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META-ANALYSIS

Gastrointestinal symptoms in patients with mild and severe COVID-19: a scoping review and meta-analysis

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ABSTRACT

Aim: The current research aimed to analyze and summarize observational studies that compared the incidence of gastrointestinal symptoms in mild and severe COVID-19 infection.

Background: Coronavirus disease 2019 (COVID-19) has been identified as a public health threat worldwide. Previous studies, however, have reported contradictory results of COVID-19-related gastrointestinal symptoms in severe and mild forms.

Methods: A search of Medline, ISI Web of Science, EMBASE, and Cochrane Library databases was conducted for articles published up to May 2020. Data from each study was combined using the random-effects model to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Sensitivity was examined by sequentially excluding one study in each turn. Publication bias was evaluated using the Egger's and Begg's tests.

Results: Twenty studies (4,265 patients) were reviewed. It was found that the prevalence of diarrhea [OR (0.40), (95% CI 0.91, -2.16), p = 0.03, I2 = 88.1%, PHeterogenity = 0.00)] and nausea and vomiting [OR (0.27), (95% CI 0.07, 1.01), p = 0.05, I2 = 89.3%, PHeterogenity = 0.00)] increased significantly in the severe form compared to the mild form of COVID-19, while abdominal pain and anorexia had no significant increased prevalence in admitted and hospitalized COVID-19 patients. Moreover, COVID-19-related gastrointestinal symptoms were seen in higher rates in males [OR (1.42), (95% CI 1.23, 1.65), p < 0.05, I2= 18.4%, PHeterogenity = 0.23] than in females. No significant publication bias was observed in the meta-analysis. Sensitivity analyses showed a similar effect size while reducing the heterogeneity.

Conclusion: The data provides valuable information for the discovery of prognosis biomarkers to diagnosis more severe disease in the early stages of COVID-19.

Keywords: COVID-19, Coronavirus, Gastrointestinal symptoms, Digestive symptoms, Meta-analysis.

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Introduction

A new coronavirus recently emanated as a pathogen causing pneumonia named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the disease called coronavirus disease 2019 (COVID-19) (1-3). The disease was initially seen in December 2019 in Wuhan, China, and then quickly spread to many countries. On March 11, 2020, the World Health Organization (WHO) declared it a pandemic (4). Mounting evidence has shown that COVID-19 and SARS-CoV-2 can be transmitted between people through respiratory droplets and close contact with an infected person, posing a major challenge for the global public health system and healthcare settings (5, 6). Currently, there is no vaccine or specific antiviral drug to treat COVID-19 infection. The available antiviral

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drugs, like HIV-protease inhibitors and nucleoside analogues, are used as supportive therapy to reduce the symptoms and protect organ function (3, 7, 8). The main signs and symptoms of COVID-19 disease include fever, dry cough, tiredness, and breathing difficulty (3, 9, 10). On average, the symptoms of COVID-19 infection appear about 5 days after exposure (11). Gastrointestinal symptoms such as nausea, vomiting, and less commonly diarrhea have also been observed in some COVID-19 patients. Recent studies have reported conflicting results concerning the gastrointestinal symptoms. For example, one study reported digestive symptoms including diarrhea (2.0%) and nausea and vomiting (1.0%) (12). In another research, the patients had clinical characteristics of diarrhea (28%), nausea (9.0%), vomiting (6.0%), and abdominal pain (7.0%) (8). Fan et al. reported the clinical features of diarrhea (4.1%) and nausea and vomiting (2.0%) (13). Pan et al. investigated 99 COVID-19 patients with digestive symptoms. The patients had symptoms of anorexia (83.8%), diarrhea (29.3%), vomiting (8.1%), and abdominal pain (4.0%). In this study, patients with severe infection (n=13) had symptoms of anorexia (100%) and diarrhea (23.1%), whereas patients with moderate symptoms (n=63) displayed anorexia (76.2%) and diarrhea (30.2%) (14). Additionally, Chen et al. recently demonstrated that SARS-CoV-2 RNA is found in the feces of COVID-19 patients (15). Accordingly, more research is needed to determine the relationship between the presence of the virus in the feces samples and gastrointestinal symptoms in order to introduce an indicator for the diagnosis and prognosis of patients.

The current study aimed to clarify the clinical characteristics and systematically review changes in the gastrointestinal function in SARS-CoV2-infected patients. The results indicate that there is a need to collect sufficient data to aid in the appropriate interpretation of the results.

Methods

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

Information source and search strategy

An electronic search of PubMed, Web of Sciences, Scopus, Google Scholar, and Cochran Library was performed for original research articles published up to May 8, 2020, using the following query: ("Digestive Symptoms" OR "Gastrointestinal Symptoms" AND "COVID-19" OR "SARS-Cov19" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "Coronavirus"), ("Diarrhea" AND "COVID-19" OR "SARS-CoV19" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "Coronavirus"), ("Nausea & Vomiting" AND "COVID-19" OR "SARS-CoV19" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "Coronavirus"), ("Anorexia" AND "COVID-19" OR "SARS-Cov19" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "Coronavirus") and ("Abdominal Pain" AND "COVID-19" OR "SARS-CoV19" OR "Severe Acute Respiratory Syndrome Coronavirus" OR "Coronavirus").

Selection of studies

All articles were exported to EndNote software, and duplicated records were removed. There were no restrictions on the language were applied, although all articles used in this meta-analysis were available in English. The reference lists of the included articles were also reviewed manually. Selected articles were screened by title and abstract for eligibility, and the full text was examined by three authors (Nasrin Amiri-Dashatan, Mehdi Koushki, and Masoumeh Farahani) independently. The inclusion criteria included full and observational studies with a retrospective design that focused on COVID-19 patients and published a description of gastrointestinal and digestive symptoms in coronavirus patients.

Data extraction

Data was extracted from full-text records using a standard complete extraction sheet. For each included article, data on the first author, publication year, country of study, sample size, mean (SD) age, gender type (female/male), and gastrointestinal symptoms including diarrhea, nausea and vomiting, anorexia and abdominal pain in total in severe and mild groups of COVID-19-affected patients was recorded.

Quality of evidence assessment

The quality of the evidence in the design, analysis, and reporting of outcomes was assessed independently by two reviewers using the Newcastle-Ottawa Quality Assessment Scale (NOS) (16). The studies were

assessed across 4 domains: 1) study population selection, 2) exposure, 3) comparability, and 4) outcome. The maximum score for a study was 9 points. Based on the scoring, the studies were classified as I) low quality (0 to 4 points) or II) high quality (5 to 9 points). Disagreements in scoring were resolved through discussion.

Statistical analysis

The building of forest plots of binary data on diarrhea, nausea and vomiting, anorexia, and abdominal pain in patients with mild and severe COVID-19 infection was performed using odds ratios (ORs) and 95% confidence intervals (95% CI). In this meta-analysis, the ORs and 95% CI were considered as the effect size to estimate sex (male, female) with severity risk of COVID-19 infection. For each group of variables, a random-effects model was used to calculate ORs of the severity of COVID-19 infection. The heterogeneity among studies was estimated by Q test (significance level at $p < 0.1$) and I^2 statistics. The I^2 statistics were characterized by the percentage of the total variation in effect size that can be associated with heterogeneity. Values greater than 50% and 70% were considered as moderate to high heterogeneity, respectively. Sensitivity was analyzed by sequentially excluding one study in each turn to evaluate the robustness of the results. The Begg's rank correlation test and Egger's regression asymmetry test were also applied to evaluate the potential publication bias obtained by the funnel plot (17, 18). Trim-and-fill analysis was used to regulate any significant publication bias detected. Lastly, a restricted maximum likelihood-based random effects meta-regression analysis was performed to evaluate the relationship between the confounder variable of gender on overall effect size. The CMA (comprehensive meta-analysis) V2 software (Biostat, NJ, USA) (19) was used for this meta-analysis. A p-value < 0.05 was considered statistically significant.

Results

Overview of included studies

The electronic databases were searched for articles published through May 8, 2020. A total of 117 articles were initially found, including 114 English and 3 Chinese articles, respectively. Of these, 79 records were excluded from our analysis due to duplication or because they were reviews or letters. Of the remaining 38 articles, 15 articles were rejected for lack of enough relevant information, and 3 articles were removed due to incomplete reports and not published in the English language. Finally, 20 eligible articles were included in this study. The outline of the flowchart of study selection is summarized in Figure 1.

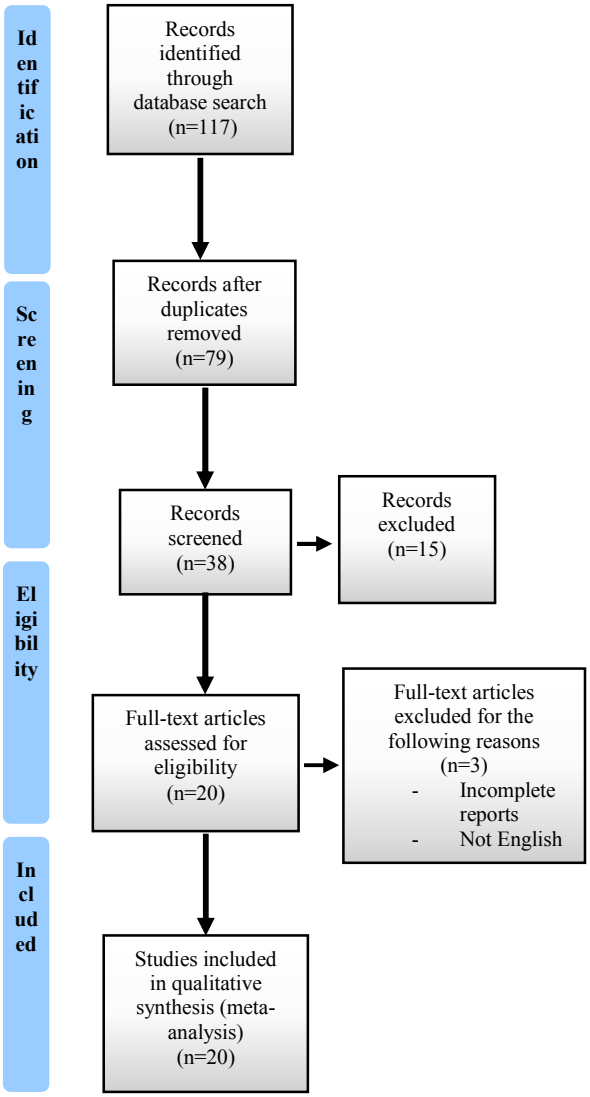


Figure 1. Flow chart of study selection for meta-analysis

Characteristics and quality of included studies

The baseline characteristics of the 20 studies are summarized in Table 1.The cases evaluated by the studies included in this meta-analysis comprised patients with mild and severe COVID-19 infections.

Table 1. Baseline characteristics of the included studies.

Athour's name/ Country (ref)	Samples (N)	Sex (M/ F)	Age (year) Mean ± SD	Digestive symptom				Study Quality
				abdominal PainN (%)	Anorexia N (%)	Diarrhea N (%)	Nausea & Vomiting N (%)	
Zhou F et al. (2020)/ China (20)	Total: 191 Mild: 137 Severe: 54	Total: 119/72 Mild: 81/56 Severe: 38/16	Total: 56.25 ± 3.5 Mild: 51.75 ± 2.16 Severe: 69.25 ± 3.25	-	-	Total: 9 (5) Mild: 7 (5) Severe: 2 (4)	Total: 7 (4) Mild: 4 (3) Severe: 3 (6)	8
Huang C et al. (2020)/ China (9)	Total: 38 Mild: 25 Severe: 13	Total: 30/11 Mild: 19/9 Severe: 11/2	Total: 49.2 ± 4.25 Mild: 49.12 ± 4.12 Severe: 50 ± 5	-	-	Total: 25 (3) Mild: 1 (12) Severe: 0 (0)	-	6
Pan L et al. (2020)/ China (14)	Total: 99 Mild: 64 Severe: 35	Total: 54/45 Mild: 33/31 Severe: 21/14	Total: 54.6 ± 16.1	Total: 4 (4) Mild: 2 (3.2) Severe: 2 (9.1)	Total: 83 (83.8) Mild: 48 (76.2) Severe: 35 (100)	Total: 29 (29.3) Mild:: 20 (31.2) Severe: 9 (25.7)	Total: 8 (8.1) Mild: 4 (6.4) Severe: 4 (11.4)	6
Guan W et al. (2020)/ China (21)	Total: 1096 Mild: 923 Severe: 173	Total:637/ 459 Mild: 537/3861 Severe: 100/73	Total: 46.75 ± 4.16 Mild: 45.25 ± 3.83 Severe: 52.25 ± 4.16	-	-	Total:42 (3.8) Mild: 32 (3.5) Severe: 10 (5.8)	Total:55 (5) Mild: 43 (4.6) Severe: 12 (6.9)	5
Wang D et al. (2020)/China (22)	Total: 138 Mild: 102 Severe: 36	Total: 75/63 Mild: 53/49 Severe: 22/14	Total: 55.5 ± 4.33 Mild: 50.25 ± 4.16 Severe: 66.75 ± 5.25	Total: 3 (2.2) Mild: 0 (0) Severe: 3 (8.3)	Total: 55 (39.9) Mild: 31 (30.4) Severe: 24 (66.7)	Total: 14 (10.1) Mild: 8 (7.8) Severe: 6 (16.7)	Total: 19 (13.7) Mild: 12 (11.76) Severe: 7 (19.44)	8
Zhang JJ et al. (2020)/ China (23)	Total: 140 Mild: 82 Severe: 58	Total: 71/69 Mild: 38/44 Severe: 33/25	Total: 56.6 ± 10.33 Mild: 51.75 ± 8.66 Severe: 60 ± 15.5	Total: 8 (5.8) Mild: 2 (5.8) Severe: 6 (10.2)	Total:17 (12.2) Mild: 9 (11) Severe: 8 (14)	Total: 18 (12.9) Mild: 9 (11) Severe: 9 (15.8)	Total:31 (22.3) Mild: 24 (29.2) Severe: 7 (12.2)	6
Zhang X et al. (2020)/ China (24)	Total: 645 Mild: 72 Severe: 573	Mild: 33/39 Severe: 295/278	Mild: 34.9 (14.2) Severe: 46.65 ± 13.82	-	-	Mild: 8 (11.1) Severe: 45 (7.9)	Mild: 0 (0) Severe: 22 (3.8)	7
Zhang et al. (2020)/ China (25)	Severe: 82	Severe: 54/28	Severe: 72.5 ± 2.5	-	-	Severe: 10 (12.2)	Severe: 2 (2.3)	4
Cai J et al. (2020)/ China (26)	Total:298 Mild: 240 Severe: 58	Total: 145/153 Mild: 106/134 Severe: 39/19	Total: 47.2 ± 4.6 Mild: 42.25 ± 4.16 Severe: 61.75 ± 2.5	-	-	Total: 9 (3.02) Mild: 5 (2.08) Severe: 4 (6.9)	-	5
Chen G et al. (2020)/ China (27)	Total:21 Mild: 10 Severe: 11	Total:17/4 Mild: 7/3 Severe: 10/1	Total:56.3 ± 14.3 Mild: 51.4 ± 13.7 Severe: 63.9 ± 9.6	-	-	Total: 4 (20) Mild: 3 (10) Severe: 1 (10)	-	7
Chen T et al. (2020)/ China (8)	Total:274 Mild: 161 Severe: 113	Total:171/102 Mild: 88/73 Severe: 83/30	Total:59.5 ± 4.33 Mild: 51.25 ± 4.83 Severe: 68.75 ± 2.5	Total: 19 (7) Mild: 13 (8) Severe: 6 (5)	-	Total: 77 (28) Mild: 50 (31) Severe: 27 (24)	Total: 40 (15) Mild: 26 (16) Severe: 14 (12)	6
Deng Y et al. (2020)/ China (28)	Mild: 116 Severe: 109	Mild: 51/73 Severe: 65/36	Mild: 42.5 ± 4 Severe: 68.5 ± 2	-	-	Mild: 14 (12.1) Severe: 19 (17.4)	-	6
M o P et al. (2020)/ China (29)	Total: 155 Mild: 70 Severe: 85	Total: 86/69 Mild: 31/39 Severe: 55/30	Total: 54 ± 4 Mild: 45.75 ± 3.5 Severe: 60.75 ± 3.16	Total: 3 (1.9) Mild: 0 (0) Severe: 2 (2.4)	Total: 26 (31.7) Mild: 8 (18.2) Severe: 18 (47.4)	Total: 7 (4.5) Mild: 2 (2.9) Severe: 5 (5.9)	Total:6 (7.4) Mild: 2 (4.5) Severe: 2 (5.3)	7
Wan S et al. (2020)/ China (30)	Total: 135 Mild: 95 Severe: 40	Total: 72/63 Mild: 52/43 Severe: 21/19	Total: 46.25 ± 3.16 Mild: 42.5 ± 2.66 Severe: 59.25 ± 3.5	-	Total: 6 (4.4) Mild:: 0 (0) Severe: 6 (15)	Total:18 (13.1) Mild: 5 (5.3) Severe: 13 (32.5)	-	7
Xie H et al. (2020)/ China (31)	Total: 79 Mild: 51 Severe: 28	Total: 44/34 Mild: 26/25 Severe: 18/10	Total: 58.5 ± 3 Mild: 57.5 ± 5 Severe: 60.82 ± 4.32	-	-	Total:7 (8.9) Mild: 3 (5.9) Severe: 4 (14.3)	-	6
Yang X et al. (2020)/ China (32)	Total: 52 Mild: 20 Severe: 32	Total: 35/17 Mild: 14/6 Severe: 21/11	Total: 59.7 ± 13.3 Mild: 51.9 ± 12.9 Severe: 64.6 ± 11.2	-	-	-	Total:2 (4) Mild: 1 (5) Severe: 1 (3)	4
Lin L et al. (2020)/ China (33)	Total: 58 Mild: 47 Severe: 11	Total: 27/ 31	Total: 48 ± 17.1	-	Total: 17 (17.9) Mild:: 12 (12.6) Severe: 5 (5.3)	Total: 23 (24.2) Mild:: 18 (18.9) Severe: 5 (5.3)	Total: 21(22.1) Mild:: 18 (18.9) Severe: 3 (3.2)	6
Qin C et al. (2020)/ China (34)	Total: 452 Mild: 166 Severe: 286	Total: 235/217 Mild: 80/86 Severe: 155/131	Total: 57.5 ± 3.33 Mild: 52.3 ± 3.45 Severe: 60.5 ± 3.0	Total: 23 (5.0) Mild: 4 (2.4) Severe: 19 (6.6)	Total: 92 (21) Mild: 30 (18.1) Severe: 66 (23.1)	Total: 122 (26.7) Mild: 44 (26.5) Severe: 78 (27.3)	Total: 42 (9.2) Mild: 10 (6.0) Severe: 32 (11.2)	7
Yang B et al. (2020)/ China (35)	Total: 18 Mild: 12 Severe: 6	Total: 9/9 Mild: 7/5 Severe: 2/4	Total: 49.5 ± 10.5 Mild: 40.25 ± 6.25 Severe: 58 ± 6.5	-	-	Total: 3 (17.0) Mild: 3 (25.0) Severe: 0 (0.0)	-	5
Wang Z et al. (2020)/ China (36)	Total: 69 Mild: 55 Severe: 14	Total: 32/37 Mild: 25/30 Severe: 7/7	Total: 45.25 ± 4.5 Mild: 39.25 ± 4.75 Severe: 70 ± 3.75	-	Total: 7 (10.0) Mild: 6 (11.0) Severe: 1 (7.0)	Total: 10 (14.0) Mild: 8 (15.0) Severe: 2 (14.0)	Total: 3 (4.0) Mild: 2 (4.0) Severe: 1 (7.0)	7

M: Male; F: Female

A total of 1817 and 2448 COVID-19 patients with severe and mild phenotypes, respectively, were evaluated in this meta-analysis. All included articles were published in 2020 by China and were observational in design. COVID-19 was diagnosed based on real-time RT-PCR in all studies. Only 4 (26.6%) of the included studies evaluated all

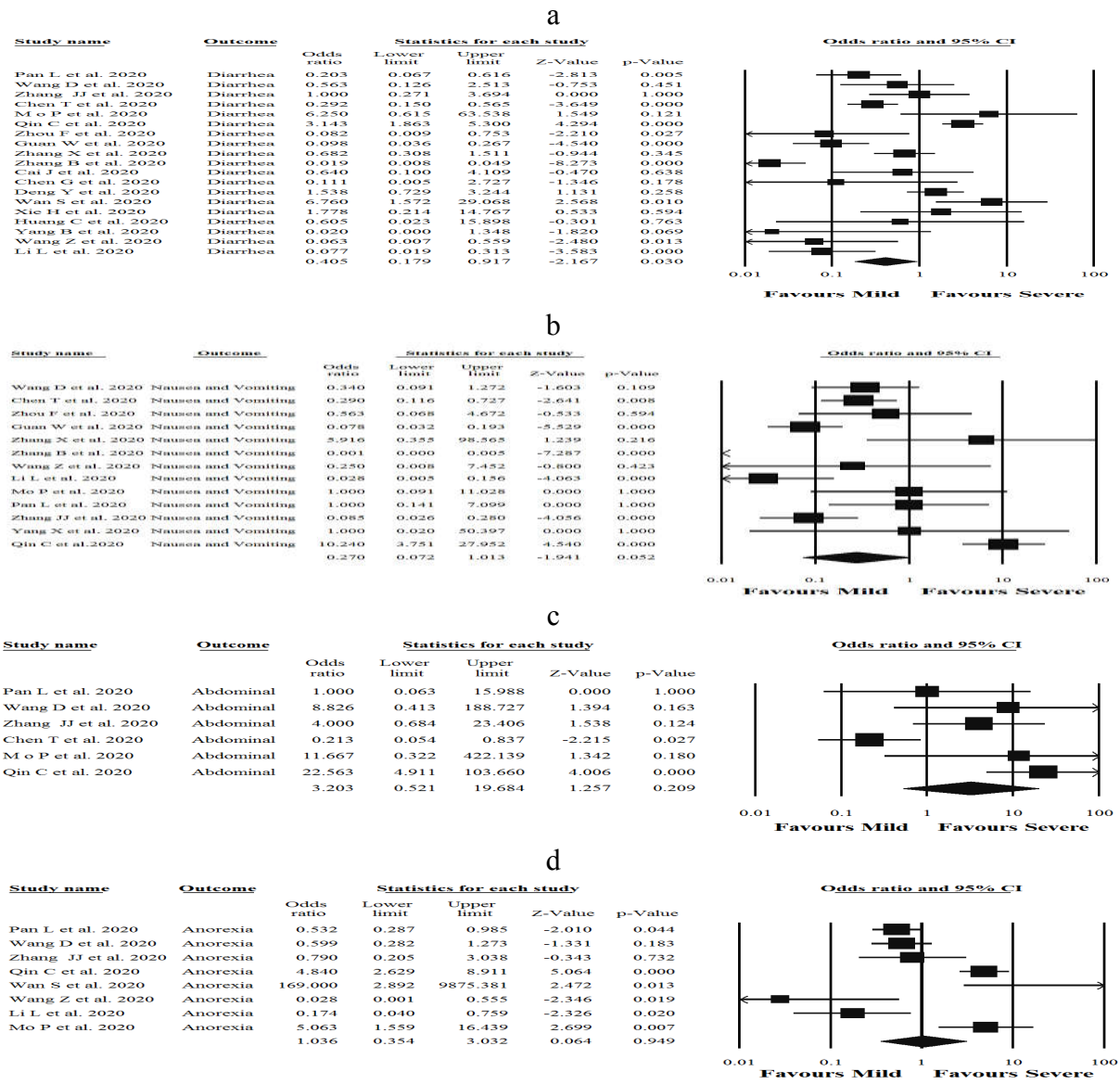


Figure 2. Forest plots detailing odds ratio (OR) and 95% confidence intervals of the incidence of COVID-19-related gastrointestinal symptoms of a) diarrhea, b) nausea and vomiting, c) abdominal pain, and d) anorexia in admitted and hospitalized patients. Meta-analysis was performed using a random-effects model

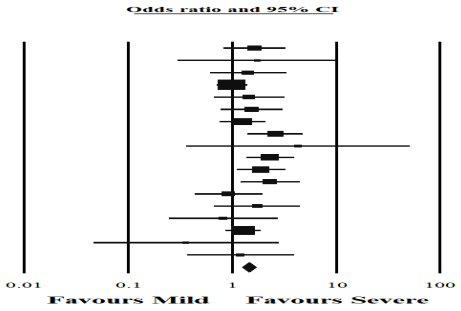
gastrointestinal symptoms including diarrhea, nausea and vomiting, anorexia, and abdominal pain. The quality of the studies is presented in Table 1, indicating the overall admissible quality of the included studies. As can be seen, 2 and 18 articles were considered as low and moderate to high quality, respectively.

Gastrointestinal symptoms in severe and mild COVID-19 infection

The current study evaluated whether patients with gastrointestinal symptoms including abdominal pain, anorexia, nausea and vomiting, or diarrhea may be at elevated risk for the severe form of COVID-19, and the results are shown in Fig. 2. Diarrhea [OR (0.40), (95% CI 0.91, -2.16), p = 0.03, I^2 = 88.1%, $P_{Heterogenity}$ = 0.00)] (Fig. 2a) and nausea and vomiting [OR (0.27), (95% CI 0.07, 1.01), p = 0.05, I^2 = 89.3%, $P_{Heterogenity}$ = 0.00)] (Figure. 2b) were found to be significantly associated with severity of COVID-19, while abdominal pain [OR (3.2), (95% CI 0.52, 19.6), p = 0.20, I^2 = 77.7%, $P_{Heterogenity}$ = 0.00)] (Fig. 2c), and anorexia [OR (1.03), (95% CI 0.35, 3.03), p = 0.94, I^2 = 87.1%, $P_{Heterogenity}$ = 0.00)] (Fig. 2d) were not

a

Study name	Outcome	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhou F et al. 2020	Male	1.642	0.835	3.229	1.437	0.151
Huang C et al. 2020	Male	1.737	0.298	10.138	0.613	0.540
Pan L et al. 2020	Male	1.409	0.611	3.249	0.805	0.421
Guan W et al. 2020	Male	0.985	0.709	1.368	-0.092	0.927
Wang D et al. 2020	Male	1.453	0.670	3.152	0.945	0.345
Zhang JJ et al. 2020	Male	1.528	0.777	3.008	1.228	0.219
Zhang X et al. 2020	Male	1.254	0.767	2.051	0.903	0.367
Cai J et al. 2020	Male	2.595	1.417	4.750	3.091	0.002
Chen G et al. 2020	Male	4.286	0.366	50.197	1.159	0.246
Chen T et al. 2020	Male	2.295	1.364	3.861	3.130	0.002
Deng Y et al. 2020	Male	1.883	1.108	3.199	2.340	0.019
Mo P et al. 2020	Male	2.306	1.206	4.411	2.526	0.012
Wan S et al. 2020	Male	0.914	0.436	1.917	-0.238	0.812
Xie H et al. 2020	Male	1.731	0.671	4.467	1.134	0.257
Yang X et al. 2020	Male	0.818	0.246	2.724	-0.327	0.744
Qin C et al.2020	Male	1.272	0.867	1.866	1.231	0.218
Yang B et al. 2020	Male	0.357	0.046	2.771	-0.985	0.325
Wang Z et al. 2020	Male	1.200	0.371	3.884	0.304	0.761
		1.429	1.231	1.658	4.695	0.000



b

Study name	Outcome	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhou F et al. 2020	Female	0.609	0.310	1.198	-1.437	0.151
Huang C et al. 2020	Female	0.323	0.058	1.794	-1.292	0.196
Pan L et al. 2020	Female	0.710	0.308	1.636	-0.805	0.421
Guan W et al. 2020	Female	1.016	0.731	1.411	0.092	0.927
Wang D et al. 2020	Female	0.688	0.317	1.493	-0.945	0.345
Zhang JJ et al. 2020	Female	0.654	0.332	1.288	-1.228	0.219
Zhang X et al. 2020	Female	0.797	0.488	1.304	-0.903	0.367
Cai J et al. 2020	Female	0.385	0.211	0.705	-3.091	0.002
Chen G et al. 2020	Female	0.233	0.020	2.733	-1.159	0.246
Chen T et al. 2020	Female	0.436	0.259	0.733	-3.130	0.002
Deng Y et al. 2020	Female	0.290	0.168	0.503	-4.414	0.000
Mo P et al. 2020	Female	0.434	0.227	0.829	-2.526	0.012
Wan S et al. 2020	Female	1.094	0.522	2.294	0.238	0.812
Xie H et al. 2020	Female	0.578	0.224	1.491	-1.134	0.257
Yang X et al. 2020	Female	1.222	0.367	4.069	0.327	0.744
Qin C et al.2020	Female	0.786	0.536	1.153	-1.231	0.218
Yang B et al. 2020	Female	2.800	0.361	21.727	0.985	0.325
Wang Z et al. 2020	Female	0.833	0.257	2.697	-0.304	0.761
		0.636	0.511	0.793	-4.033	0.000

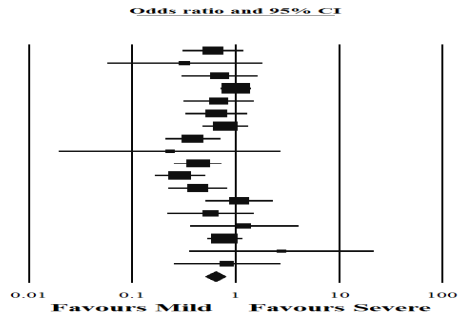


Figure 3. Forest plots assessing odds ratio (OR) and 95% confidence intervals between genders, a) male and b) female, and risk of increased incidence of COVID-19-related gastrointestinal symptoms in admitted and hospitalized patients. Meta-analysis was performed using a random-effects model.

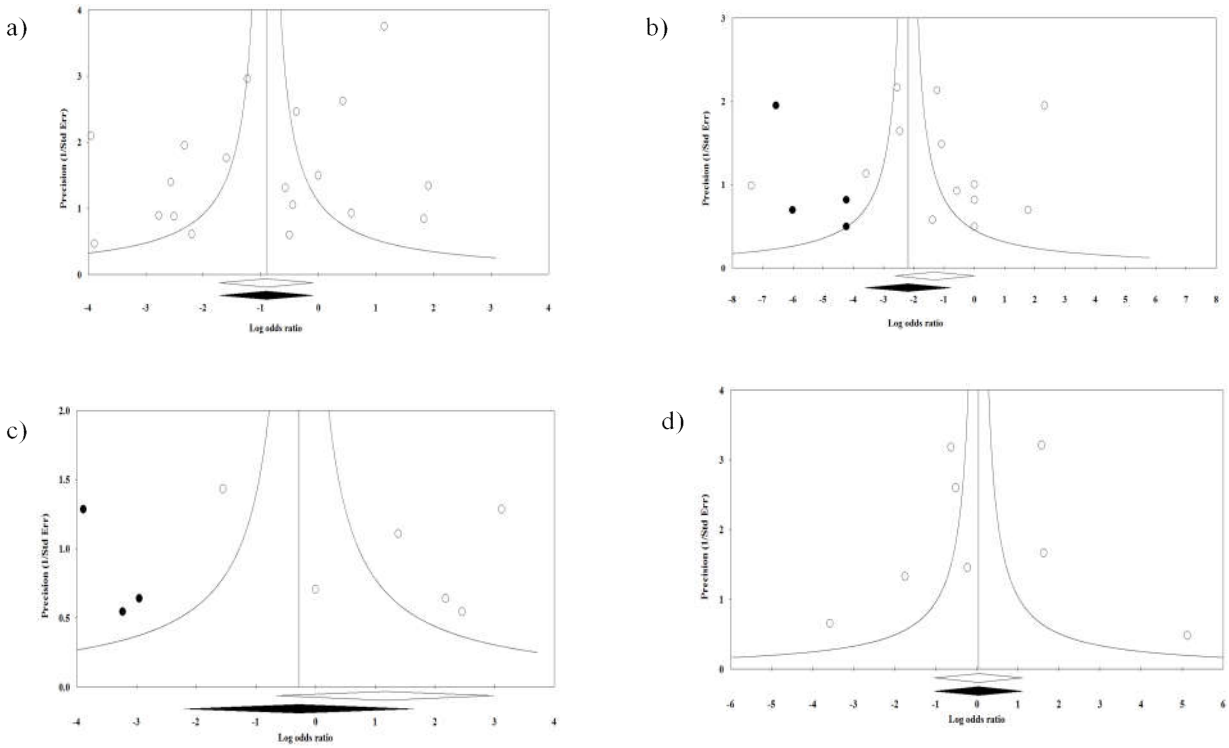


Figure 4. Random effects funnel plots detailing publication bias in the studies investigating the gastrointestinal symptoms of a) diarrhea, b) nausea and vomiting, c) abdominal pain, and d) anorexia in severe and mild forms of COVID-19 in admitted and hospitalized patients after trimming and filling. Open circles represent observed published studies; closed circles represent imputed unpublished studies

significantly associated with increased COVID-19 severity. On the other hand, the summary OR for male patients with severe COVID-19 infection was [OR (1.42), (95% CI 1.23, 1.65), $p < 0.05$, I^2= 18.4%, $P_{Heterogenity}$ = 0.23] (Fig. 3a) compared to females [OR (0.63), (95% CI 0.79, -4.03), $p < 0.05$, I^2= 43.3%, $P_{Heterogenity}$ = 0.02] (Fig. 3b). Strikingly, it was found that males are associated with a near 2.5-fold increase in odds of having severe COVID-19. Overall, these findings confirm that gender is an important factor that can affect the severity of COVID-19 infection. Statistical significant heterogeneity was observed within the studies included in the present meta-analysis. Sensitivity was evaluated using the leave-one-out method. Interestingly, when every single low-quality study was removed, the overall effect size of the variables was not changed. In addition, the overall effect size remained significantly higher in patients with severe COVID-19 following the removal of studies with larger sample sizes, which was nearly 49% of the pooled sample size.

Publication bias

The Begg's rank correlation tests (diarrhea; Kendall's tau with continuity correction = 0.00, Z=0.00, 2-tailed *p*-value= 1.00), (nausea and vomiting; Kendall's tau with continuity correction = 0.16, Z = 0.79, 2-tailed *p*-value = 0.42), (abdominal pain; Kendall's tau with continuity correction = 0.26, Z = 0.75, 2-tailed *p*-value = 0.45) and (anorexia; Kendall's tau with continuity correction = -0.03, Z = 0.12, 2-tailed *p*-value = 0.90) and the Egger's linear regression tests (diarrhea; $p = 0.25$, nausea and vomiting; $p = 0.87$, abdominal pain; $p = 0.57$, and anorexia; $p = 0.80$) were not statistically significant. Also, the funnel plot of the study precision (inverse standard error) per effect size (Log OR) was symmetric and indicated no potential publication bias in reporting the primary outcomes in patients with severe or mild COVID-19 (Fig. 4). It was observed that trim-and-fill correction was similar in the values of the observed studies and imputed missing studies in those reporting the primary outcomes of diarrhea and anorexia in patients with COVID-19. As for abdominal pain in patients with COVID-19, trim-and-fill correction imputed 3 possibly missing studies, resulting in a correct effect size of (OR: 0.75) (95% CI 0.11, 5.16). As reported by "fail safe N", 4 theoretically missing studies were needed to import the *p*-value to lower than 0.05. In addition, in presenting studies of nausea or vomiting in patients with severe and mild COVID-19 in which there was no funnel plot asymmetry, trim-and-fill correction imputed 4 potentially missing studies which led to a correct effect size of (OR: 0.11) (95% CI 0.02, 0.46). The "fail safe N" method showed that 99 theoretically missing studies were needed to create a significant effect.

Restricted maximum likelihood meta-regression

Random effects meta-regression was performed to assess whether the prevalence of gastrointestinal symptoms was associated with gender. The results indicated that males significantly influence the pooled effect size of the incidence of gastrointestinal symptoms compared to females (Figure 5).

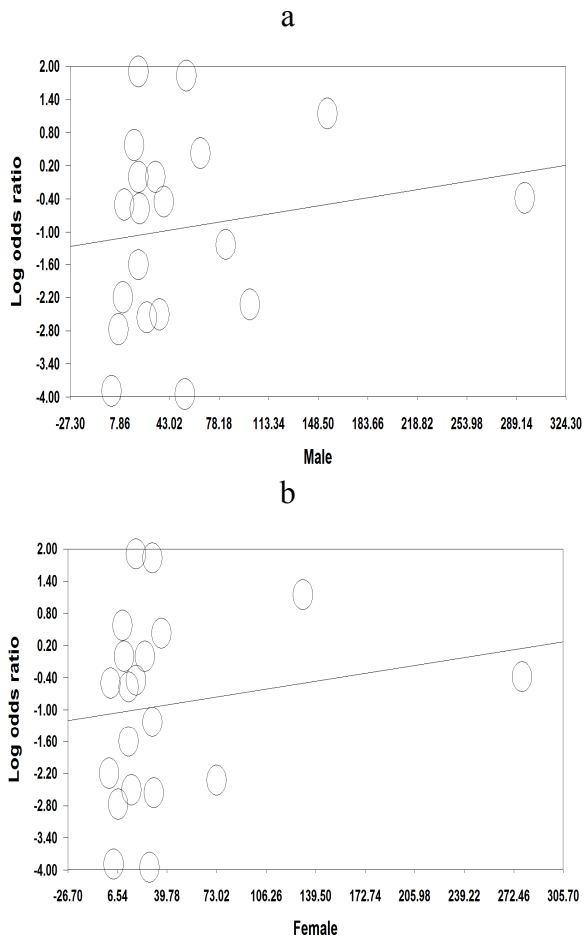


Figure 5. Random effects meta-regression plots of the association between the prevalence of gastrointestinal symptoms in COVID-19 patients with the variable of gender. The size of each circle is inversely proportional to the variance of change. Meta-analysis was performed using a random-effects model

Discussion

In the current study, all articles reporting gastrointestinal symptoms among patients with mild and severe COVID-19 infection published up to May 8, 2020 were reviewed. All of the included studies came from China. COVID-19 patients are still mainly known by the respiratory system, but evidence of other organ involvement, such as gastrointestinal (GI) symptoms, has been reported. In the present study, a pooled analysis of studies including COVID-19-related gastrointestinal symptoms through a systematic review and meta-analysis demonstrated that diarrhea and nausea and vomiting were found to be associated with an increased risk of severe COVID-9, whereas abdominal pain and anorexia had no significant increased prevalence in severe cases of COVID-19 compared to milder forms. Based on these results, it was hypothesized that diarrhea and nausea and vomiting in severe cases are promoted through direct injury to the intestinal mucosa following virus accumulation in the gut. The results revealed that the variable of gender has a significant effect on the severity of COVID-19, a finding which was confirmed by meta-regression analysis. The prevalence of COVID-19-related gastrointestinal symptoms was significantly increased in males compared to females. The current results support that the prevalence of diarrhea and nausea and vomiting in male patients referring to a hospital should be considered to better understand how COVID-19 affects the gastrointestinal tract.

The frequency of GI symptoms varied widely, from 3.0% to 39.6%, in the published papers (37). A recent study reported that nearly one-half of COVID-19 patients showed GI symptoms as their main complaint, and among the GI symptoms, diarrhea was the most commonly reported symptom. Hence, the diagnosis of COVID-19 in patients with GI symptoms is delayed, which can lead to exacerbation of the disease (14). Several recent studies have reported patients initially presenting with GI symptoms only; therefore, medical staff should be vigilant in examining clients presenting with GI symptoms. There are several reasons for the appearance of digestive symptoms among COVID-19 patients. The direct interacting and binding of the virus to the host cells and inflammatory chain response are two main points in this regard. The results of previous studies have shown that angiotensin-converting enzyme 2 (ACE2) is the main receptor to the entry of COVID-19 into the cells. Although cholangiocytes, type II alveolar, and kidney cells have been introduced as cells that express ACE2, the expression of this receptor in the mucosa of the oral cavity and GI tract has recently been reported (38). On the other hand, some studies isolated the viral from stool samples of COVID-19 patients. Therefore, based on the available evidence, the appearance of GI symptoms in COVID-19 patients can be the result of a direct attack of the virus on the cells of the GI tract and their entry through the ACE2 receptor, altering the natural flora of the intestines, and indirectly through systemic inflammation (39). These possible mechanisms are hypothesized, and further investigation is required to explore the underlining mechanisms for GI damage in COVID-19 patients.

Diarrhea and vomiting were found to have a relationship with the severity of COVID-19 infection. It is thought that diarrhea and vomiting may possibly be related to the amount of the virus in the intestine, which may lead to increased severity of illness observed to be related to a high viral load. These results are in agreement with the results of previous studies (24, 28). In contrast, however, the relationship between abdominal pain and anorexia with COVID-19 severity has not been shown in this study, which can be explained by the small number of examined samples and studies reporting these variables.

This meta-analysis has several limitations: 1) Most of the included studies were performed in one specified geographical region of the world; 2) Clinical trials are needed to focus more intently on the better identification of diagnostic and prognostic indicators in COVID-19 patients with digestive symptoms; 3) Finally, given the incidence of digestive symptoms in the early stages of infection, most of the included studies were conducted in hospitalized patients after admission.

In conclusion, this meta-analysis noted that of 4,265 patients with confirmed COVID-19 in China, diarrhea, nausea and vomiting were associated with severe outcomes from COVID-19 infection, whereas abdominal pain and anorexia had no significant increased prevalence in hospitalized patients with

severe COVID-19. We suggest that gastrointestinal symptoms of diarrhea, nausea and vomiting may be used as clinical prognosticators of severe COVID-19. Such consideration can lead to a more appropriate treatment protocol for the treatment of people with more severe disease.

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Conflict of interests

The authors declare that they have no conflict of interest.

References

1.Phelan AL, Katz R, Gostin LO. The novel coronavirus originating in Wuhan, China: challenges for global health governance. JAMA 2020;323:709-10.

2.Wu Y, Ho W, Huang Y, Jin DY, Li S, Liu SL, et al. SARS-CoV-2 is an appropriate name for the new coronavirus. The Lancet 2020;395:949-50.

3.Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020:102433.

4.Legido-Quigley H, Asgari N, Teo YY, Leung GM, Oshitani H, Fukuda K, et al. Are high-performing health systems resilient against the COVID-19 epidemic? The Lancet 2020;395:848-50.

5.Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020;382:1199-207.

6.Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. The Lancet 2020;395:514-23.

7.Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). BiosciI Trends 2020;14:69-71.

8.Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368.

9.Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497-506.

10.Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. J Med Virol 2020;92:441-7.

11.Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020;10:M20-0504.

12.Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020;395:507-13.

13.Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical features of COVID-19-related liver damage. Clin Gastroenterol Hepatol 2020;18:1561-6.

14.Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol Suppl 2020;115.

15.Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The presence of SARS-CoV-2 RNA in feces of COVID-19 patients. J Med Virol 2020;92:833-40.

16.Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. World J Meta-Anal 2017;5:80-4.

17.Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994:1088-101.

18.Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

19.Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis, version 2. Englewood, NJ:Biostat. 2005;104.

20.Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-62.

21.Guan Wj, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.

22.Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.

23.Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75:1730-41.

24.Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis 2020;94:81-7.

25.Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, et al. Clinical characteristics of 82 death cases with COVID-19. medRxiv 2020.

26.Cai Q, Huang D, Ou P, Yu H, Zhu Z, Xia Z, et al. COVID-19 in a Designated Infectious Diseases Hospital Outside Hubei Province, China. Allergy 2020;75:1742–52.

27.Chen G, Wu D, Guo W. Clinical and immunologic features in severe and moderate forms of Coronavirus Disease 2019. J Clin Invest 2020;130:2620-9.

28.Deng Y, Liu W, Liu K, Fang YY, Shang J, Wang K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J 2020;133:1261-7.

29.Mo P, Xing Y, Xiao Y, Deng L, Zhao Q, Wang H, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. Arch. Clin Infect Dis 2020;ciaa270.

30.Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020;92:797-806.

31.Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of Non-ICU hospitalized patients with coronavirus disease 2019 and liver injury : A Retrospective study. Liver Int 2020;40:1321-6.

32.Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475-81.

33.Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020;69:997-1001.

34.Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;71:762-8.

35.Young BE, Ong SWX, Kalimuddin S, Low JG, Tan SY, Loh J, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. JAMA 2020;323:1488-94.

36.Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis 2020;71:769-77.

37.Schmulson M, Davalos MF, Berumen J. Beware: Gastrointestinal symptoms can be a manifestation of COVID-19. Rev Gastroenterol Mex 2020;85:282-87.

38.Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int. J Oral Sci 2020;12:1-5.

39.He Y, Wen Q, Yao F, Xu D, Huang Y, Wang J. Gut–lung axis: the microbial contributions and clinical implications. Crit. Rev. Microbiol 2017;43:81-96.