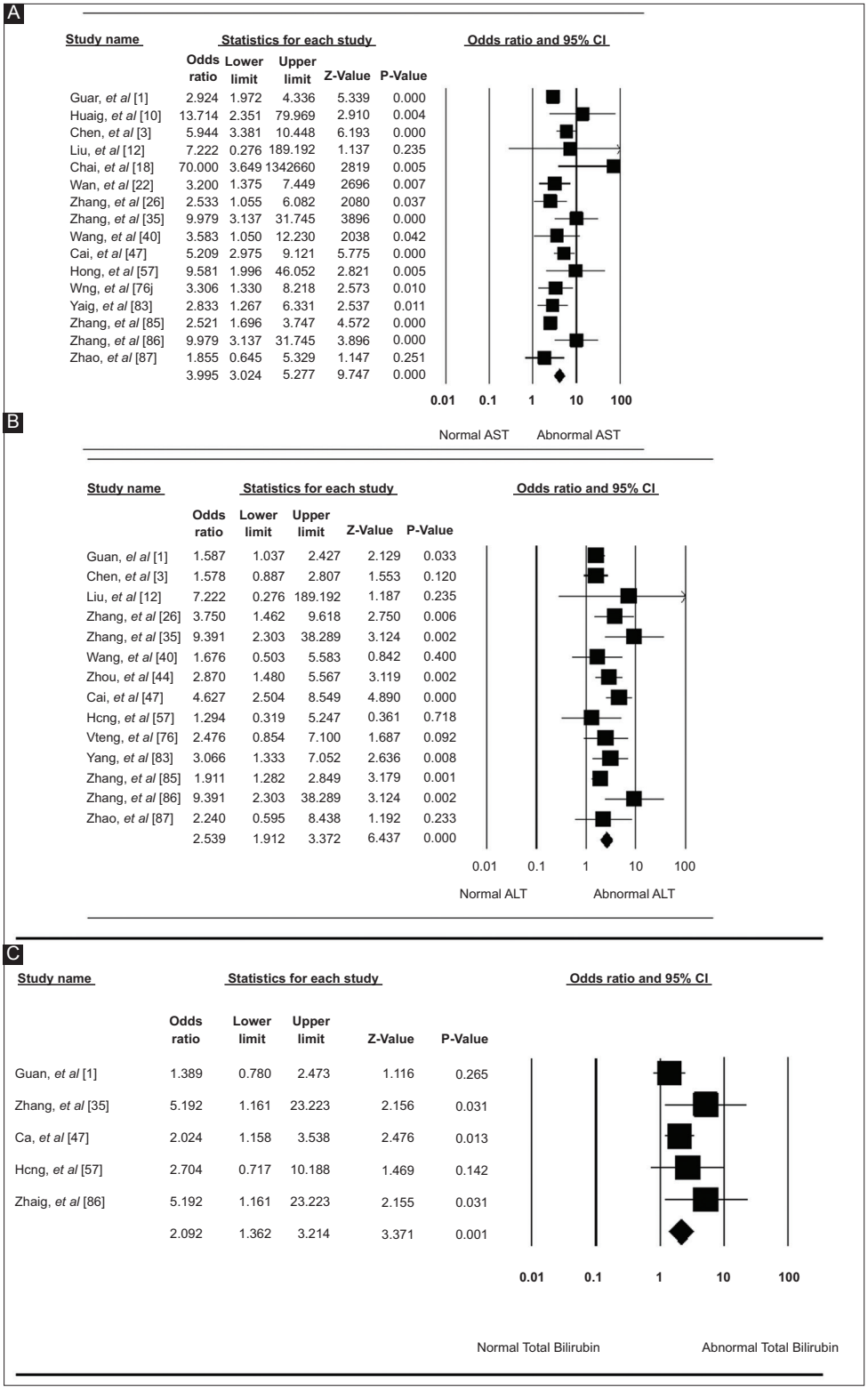

Figure 3 Forest plot demonstrating (A) severe disease in elevated AST vs, normal AST, (B) severe disease in elevated ALT vs. normal ALT, and (C) severe disease in elevated TB vs. normal TB
AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin

undergo COVID-19 testing because they do not fulfill local hospital or laboratory criteria.

The mechanism behind gastrointestinal symptoms is thought to be secondary to viral attachment and entry via angiotensin-

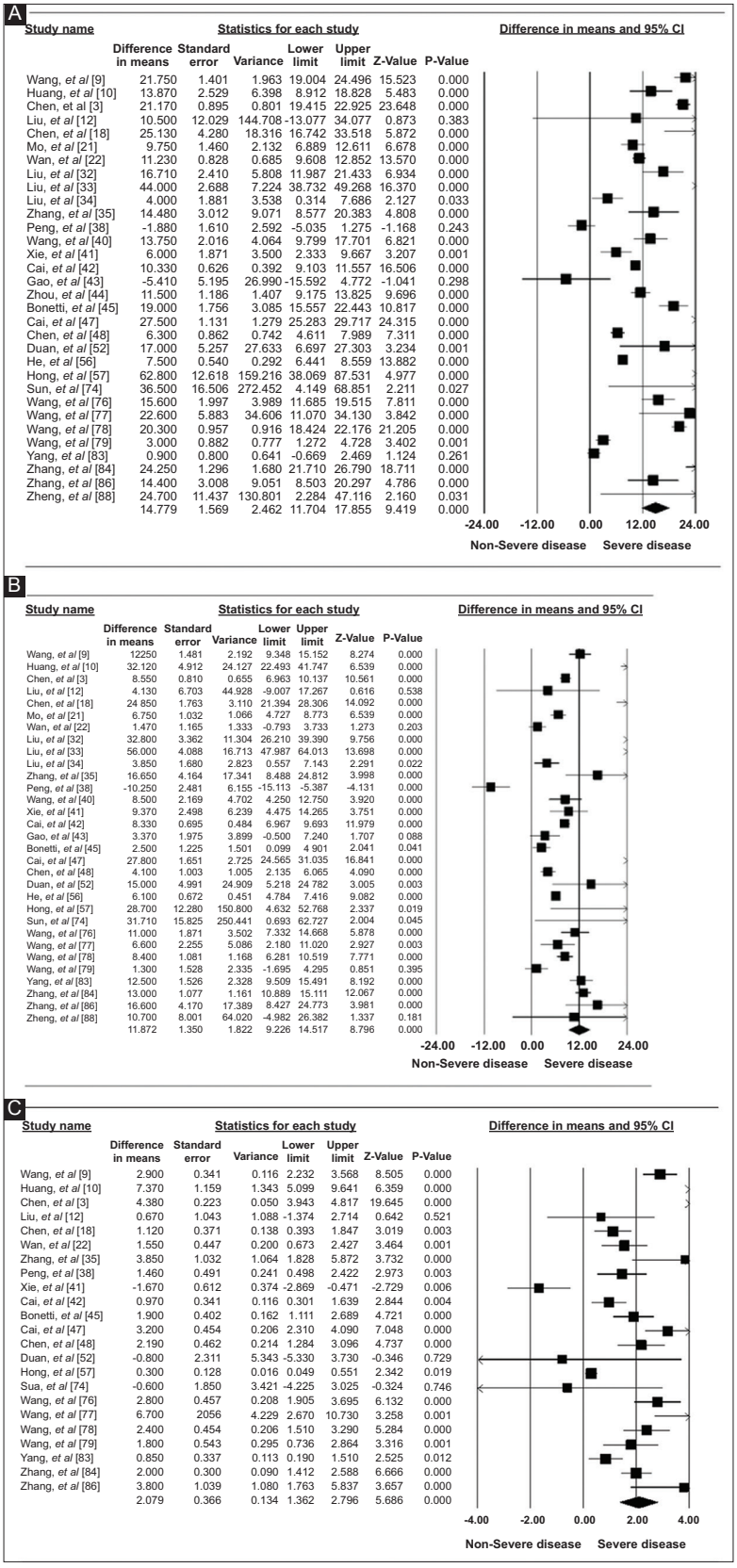

Figure 4 Forest plot demonstrating (A) mean serum AST in severe vs. non-severe disease, (B) mean serum ALT in severe vs. non-severe disease, and (C) mean serum TB in severe vs. non-severe disease

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TB, total bilirubin

Table 2 Admission symptoms and laboratory findings on admission

Study, year	Symptoms, n (%)		Laboratory Findings, n (%)			Laboratory findings, mean (SD)					
	Diarrhea	Nausea/ Vomiting	Abnormal AST	Abnormal ALT	Abnormal TB	AST U/L		ALT U/L		TB mmol/L	
						Severe	Non-severe	Severe	Non-severe	Severe	Non-severe
Guan, 2020 [1]	42 (3.8%)	55 (5.0%)	168 (22.2%)	158 (21.3%)	76 (10.5%)	-	-	-	-	-	-
Wang, 2020 [9]	14 (10.1%)	14 (10.1%)	-	-	-	51 (11.55)	29.25 (4.91)	36.5 (10.97)	24.25 (6.07)	12.8 (2.63)	9.9 (1.33)
Huang, 2020 [10]	1 (2.4%)	-	15 (36.6%)	-	-	47 (11.56)	33.13 (4.76)	60.5 (24.84)	28.38 (5.93)	18.2 (6.09)	10.83 (0.86)
Chen, 2020 [11]	2 (2.0%)	1 (1.0%)	35 (35.4%)	28 (28.3%)	18 (18.2%)	-	-	-	-	-	-
Chen, 2020 [3]	-	-	-	60 (21.9%)	-	47 (10.4)	25.83 (3.84)	30.25 (8.39)	21.7 (4.97)	12.83 (2.12)	8.45 (1.57)
Liu, 2020 [12]	2 (16.7%)	2 (16.7%)	2 (16.7%)	2 (16.7%)	0 (0%)	45.3 (29.1)	34.8 (4.63)	33.68 (15.39)	29.55 (5.72)	9.27 (1.73)	8.6 (1.88)
Liu, 2020 [13]	11 (8.0%)	-	-	-	-	-	-	-	-	-	-
Wu, 2020 [14]	1 (1.3%)	1 (1.3%)	3 (3.8%)	3 (3.8%)	1 (12.5%)	-	-	-	-	-	-
Wu, 2020 [15]	6 (15.0%)	3 (7.5%)	-	-	-	-	-	-	-	-	-
Xu, 2020 [16]	3 (4.8%)	-	10 (16.1%)	-	-	-	-	-	-	-	-
Luo, 2020 [17]	68 (6.0%)	253 (22.2%)	-	-	-	-	-	-	-	-	-
Chen, 2020 [18]	4 (20.0%)	-	6 (28.6%)	-	-	49.13 (13.43)	24 (1.46)	41.63 (5.05)	16.78 (2.46)	9 (0.78)	7.88 (0.92)
Lei, 2020 [19]	4 (12.8%)	-	7 (24.1%)	5 (17.2%)	1 (3.4%)	-	-	-	-	-	-
Jin, 2020 [20]	56 (8.6%)	28 (4.3%)	-	-	-	-	-	-	-	-	-
Mo, 2020 [21]	7 (4.5%)	6 (3.9%)	-	-	-	41 (34.28)	31.25 (4.33)	28.75 (7.22)	22 (5.22)	-	-
Wan, 2020 [22]	18 (13.3%)	-	30 (22.2%)	-	-	34.28 (5.24)	23.05 (3.93)	25.25 (5.41)	23.78 (6.4)	10.75 (2.26)	9.2 (2.42)
Xiao, 2020 [23]	26 (35.6%)	-	-	-	-	-	-	-	-	-	-
Yao, 2020 [24]	3 (7.5%)	3 (7.5%)	16 (40.0%)	21 (52.5%)	10 (25.0%)	-	-	-	-	-	-
Young, 2020 [25]	4 (22.2%)	4 (22.2%)	3 (16.7%)	3 (16.7%)	-	-	-	-	-	-	-
Zhang, 2020 [26]	-	-	45 (47.4%)	52 (54.7%)	-	-	-	-	-	-	-
Zhang, 2020 [27]	18 (12.9%)	24 (17.1%)	-	-	-	-	-	-	-	-	-
Zhang, 2020 [28]	53 (8.2%)	22 (3.4%)	-	-	-	-	-	-	-	-	-
Zhou, 2020 [29]	46 (18.1%)	21 (8.3%)	-	-	-	-	-	-	-	-	-
Zhao, 2020 [30]	1 (5.3%)	-	5 (27.8%)	5 (27.8%)	-	-	-	-	-	-	-
Shi, 2020 [31]	3 (3.7%)	4 (4.9%)	43 (53.1%)	-	-	-	-	-	-	-	-
Liu. 2020 [32]	-	-	-	-	-	39.83 (12.59)	23.12 (2.23)	57.57 (8.07)	24.77 (6.06)	-	-

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Table 2 (*Continued*)

Study, year	Symptoms, n (%)		Laboratory Findings, n (%)			Laboratory findings, mean (SD)					
	Diarrhea	Nausea/ Vomiting	Abnormal AST	Abnormal ALT	Abnormal TB	AST U/L		ALT U/L		TB mmol/L	
						Severe	Non-severe	Severe	Non-severe	Severe	Non-severe
Liu. 2020 [33]	-	-	-	-	-	64 (11.55)	20 (3.47)	74 (19.05)	18 (4.62)	-	-
Liu. 2020 [34]	-	-	-	-	-	25.2 (9.71)	21.2 (4.92)	23.15 (8.69)	19.3 (4.36)	-	-
Zhang, 2020 [35]	-	-	-	-	-	38.87 (22.55)	24.39 (9.79)	37.87 (32.17)	21.22 (12.67)	14.12 (6.37)	10.27 (4.26)
Zhou, 2020 [36]	0 (0%)	-	-	-	-	-	-	-	-	-	-
Han, 2020 [37]	15 (13.9%)	-	-	-	-	-	-	-	-	-	-
Peng, 2020 [38]	-	-	-	-	-	29.75 (4.05)	31.63 (6.21)	24.63 (5.06)	34.88 (9.68)	13.04 (2.1)	11.58 (1.77)
Shi, 2020 [39]	16 (3.8%)	-	-	-	-	-	-	-	-	-	-
Wang, 2020 [40]	10 (14.5%)	3 (4.3%)	19 (27.5%)	23 (33.3%)	-	41.75 (10.98)	28 (5.22)	34.5 (8.39)	26 (6.94)	-	-
Xie, 2020 [41]	7 (8.9%)	-	-	-	-	37.5 (8.7)	31.5 (7.52)	40.5 (15.6)	31.13 (6.5)	12.23 (2.09)	13.9 (2.84)
Cai, 2020 [42]	9 (3.0%)	-	-	-	-	37.08 (5.87)	26.75 (3.8)	28.63 (6.01)	20.3 (4.4)	12.3 (2.88)	11.33 (2.18)
Gao, 2020 [43]	-	-	-	-	-	27.8 (11.42)	33.21 (18.24)	29 (5.79)	25.63 (6.36)	-	-
Zhou, 2020 [44]	9 (4.7%)	7 (3.7%)	-	59 (31.2%)	-	38.75 (7.78)	27.25 (7.22)	-	-	-	-
Bonetti, 2020 [45]	-	-	-	-	-	62.5 (11.26)	43.5 (9.8)	35 (7.5)	32.5 (7.2)	12.9 (3.1)	11 (1.5)
Buscarini, 2020 [46]	15 (3.6%)	18 (4.4%)	-	-	-	-	-	-	-	-	-
Cai, 2020 [47]	-	-	150 (47.2%)	187 (58.8%)	204 (64.2%)	62.5 (15)	35 (5.2)	70.3 (15.3)	42.5 (12.1)	22.5 (2.9)	19.3 (3.8)
Chen, 2020 [48]	39 (26.9%)	24 (16.6%)	-	-	-	30.3 (7.2)	24 (3.2)	25.5 (6.4)	21.4 (5.1)	15 (2.4)	12.8 (2.6)
Chen, 2020 [49]	51 (50.5%)	30 (29.7%)	-	-	-	-	-	-	-	-	-
Cholankeril, 2020 [50]	12 (10.3%)	12 (10.3%)	-	-	-	-	-	-	-	-	-
Diaz, 2020 [51]	512 (7.3%)	-	-	-	-	-	-	-	-	-	-
Duan, 2020 [52]	-	-	-	-	-	45 (34)	28 (22)	43 (31)	28 (21)	13.4 (6.6)	14.2 (10.2)
Fan, 2020 [53]	-	-	32 (21.6%)	27 (18.2%)	9 (6.1%)	-	-	-	-	-	-
Hajifathalian, 2020 [54]	234 (22.1%)	168 (15.9%)	-	-	-	-	-	-	-	-	-
Han, 2020 [55]	67 (32.5%)	24 (11.7%)	-	-	-	-	-	-	-	-	-
He, 2020 [56]	19 (9.3%)	-	-	-	-	29.5 (4.1)	22 (3.4)	23.8 (4.8)	17.7 (4.4)	-	-
Hong, 2020 [57]	-	-	42 (42.9%)	19 (19.4%)	16 (16.3%)	100.3 (97)	37.5 (26.6)	58.8 (93.6)	30.1 (26.3)	18.8 (10.3)	13.7 (8.6)

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Table 2 (*Continued*)

Study, year	Symptoms, n (%)		Laboratory Findings, n (%)			Laboratory findings, mean (SD)					
	Diarrhea	Nausea/ Vomiting	Abnormal AST	Abnormal ALT	Abnormal TB	AST U/L		ALT U/L		TB mmol/L	
						Severe	Non-severe	Severe	Non-severe	Severe	Non-severe
Kaafarani, 2020 [58]	30 (28.8%)	44 (42.3%)	-	-	-	-	-	-	-	-	-
Kim, 2020 [59]	3 (10.7%)	-	-	6 (21.4%)	-	-	-	-	-	-	-
Klopfenstein, 2020 [60]	55 (48.2%)	25 (21.9%)	-	-	-	-	-	-	-	-	-
Kluytmans-van den Bergh, 2020 [61]	16 (18.6%)	15 (17.4%)	-	-	-	-	-	-	-	-	-
Lian, 2020 [62]	36 (7.7%)	22 (4.7%)	52 (11.2%)	47 (10.1%)	13 (2.8%)	-	-	-	-	-	-
Lin, 2020 [63]	23 (24.2%)	17 (17.9%)	4 (4.2%)	5 (5.2%)	22 (23.2%)	-	-	-	-	-	-
Liu, 2020 [64]	23 (7.2%)	3 (0.9%)	-	-	-	-	-	-	-	-	-
Liu, 2020 [65]	5 (5.9%)	3 (3.5%)	-	-	-	-	-	-	-	-	-
Meng, 2020 [66]	44 (26.2%)	18 (10.7%)	54 (32.1%)	41 (24.4%)	18 (10.7%)	-	-	-	-	-	-
Nobel, 2020 [67]	56 (20.1%)	63 (22.7%)	-	-	-	-	-	-	-	-	-
Palaiodimos, 2020 [68]	66 (33.0%)	35 (17.5%)	72 (36.0%)	36 (18.0%)	-	-	-	-	-	-	-
Pan, 2020 [69]	35 (17.2%)	4 (2.0%)	-	-	-	-	-	-	-	-	-
Phipps, 2020 [70]	-	-	1280 (56.3%)	537 (23.6%)	-	-	-	-	-	-	-
Redd, 2020 [71]	107 (33.6%)	84 (26.4%)	-	-	-	-	-	-	-	-	-
Remes-Troche, 2020 [72]	20 (17.9%)	8 (7.1%)	-	-	-	-	-	-	-	-	-
Shang, 2020 [73]	16 (5.7%)	11 (3.6%)	-	-	-	-	-	-	-	-	-
Sun, 2020 [74]	5 (7.9%)	-	14 (22.2%)	16 (25.4%)	-	66.4 (108.1)	29.9 (15.4)	61.2 (101.8)	29.5 (19.4)	11.5 (4.8)	12.1 (7.4)
Wan, 2020 [75]	49 (21.3%)	-	-	-	-	-	-	-	-	-	-
Wang, 2020 [76]	6 (7.1%)	-	33 (38.8%)	19 (22.4%)	-	50.9 (11.7)	35.3 (6.3)	39.2 (10.9)	28.2 (6)	13 (2.7)	10.2 (1.4)
Wang, 2020 [77]	12 (42.9%)	9 (32.1%)	-	-	-	44.8 (20.8)	22.2 (7.2)	24.5 (7.2)	17.9 (4.4)	15.8 (6.8)	9.1 (3.6)
Wang, 2020 [78]	-	-	-	-	-	45.3 (7.5)	25 (3.7)	27 (10.3)	18.6 (3.9)	10.8 (3.2)	8.4 (1.8)
Wang, 2020 [79]	50 (40.0%)	24 (19.2%)	27 (21.6%)	26 (20.8%)	9 (7.2%)	29.5 (3.7)	26.5 (4)	26.1 (5.6)	24.8 (7.1)	11.4 (3.2)	9.6 (2.2)
Wang, 2020 [80]	152 (15.0%)	36 (3.6%)	-	-	-	-	-	-	-	-	-
Wei, 2020 [81]	26 (31.0%)	25 (29.8%)	-	-	-	-	-	-	-	-	-

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Table 2 (*Continued*)

Study, year	Symptoms, n (%)		Laboratory Findings, n (%)			Laboratory findings, mean (SD)					
	Diarrhea	Nausea/ Vomiting	Abnormal AST	Abnormal ALT	Abnormal TB	AST U/L		ALT U/L		TB mmol/L	
						Severe	Non-severe	Severe	Non-severe	Severe	Non-severe
Yan, 2020 [82]	51 (26.4%)	19 (9.9%)	-	-	-	-	-	-	-	-	-
Yang, 2020 [83]	14 (7.0%)	4 (2.0%)	74 (37.0%)	44 (22.0%)	-	32.4 (3.9)	31.5 (4)	39.3 (16.2)	26.8 (4.9)	13.7 (2.3)	12.9 (1.6)
Zhang, 2020 [84]	25 (11.3%)	-	-	-	-	52.3 (14.1)	28 (5.2)	35.8 (10.1)	22.8 (5.5)	12.2 (2.5)	10.2 (1.7)
Zhang, 2020 [85]	61 (9.2%)	48 (7.3%)	171 (25.8%)	151 (22.8%)	-	-	-	-	-	-	-
Zhang, 2020 [86]	-	-	17 (14.8%)	11 (9.6%)	8 (7.0%)	38.8 (22.5)	24.4 (9.8)	37.8 (32.2)	21.2 (12.7)	14.1 (6.4)	10.3 (4.3)
Zhao, 2020 [87]	14 (15.4%)	19 (20.9%)	18 (19.8%)	10 (11.0%)	-	-	-	-	-	-	-
Zheng, 2020 [88]	-	-	-	-	-	51.2 (88.7)	26.5 (12.7)	42.4 (48.9)	31.7 (27.8)	-	-
Zhou, 2020 [89]	46 (18.1%)	36 (14.2%)	-	-	-	-	-	-	-	-	-

ALT, alanine aminotransferase; AST, aspartate aminotransferase; n, no. of patients; SD, standard deviation; TB, total bilirubin

converting enzyme 2 (ACE2), readily expressed in ileal and colonic epithelium [92]. This can explain symptoms such as diarrhea and nausea/vomiting. Furthermore, researchers have also identified viral RNA in the stool of patients infected with COVID-19, making diarrhea not only a marker for disease severity but a potential route of contagion [22]. Given the association of diarrhea with severe COVID-19 disease, based on our meta-analysis results, COVID-19 patients with diarrhea should be stratified into a high-risk group for developing severe disease as described above and managed accordingly.

Several mechanisms have been postulated to explain the hepatotoxicity seen in COVID-19 patients. One possible mechanism of hepatotoxicity of COVID-19 is immune system activation. It has been shown that many of the respiratory viruses, including COVID-19, lead to an activation of cytotoxic T cells and Kupffer cells in the liver that eventually damage hepatocytes [93]. Another mechanism is the triggering of a "cytokine storm," leading to a massive surge in mediators such as interleukin-6, associated with sepsis, multiorgan dysfunction and death [8,94,95]. Direct viral entry through the intestines and invasion of the portal system and, subsequently, cholangiocytes, is another hypothesized mechanism [96]. Lastly, drug-induced hepatotoxicity should also be considered, as currently researchers are investigating all possible therapeutic options [97]. We demonstrated significantly increased elevation of ALT, AST and TB in patients with severe COVID-19 compared to non-severe patients, which can be attributed to some or all of the aforementioned mechanisms.

Several limitations exist with our analysis. The most notable was the lack of high quality randomized controlled trials and cohort studies. We relied on data from observational studies that reported admission data. Observational studies have their own inherent biases that limit data interpretation, including selection, recall, and confounding bias. It is difficult to establish a temporal relation between cause and event using observational studies, as there is no follow up. However, as we reported admission data, we propose screening and risk-stratifying individuals, based on their admission laboratory findings and symptoms, into severe and non-severe categories. We were not able to account for factors such as comorbidities, timing of hospitalization and routine home medications. We were also not able to account for these related gastrointestinal symptoms due to lack of stratified data. Lastly, given that the major manifestations of COVID-19 are respiratory symptoms (cough, shortness of breath, sputum production) and fever, gastrointestinal symptoms may have been underreported.

Despite the limitations, our analysis combines data from a large number of studies with a robust number of patients. We used admission data to avoid potential heterogeneity introduced by other factors, such as in-hospital medications, nosocomial infections, intubation, etc. The results of our study were consistent on both subgroup and sensitivity analysis. Furthermore, we provided subgroup prevalence based on region, i.e., Asia, Europe and North America where applicable.

In conclusion, patients presenting with diarrhea or elevated ALT, AST and/or TB and diagnosed with COVID-19 should be stratified into a high-risk group for developing severe disease outcomes (i.e., respiratory distress, ICU admission, and/or death) and managed appropriately.

Summary Box

What is already known:

- Gastrointestinal manifestations (diarrhea, nausea/vomiting, abnormal aspartate aminotransferase [AST], abnormal alanine aminotransferase[ALT], and abnormal total bilirubin [TB]) have been demonstrated in several studies in patients with COVID-19
- A recent meta-analysis accounted for these manifestations in the form of pooled analysis

What the new findings are:

- We performed a comprehensive systematic review and meta-analysis of the available literature through May 31st, 2020 to assess these manifestations with respect to disease severity
- Our results indicate that diarrhea, abnormal ALT, AST and TB were associated with severe disease (intensive care unit admission, respiratory distress, and/or mortality)
- Based on the current study results, patients with these manifestations should be stratified as high-risk and managed appropriately

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Supplementary material

Supplementary Table 1 EMBASE search strategy

No.	Query	Results
1.	gi OR 'gastro intestin*' OR gastrointestin* OR diarrhea* OR constipate* OR dyspep* OR dyschezia* OR obstipat* OR dysbiosis* OR indigestion* OR dysmotilit* OR nausea* OR vomit* OR emesis* OR hematemesis* OR 'abdominal pain*' OR amylase OR lipase OR alt OR 'alanine aminotransferase*' OR ast OR 'aspartate aminotransferase*' OR bilirubin OR 'alk phos' OR 'alkaline phosphatase*' OR cea OR 'carcinoembryonic antigen*' OR 'ca19 9' OR 'carbohydrate antigen 19 9' OR ggt OR 'γ glutamyltransferase*' OR 'gamma glutamyltransferas3*' OR 'γ glutamyltransferase*' OR 'fecal calprotectin*' OR 'fecal leukocyte*'	1858951
2.	(('coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw) AND (outbreak:ti,ab,kw OR wuhan:ti,ab,kw) OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR ((coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw) AND 2019:ti,ab,kw) OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'ncov 2019':ti,ab,kw OR ncov:ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw) AND [2019-2020]/py	20818
3.	#1 AND #2	1170
4.	#3 NOT ('conference abstract'/it OR 'editorial'/it OR 'review'/it OR 'short survey'/it)	1021
5.	#4 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'meta analysis'/de OR 'practice guideline'/de OR 'systematic review'/de)	825
6.	#4 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'meta analysis'/de OR 'practice guideline'/de OR 'systematic review'/de) AND [1-4-2020]/sd NOT [1-8-2020]/sd	749

*Searches for human or excluding nonhuman or animal studies were inconsistently indexed, so were abandoned as a strategy

Supplementary Table 2 QUIPS table for risk of bias

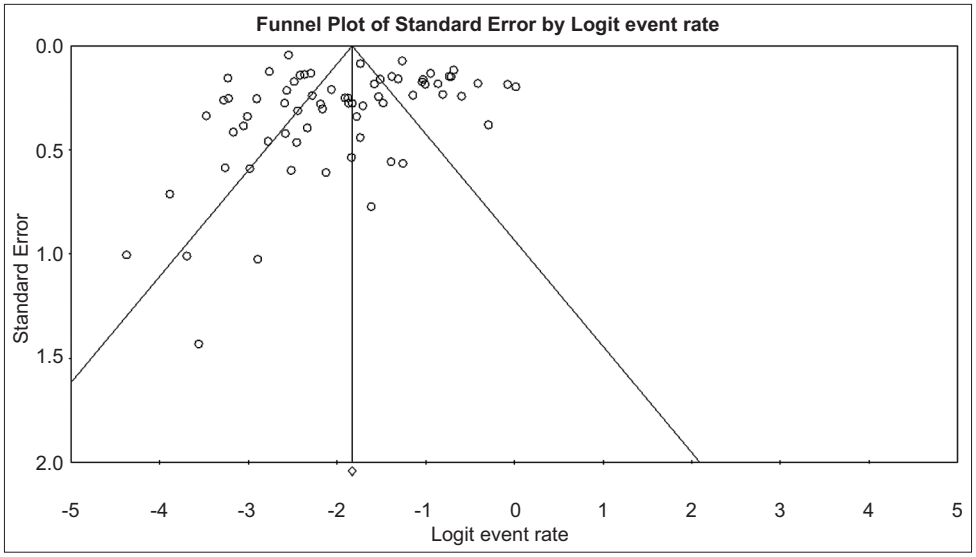
Study, year	Participation (The study sample represents population of interest on key characteristics?)	Attrition (The proportion of study sample providing outcome data is adequate?)	Prognostic factor measurement (Prognostic factor is adequately measured in study subjects?)	Outcome measurement (The outcome of interest is adequately measured in study subjects?)	Study confounders (Potential confounders are accounted for?)	Statistical analysis? (Statistical analysis appropriately designed for the study?)
Guan, 2020 [1]	Yes	Yes	Yes	Yes	Partly	Yes
Wang, 2020 [9]	Yes	Yes	Yes	Yes	No	Yes
Huang, 2020 [10]	Yes	Partly	Yes	Yes	Partly	Yes
Chen, 2020 [11]	Yes	Yes	No	Yes	No	Yes
Chen, 2020 [3]	Yes	Yes	Yes	Yes	Partly	Yes
Liu, 2020 [12]	Yes	Yes	Yes	Yes	No	Yes
Liu, 2020 [13]	Yes	Yes	No	Yes	No	Yes
Wu, 2020 [14]	Yes	Yes	No	Yes	Partly	Yes
Wu, 2020 [15]	Yes	Partly	No	Yes	Partly	Yes
Xu, 2020 [16]	Yes	Yes	No	Yes	Partly	Yes
Luo, 2020 [17]	Yes	Yes	No	Yes	No	Partly
Chen, 2020 [18]	Yes	Yes	Yes	Yes	No	Yes
Lei, 2020 [19]	Yes	Partly	No	Yes	No	Partly
Jin, 2020 [20]	Yes	Yes	No	Yes	Partly	Yes
Mo, 2020 [21]	Yes	Yes	Yes	Yes	No	Yes
Wan, 2020 [22]	Yes	Yes	Yes	Yes	No	Yes
Xiao, 2020 [23]	Yes	Yes	No	Yes	No	Partly
Yao, 2020 [24]	Yes	Yes	No	Yes	No	Yes
Young, 2020 [25]	Yes	Yes	No	Yes	No	Partly
Zhang, 2020 [26]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [27]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [28]	Yes	Yes	No	Yes	No	Yes
Zhou, 2020 [29]	Yes	Yes	No	Yes	No	Yes
Zhao, 2020 [30]	Yes	Partly	No	Yes	No	Partly
Shi, 2020 [31]	Yes	Yes	No	Yes	No	Yes
Liu. 2020 [32]	Yes	Yes	Yes	Yes	Partly	Yes
Liu. 2020 [33]	Yes	Yes	Yes	Yes	No	Partly
Liu. 2020 [34]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [35]	Yes	Yes	Yes	Yes	Partly	Yes
Zhou, 2020 [36]	Yes	Partly	No	Yes	No	Yes
Han, 2020 [37]	Yes	Yes	No	Yes	No	Partly
Peng, 2020 [38]	Yes	Yes	Yes	Yes	No	Partly
Shi, 2020 [39]	Yes	Partly	No	Yes	Partly	Yes
Wang, 2020 [40]	Yes	Yes	Yes	Yes	No	Yes
Xie, 2020 [41]	Yes	Yes	Yes	Yes	Partly	Yes
Cai, 2020 [42]	Yes	Yes	Yes	Yes	No	Yes
Gao, 2020 [43]	Yes	Yes	Yes	Yes	No	Yes
Zhou, 2020 [44]	Yes	Yes	Yes	Yes	Partly	Yes
Bonetti, 2020 [45]	Yes	Partly	Yes	Yes	Partly	Yes
Buscarini, 2020 [46]	Yes	Yes	No	Yes	No	Partly
Cai, 2020 [47]	Yes	Yes	Yes	Yes	Yes	Yes
Chen, 2020 [48]	Yes	Yes	Yes	Yes	Partly	Yes

(*Contd...*)

Supplementary Table 2 (*Continued*)

Study, year	Participation (The study sample represents population of interest on key characteristics?)	Attrition (The proportion of study sample providing outcome data is adequate?)	Prognostic factor measurement (Prognostic factor is adequately measured in study subjects?)	Outcome measurement (The outcome of interest is adequately measured in study subjects?)	Study confounders (Potential confounders are accounted for?)	Statistical analysis? (Statistical analysis appropriately designed for the study?)
Chen, 2020 [49]	Yes	Yes	No	Partly	No	Yes
Cholankeril, 2020 [50]	Yes	Yes	No	Yes	No	Partly
Diaz, 2020 [51]	Yes	Yes	No	Yes	No	No
Duan, 2020 [52]	Yes	Yes	Yes	Yes	No	Yes
Fan, 2020 [53]	Yes	Yes	Partly	Yes	No	Yes
Hajifathalian, 2020 [54]	Yes	Yes	No	Yes	No	Partly
Han, 2020 [55]	Yes	Yes	No	Yes	No	Yes
He, 2020 [56]	Yes	Yes	Yes	Yes	No	Yes
Hong, 2020 [57]	Yes	Yes	Yes	Yes	No	Yes
Kaafarani, 2020 [58]	Yes	Yes	No	Yes	No	No
Kim, 2020 [59]	Partly	Yes	No	Yes	No	Partly
Klopfenstein, 2020 [60]	Yes	Yes	No	Yes	No	No
Kluytmans-van den Bergh, 2020 [61]	Yes	Yes	No	Yes	No	Yes
Lian, 2020 [62]	Yes	Yes	No	Yes	No	Yes
Lin, 2020 [63]	Yes	Yes	No	Yes	No	Yes
Liu, 2020 [64]	Yes	Yes	No	Yes	No	Yes
Liu, 2020 [65]	Yes	Yes	No	Yes	No	Yes
Meng, 2020 [66]	Partly	Yes	No	Yes	Yes	Yes
Nobel, 2020 [67]	Yes	Yes	No	Yes	No	Yes
Palaiodimos, 2020 [68]	Yes	Yes	No	Yes	Yes	Yes
Pan, 2020 [69]	Yes	Yes	Yes	Yes	No	Yes
Phipps, 2020 [70]	Yes	Yes	No	Yes	No	Partly
Redd, 2020 [71]	Yes	Yes	No	Yes	Yes	Yes
Remes-Troche, 2020 [72]	Yes	Yes	No	Yes	No	No
Shang, 2020 [73]	Yes	Yes	No	Yes	No	Yes
Sun, 2020 [74]	Yes	Yes	Yes	Yes	No	Yes
Wan, 2020 [75]	Yes	Yes	No	Yes	Partly	No
Wang, 2020 [76]	Yes	Yes	Yes	Yes	No	Yes
Wang, 2020 [77]	Partly	Yes	Yes	Yes	No	Partly
Wang, 2020 [78]	Yes	Yes	Yes	Yes	No	Yes
Wang, 2020 [79]	Yes	Yes	Yes	Yes	Yes	Yes
Wang, 2020 [80]	Yes	Yes	Yes	Yes	No	Partly
Wei, 2020 [81]	Yes	Yes	No	Yes	No	Yes
Yan, 2020 [82]	Yes	No	No	Yes	No	Yes
Yang, 2020 [83]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [84]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [85]	Yes	Yes	Yes	Yes	No	Yes
Zhang, 2020 [86]	Yes	Yes	Yes	Yes	No	Yes
Zhao, 2020 [87]	Yes	Yes	Yes	Yes	No	Yes
Zheng, 2020 [88]	Yes	Yes	Yes	Yes	No	Yes
Zhou, 2020 [89]	Yes	Yes	No	Yes	No	Yes

Yes: study accounted for the variable, No: Study did not account for the variable, Partly: Study accounted somewhat for the variable



Supplementary Figure 1 Funnel plot signifying visible asymmetry based on diarrhea for COVID-19 patients

PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
		ABSTRACT	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
		METHODS	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, Supplementary Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6

(*Contd...*)

PRISMA CHECKLIST (*Continued*)

Section/topic	#	Checklist item	Reported on page #
		TITLE	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6, 7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, 7
		RESULTS	
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Supplementary Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 - 12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 - 12
		DISCUSSION	
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
		FUNDING	
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;**6**:e1000097.*