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REVIEW

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Gastroenterology manifestations and COVID-19 outcomes: A meta-analysis of 25,252 cohorts among the first and second waves

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Abstract

A meta-analysis was performed to identify patients with coronavirus disease 2019 (COVID-19) presenting with gastrointestinal (GI) symptoms during the first and second pandemic waves and investigate their association with the disease outcomes. A systematic search in PubMed, Scopus, Web of Science, ScienceDirect, and EMBASE was performed up to July 25, 2020. The pooled prevalence of the GI presentations was estimated using the random-effects model. Pairwise comparison for the outcomes was performed according to the GI manifestations' presentation and the pandemic wave of infection. Data were reported as relative risk (RR), or odds ratio and 95% confidence interval. Of 125 articles with 25,252 patients, 20.3% presented with GI manifestations. Anorexia (19.9%), dysgeusia/ageusia (15.4%), diarrhea (13.2%), nausea (10.3%), and hematemesis (9.1%) were the most common. About 26.7% had confirmed positive fecal RNA, with persistent viral shedding for an average time of 19.2 days before being negative. Patients presenting with GI symptoms on admission showed a higher risk of complications, including acute

respiratory distress syndrome (RR = 8.16), acute cardiac injury (RR = 5.36), and acute kidney injury (RR = 5.52), intensive care unit (ICU) admission (RR = 2.56), and mortality (RR = 2.01). Although not reach significant levels, subgroup-analysis revealed that affected cohorts in the first wave had a higher risk of being hospitalized, ventilated, ICU admitted, and expired. This meta-analysis suggests an association between GI symptoms in COVID-19 patients and unfavorable outcomes. The analysis also showed improved overall outcomes for COVID-19 patients during the second wave compared to the first wave of the outbreak.

KEYWORDS
COVID-19, GIT, meta-analysis, pandemic, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has demonstrated the deadly impact of a highly transmissible, novel respiratory pathogen infecting humans.[1] Much of the initial response to the pathogen was centered around finding ways to prevent patients from developing severe respiratory symptoms, often with poor outcomes.[2] The patients' risk for developing complications was comorbid conditions or abnormal laboratory values on presentation.[3,4] The typical symptoms of the illness are fever, dry cough, loss of taste or smell, fatigue, and shortness of breath. While acute respiratory manifestations of the disease are still the focal point of clinical research, the Centers for Disease Control and Prevention reports that gastrointestinal (GI) symptoms may be indicators of COVID-19 infection.[5] Also, viral shedding in the feces of infected patients is not uncommon.[6] There are conflicting reports of the significance of GI symptoms in predicting the outcome of patients with COVID-19. Therefore, GI symptoms have not been used as a predictive tool by healthcare providers.[7,8]

However, we believe the further analysis is indicated for several reasons. First, GI pathology in COVID-19 infections is attributed to the angiotensin-converting enzyme-2 (ACE-2) receptor expressed in epithelial cells of the GI tract, which mediates direct viral entry and damage.[5,6] Second, the gut-lung axis is thought to play a role in indirect GI damage via the exaggerated immune reaction typical in these patients.[6] Third, respiratory viruses have been demonstrated to increase CD4+ T-cell entry into the small intestine leading to a surge of cytokine release.[9] Fourth, hepatocytes also express the ACE-2 receptor, which may play a role in acute liver injuries often seen in hospitalized patients with COVID-19.[10] Lastly, the fecal–oral transmission may be a major source of spread, particularly in healthcare settings.[11]

In this sense, the purpose of this meta-analysis is to analyze patients with COVID-19 in terms of the presence of GI symptoms and its potential contribution to the outcomes of the disease. We also compared the differences in presentation and outcome between the first and the second wave of patients with COVID-19.

2 | METHODS

2.1 | Search strategy

The study protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] A comprehensive literature search of all eligible articles was conducted by two reviewers (RME and RM) utilizing the electronic medical databases; Web of Science, PubMed, Scopus, Science Direct, and Embase up to July 25, 2020. The subsequent set of MeSH terms and keywords related to gastrointestinal manifestations and COVID-19 were applied, including ("2019-ncov," "SARS-COV-2," "Wuhan coronavirus," OR "COVID-19") AND ("Gastrointestinal manifestations," "Gastrointestinal symptoms," "Gastrointestinal presentations," "GI symptoms," "Digestive symptoms," "Gastric symptoms," "Digestive manifestations," "Gastrointestinal features" OR "Gastrointestinal involvement") AND ("Viral shedding," "Fecal shedding," "Feces," OR "Fecal oral"). No language, time, and/or country limitations have been applied. We also screened manually the references list of articles for potentially relevant articles.

2.2 | Eligibility criteria

We screened the records against the following inclusion criteria: (a) study population: patients with COVID-19 (including adult, but not pediatric and/or pregnant women) enclosing data on gastrointestinal manifestations such as diarrhea, vomiting, nausea, abdominal pain, anorexia, dysgeusia/ageusia, heartburn, constipation, hemoptysis, hematochezia, hematemesis, melena or fecal occult blood or underwent fecal shedding screening using fecal RNA reverse-transcription polymerase chain reaction (RT-PCR). (b) Study design: Observational studies including case series, prospective/retrospective cohort studies, and case–control studies. (c) Articles reporting original enough data demographics, laboratory values, and/or outcomes. (d) Peer-reviewed articles. We excluded articles with the following characteristics: (a) pediatric and/or pregnant women, (b) case reports, case series with sample size less than five patients, (c) duplicate data,

(d) reviews, editorial materials, non-peer-reviewed articles, and preprint versions, and (e) articles reporting irrelevant, or insufficient data.

2.3 | Definitions and subgroup analysis

Positive GI cases were those who had at least one of the following gastrointestinal symptoms: anorexia, nausea, vomiting, diarrhea, abdominal pain, recent-onset constipation, heartburn, dysgeusia/ageusia, hematemesis, hematochezia, and/or melena. Non-GI controls were defined as asymptomatic cohorts or presenting with respiratory and/or neurologic and/or systemic symptoms, not including any reported GI symptoms. Patients with a severe phenotype should meet at least one of the following three criteria: (a) respiratory distress and respiratory rate higher than 30 per minute; (b) fingertip blood oxygen saturation less than 93% during rest; (c) partial arterial oxygen pressure (PaO_2)/fraction of inspiration oxygen (FiO_2) ≤ 300 mmHg.[13]

Regarding pairwise meta-analysis, we conducted five comparisons, including (1) severe patients with COVID-19 versus non-severe ones; (2) hospitalized patients versus discharged cases; (3) ICU admission patients versus floor hospitalization patients; (4) nonsurvived patients versus survived; and (5) finally COVID-19 patients with positive fecal RNA RT-PCR versus negative cases.

In addition, a subgroup analysis was performed according to the publication date to investigate a potential difference between the first and second waves of the pandemic. The former was defined as patients infected with COVID-19 before May 15, 2020. The latter was defined as patients infected with COVID-19 at or after May 16, 2020.[14,15] May 15 was selected for two reasons: It is closest to the median date of publication of the included 126 studies. It is approximately the date of various re-opening strategies in many geographic areas. Also, studies were categorized according to geographic distribution into Asian and non-Asian studies.

2.4 | Data extraction and covariate assessment

Independent investigators (AE, MHA, MMS, MO, RM, NM, and ASA) abstracted the reported data in a pre-specified excel sheet. Studies' characteristics, patient demographics, and clinical presentation, comorbid conditions, and results of laboratory testing were also retrieved. Complications such as acute respiratory distress syndrome (ARDS), acute cardiac injury, arrhythmias, acute liver injury, acute kidney injury (AKI), shock, and sepsis, degree of severity, intensive care unit (ICU) admission, treatment protocols, length of hospital stay, and outcomes were collected. RME has revised the whole extracted data and resolved any dissonance.

2.5 | Data synthesis and statistical analysis

All statistical analyses were processed with Comprehensive Meta-Analysis version 3.0 and STATA 16.0, and the results were considered significant at a p value less than .05. Related events or means and standard deviations (*SD*s) of each arm were extracted. Other statistical variable data, like median and interquartile range (IQR), were converted to means and *SD*s. One-arm meta-analysis was first performed using the Continuous Random-effects model and the DerSimonian–Laird method. The pooled mean effect size and proportion were estimated for quantitative and binary data, respectively. Next, a two-arms meta-analysis was performed to compare clinical outcomes and admission outcomes between cohorts presented with gastrointestinal manifestations and those without gastrointestinal symptoms. Data were reported as standardized mean difference (SMD), relative risk (RR), or odds ratio (OR), and 95% confidence interval (CI).

Heterogeneity was quantified by using I^2 statistics. Articles were considered to have significant heterogeneity between studies when the p value less than .1 or I^2 greater than 50%.[16] Subgroup analysis by the pandemic wave of infection (first/early wave vs. second/late wave) and ethnicity (Asian, American, European, and Mexican) was carried out. Random-effects Meta-regression was performed to identify the influence of potential effect modifiers on the pooled results and explain the heterogeneity between studies. Covariates as geographical distribution and date of publication were employed. Also, publication bias was evaluated by Egger's regression test.[17]

3 | RESULTS

3.1 | Characteristics of included studies

Systematic search as depicted in Figure 1A yield 125 eligible publications, including 25,252 participants.[18–141] Articles were published in 11 countries, predominated by China (101 studies; Figure 1B). They were published from January 24 to July 25, 2020, covering the two COVID-19 pandemic waves. The sample size ranged from 6 to 1452 per article. The basic characteristics of the 125 articles used for one-arm meta-analysis are listed in Table 1. For pairwise comparisons, 60 articles compared the clinical data, laboratory features, and outcomes of COVID-19 patients with and without GI symptoms (Table 2).[18,24,29,34,36,40,42–47,50,51,53,54,58,60,62,64,65,67,70,73,74,77,80,81,83,86,87,89,91–96,98,99,102,110,111,116–119,121–124,130,132,133,142] Of these, 26 studies compared severe/critical COVID-19 patients versus mild cases,[18,34,43,44,46,47,51,53,62,67,70,73,74,77,92,93,98,99,102,111,117–119,121,122,133] four articles compared between hospitalized patients and those not required hospitalization,[45,80,89,142] five studies compared ICU admitted patients versus floor hospitalization,[50,80,96,116,142] 11 publications compared between those who died with those who survived,[29,34,58,60,83,91,94,110,117,123,137] three articles reported the comparison between COVID-19 patients with positive versus

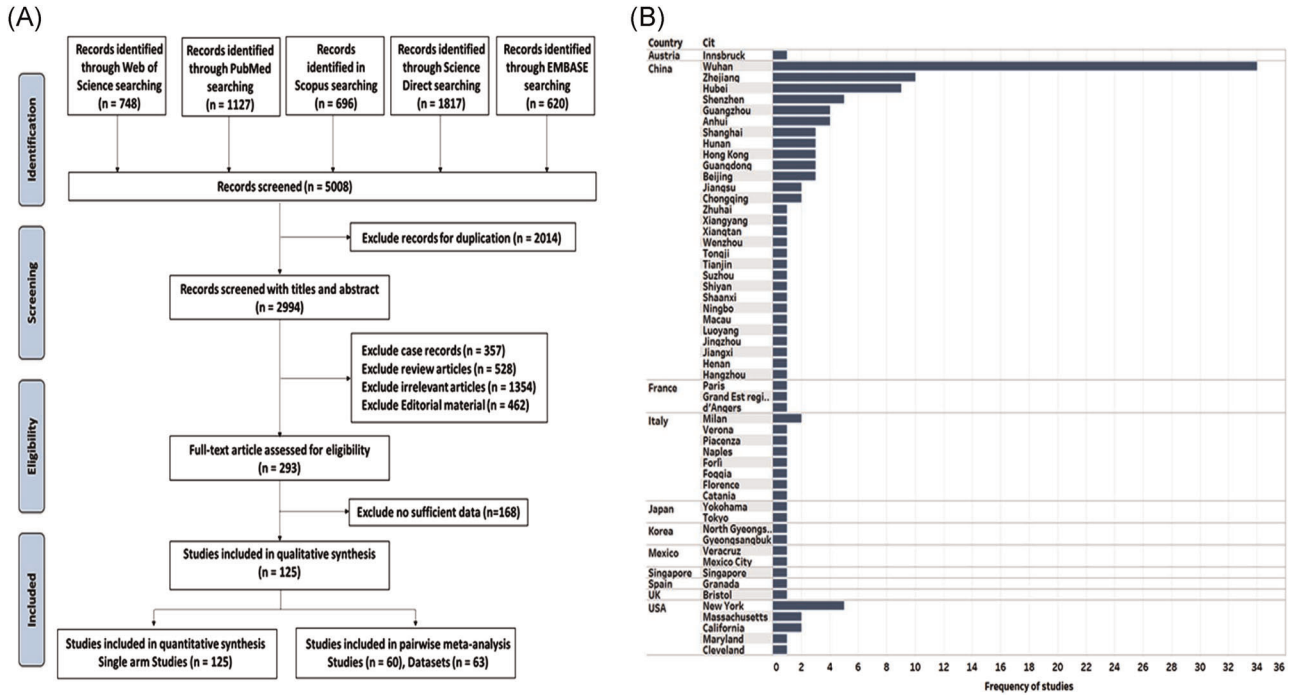

FIGURE 1 Selection of eligible studies and their geographic region. (A) Flowchart for systematic literature search (B) Mapping the geographic distribution of the studies

negative fecal shedding,[36,65,130] and of the remaining 14 studies comparing cohorts with and without GI symptoms.[24,40,42,46,54,64,81,86,87,95,101,124,133,138]

3.2 | The pooled prevalence of patients with gastrointestinal manifestations

The one-arm meta-analysis included 25,252 COVID-19 positive patients with a mean age of 52.1 years (95% CI, 49.9–54.3). The males accounted for 52.2% (95%CI, 50.8%–53.6%). Most common comorbid conditions were hypertension (22.3%, 95% CI, 19.3%–25.6%) and obesity (20.7%, 95%CI, 17.1%–24.9%).

Of the overall COVID-19 patients, 20.3% (95% CI, 16.6%–23.9%) presented with GI features, and 26.7% (95%CI, 16.9%–36.5%) had confirmed fecal viral shedding with positive fecal RNA RT-PCR test. The most common presenting gastrointestinal symptoms were anorexia (19.9%), dysgeusia/ageusia (15.4%), and diarrhea (13.2%). Fecal testing showed persistent viral shedding for an average time of 19.2 days (95%CI, 16.1–22.4) before being negative. The proportion of GI features was 18.7% (95%CI, 13.6%–23.8%) in studies published during the first pandemic wave, which was insignificant from the second wave (23.1%, 95%CI, 18.7%–27.5%). Subgroup analysis by geographical region showed a higher frequency of patients presented with gastrointestinal involvement in European studies (36.7%, 95%CI, 28.3%–45.1%) compared with Asian (18.1%, 95% CI, 13.9%–22.2%) and American (24.6%, 95% CI, 19.5%–29.6%) studies (Figure 2).

A pooled one-arm meta-analysis of detailed demographic, clinical, and laboratory features of COVID-19 patients with gastrointestinal presentations is demonstrated in Table S1. As depicted in Figure 3, subgroup analysis by the pandemic waves revealed a higher prevalence of acute cardiac injury and ICU admission (both $p < .001$) in the first wave. In contrast, second wave articles reported higher ARDS frequencies, AKI, mechanical ventilation use, and a higher risk of mortality (all $p < .001$).

3.3 | Differential outcomes of patients presenting with gastrointestinal manifestations

Pairwise comparative analysis of COVID-19 cases with and without GI symptoms is shown in Table 3. COVID-19 patients presented with GI features were more likely to be older (SMD = 0.53; 95% CI = 0.41–0.64, $p < .001$), and males (OR = 1.29; 95% CI = 1.14–1.46, $p < .001$). Black patients were also less likely to present with GI features. They had higher odds of having comorbid conditions as hypertension (OR = 2.12; 95%CI = 1.76–2.56), diabetes (OR = 2.06, 95% CI = 1.66–2.55, $p < .001$), chronic kidney disease (OR = 1.78, 95% CI = 1.21–2.63, $p = .003$), chronic liver disease (OR = 1.51, 95% CI = 1.14–2.0, $p = .004$), and malignancy (OR = 1.44, 95% CI = 1.11–1.87, $p = .005$).

As depicted in Table 3G–I, despite lack of association with the degree of COVID-19 severity and length of hospital stay, cases presenting with GI symptoms on admission were more subjected to complications including ARDS (RR = 8.16; 95% CI = 4.77–13.9,

TABLE 1 Characteristics of the included studies in the single-arm meta-analysis

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Aghemo A[19]	11-May	Milan	Italy	European	Retrospective	292	65.0 ± 14.1	68.15	69	11	–	–	–
Ai J[20]	9-Jun	Xiangyang	China	Asian	Retrospective	7	54.1 ± 15.5	57.14	6	2	4	6	7
Annweiler C[21]	18-Jun	d'Angers	France	European	Retrospective	353	84.7 ± 7.0	45.33	77	22	22	–	–
Barillari M[22]	25-Jul	Multiple	Italy	European	Observational multicenter	294	42.1 ± 12.3	50.00	81	42	42	37	84
Cai Q[23]	18-Mar	Shenzhen	China	Asian	Open-Label nonrandomized Control	80	47.9 ± 18.7	43.75	1	–	–	–	–
Cao C[24]	15-Jun	Ningbo, Jingzhou Hubei	China	Asian	Retrospective	157	49.3 ± 14.5	47.13	25	–	21	–	47
Cavaliere K[25]	20-Apr	New York	USA	American	Retrospective	6	67.8 ± 12.4	50.00	–	–	–	–	–
Chang D[26]	17-Mar	Beijing	China	Asian	Retrospective	13	38.7 ± 10.4	76.92	1	–	–	–	–
Chang D[27]	20-Jun	Beijing	China	Asian	Retrospective	67	46.6 ± 15.8	56.72	6	–	–	–	–
Chen A[28]	16-May	Maryland	USA	American	Prospective Case-Control	101	48.3 ± 14.7	40.59	51	14	30	26	54
Chen F[29]	8-Jul	Wuhan	China	Asian	Retrospective	681	63.7 ± 13.3	53.16	119	–	–	–	–
Chen J[30]	19-Mar	Shanghai	China	Asian	Retrospective	249	50.3 ± 20.7	50.60	8	–	–	–	8
Chen L[31]	13-May	Guangdong	China	Asian	Retrospective	51	59.5 ± 13.6	66.67	3	–	–	–	–
Chen M[32]	13-May	Hubei	China	Asian	Retrospective	11	48.4 ± 14.1	72.73	2	–	3	–	–
Chen N[33]	30-Jan	Wuhan	China	Asian	Retrospective	99	55.5 ± 13.1	67.68	2	1	1	–	–
Chen R[34]	11-May	Multi provinces	China	Asian	Retrospective	548	56.0 ± 14.5	57.12	14	18	–	–	–
Chen X[35]	30-Jun	Guangzhou	China	Asian	Retrospective	267	48.3 ± 20.7	45.32	19	7	14	_	47
Chen Y[36]	3-Apr	Wuhan	China	Asian	Retrospective	42	51.9 ± 14.3	35.71	7	3	4	–	–
Cholankeril G[142]	10-Jun	California	USA	American	Retrospective	207	49.3 ± 22.9	50.24	22	22	22	14	–
Cholankeril G[37]	10-Apr	California	USA	American	Retrospective	116	50.7 ± 23.7	53.45	12	12	12	10	22
Deng W[38]	19-Jun	Chongqing	China	Asian	Retrospective	61	54.8 ± 12.9	40.98	3	–	–	–	–

TABLE 1 (Continued)

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Duan X[39]	26-May	Luoyang	China	Asian	Retrospective	25	52.0 ± 19.3	60.00	2	1	1	–	3
Effenberger M[40]	20-Apr	Innsbruck	Austria	European	Retrospective	40	65.4 ± 15.1	60.00	22	5	11	–	–
Fang Z[41]	21-Mar	Xiangtan	China	Asian	Retrospective	32	43.0 ± 14.8	50.00	3	–	–	–	–
Ferm S[42]	1-Jun	New York	USA	American	Retrospective	892	59.3 ± 18.5	59.87	177	91	148	70	105
Fu J[43]	6-May	Suzhou	China	Asian	Retrospective	75	46.0 ± 14.0	60.00	6	–	–	–	–
Guan W[44]	28-Feb	Multi provinces	China	Asian	Retrospective	1099	46.7 ± 17.1	57.96	42	55	55	–	–
Hajifathalian K[45]	8-May	New York	USA	American	Retrospective	1059	61.1 ± 18.3	57.70	234	91	168	72	240
Han C[46]	15-Apr	Wuhan	China	Asian	Retrospective	206	60.5 ± 48.1	44.17	67	24	–	9	70
Han J[47]	25-Jun	Tianjin	China	Asian	Retrospective	185	44.0 ± 17.9	51.35	11	–	–	–	–
Hong L[48]	24-Jun	Zhejiang	China	Asian	Retrospective	127	45.7 ± 51.1	55.91	13	5	5	–	38
Hu J[49]	28-May	Zhejiang	China	Asian	Retrospective	884	46.0 ± 14.4	51.47	71	31	31	–	–
Huang C[50]	24-Jan	Wuhan	China	Asian	Retrospective	41	49.3 ± 12.6	73.17	1	–	–	–	–
Huang M[51]	1-Jun	Jiangsu	China	Asian	Retrospective	60	60.0 ± 52.6	58.33	4	2	2	–	–
Jehi L[52]	10-Jun	Cleveland	USA	American	Prospective	1108	52.3 ± 19.9	49.91	185	129	–	–	216
Jin A[53]	12-May	Beijing	China	Asian	Retrospective	45	58.8 ± 20.1	40.00	–	1	2	–	5
Jin X[54]	24-Mar	Zhejiang	China	Asian	Retrospective	651	45.1 ± 14.4	50.84	–	–	–	–	–
Kaafarani H[55]	1-May	Massachusetts	USA	American	Retrospective	141	58.0 ± 17.1	65.25	42	31	31	21	–
Lapostolle F[56]	30-May	Paris	France	European	Prospective observational	1452	42.9 ± 18.1	48.21	352	168	288	–	305
Lei Z[57]	9-Apr	Guangzhou	China	Asian	Retrospective	119	53.4 ± 13.2	64.71	7	4	4	–	–
Leung C[58]	27-Apr	Multi provinces	China	Asian	Retrospective	154	72.2 ± 8.5	57.79	7	2	2	–	–
Li J[59]	19-May	Wuhan	China	Asian	Retrospective	54	53.3 ± 47.4	16.67	4	6	52	–	–
Li J[60]	1-Jun	Wuhan	China	Asian	Retrospective	74	64.3 ± 12.6	59.46	6	–	–	–	41
Li K[18]	29-Feb	Chongqing	China	Asian	Retrospective	83	45.5 ± 12.3	53.01	7	–	–	7	–

(Continues)

TABLE 1 (Continued)

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Li W[61]	17-Apr	Hubei	China	Asian	Retrospective	105	47.7 ± 11.8	57.14	2	3	3	–	6
Li X[62]	12-Apr	Wuhan	China	Asian	Retrospective	548	59.0 ± 15.5	50.91	179	45	–	16	–
Liang Y[63]	29-Jun	Guangdong	China	Asian	Prospective	86	29.5 ± 37.8	51.16	6	4	–	–	15
Lin L[64]	2-Apr	Zhuhai	China	Asian	Retrospective	95	45.3 ± 18.3	47.37	23	4	17	–	17
Lin W[65]	16-Jul	Guangzhou	China	Asian	Retrospective	217	49.7 ± 20.0	49.77	17	4	9	3	38
Liu B[66]	3-Jun	Wuhan	China	Asian	Prospective	68	44.3 ± 16.4	36.76	5	4	4	–	–
Liu F[67]	14-Apr	Wuhan	China	Asian	Retrospective	140	64.3 ± 13.8	35.00	5	–	3	3	9
Liu F[68]	17-Jun	Wuhan	China	Asian	Retrospective	17	57.0 ± 9.6	76.47	4	–	–	–	–
Liu F[69]	12-Mar	Zhejiang	China	Asian	Prospective	10	42.0 ± 11.8	40.00	–	–	3	–	–
Liu J[70]	18-Apr	Wuhan	China	Asian	Retrospective	40	48.7 ± 13.9	37.50	3	1	3	1	–
Liu k[71]	5-May	Hubei	China	Asian	Retrospective	137	53.3 ± 46.7	44.53	11	–	–	–	–
Liu y[72]	9-Feb	Shenzhen	China	Asian	Retrospective	12	53.7 ± 18.0	66.67	2	2	2	–	–
Lo I[73]	15-Mar	Macau	China	Asian	Retrospective	10	48.3 ± 27.4	30.00	8	–	5	2	–
Lui G[74]	18-Apr	Hong Kong	China	Asian	prospective	11	56.7 ± 20.7	63.64	2	–	–	–	–
Luo S[75]	20-Mar	Hubei	China	Asian	Retrospective	183	53.8 ± NA	55.74	68	119	134	45	180
Mao B[76]	14-May	Shanghai	China	Asian	Retrospective	188	46.0 ± 24.0	50.00	6	1	1	–	24
Mo P[77]	16-Mar	Wuhan	China	Asian	Retrospective	155	54.0 ± 17.8	55.48	7	3	3	3	26
Nobel Y[78]	12-Apr	New York	USA	American	Retrospective case-control	278	NA	52.16	56	63	63	–	–
Noh J[79]	21-May	Gyeongsangbuk	Korea	Asian	Prospective	199	38.0 ± 13.1	34.67	9	–	–	–	1
Ortiz-Brizuela E[80]	14-May	Mexico City	Mexico	Mexican	Prospective	309	43.3 ± 15.6	59.22	94	30	–	39	–
Pan L[81]	14-Apr	Hubei	China	Asian	Retrospective	204	52.9 ± 15.9	52.45	35	4	–	2	81
Park S[82]	10-Jun	North Gyeongsang	Korea	Asian	Prospective	46	33.7 ± 28.9	45.65	7	–	1	5	1
Peng S[83]	10-Apr	Wuhan	China	Asian	Retrospective	11	60.3 ± 13.3	72.73	3	–	6	–	6
Poggiali E[84]	26-Mar	Piacenza	Italy	European	Retrospective	10	50.0 ± 18.0	60.00	6	3	–	1	–
Qi L[85]	17-May	Hunan	China	Asian	Retrospective	147	43.7 ± 14.1	45.58	–	–	–	–	–

TABLE 1 (Continued)

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Ramachandran P[86]	29-Jun	New York	USA	American	Retrospective	150	62.1 ± 15.1	55.33	15	6	6	3	–
Redd W[87]	22-Apr	Massachusetts	USA	American	Retrospective	318	63.4 ± 16.6	54.72	107	49	84	46	110
Remes-Troche J[88]	21-May	Veracruz	Mexico	Mexican	Retrospective	112	43.7 ± 15.0	72.32	20	8	–	11	–
Rivera-Izquierdo M[89]	16-Jun	Granada	Spain	European	Prospective	76	45.8 ± 11.4	30.26	31	7	17	21	12
Shi H[90]	24-Feb	Wuhan	China	Asian	Retrospective	81	49.5 ± 11.0	51.85	3	4	–	–	1
Sun H[91]	8-May	Wuhan	China	Asian	Retrospective	244	70.0 ± 8.1	54.51	72	–	–	10	–
Tabata S[92]	12-Jun	Tokyo	Japan	Asian	Retrospective	71	62.0 ± 22.9	54.93	8	–	–	–	–
To K[93]	23-Mar	Hong Kong	China	Asian	Retrospective	23	57.7 ± 27.5	56.52	2	–	1	–	–
Tomlins J[94]	27-Apr	Bristol	UK	European	Retrospective	95	72.0 ± 17.1	63.16	11	13	13	5	–
Wan Y[95]	15-Apr	Guangdong, Hubei, Jiangxi	China	Asian	Retrospective	230	47.8 ± 16.2	56.09	49	–	–	3	–
Wang D[96]	7-Feb	Wuhan	China	Asian	Retrospective	138	55.3 ± 19.3	54.35	14	5	14	3	55
Wang K[97]	23-Mar	Hubei	China	Asian	Retrospective	114	51.3 ± 40.7	50.88	3	–	–	–	–
Wang R[98]	11-Apr	Anhui	China	Asian	Retrospective	125	38.8 ± 13.8	56.80	50	24	24	–	–
Wang X[99]	3-Apr	Wuhan	China	Asian	Retrospective	1012	49.0 ± 14.1	51.78	152	36	–	37	–
Wang Z[100]	12-Mar	Wuhan	China	Asian	Retrospective	69	46.3 ± 20.0	46.38	10	3	–	–	7
Wei X[101]	18-Apr	Wuhan	China	Asian	Retrospective	84	45.0 ± 37.0	33.33	26	6	16	2	–
Wei Y[102]	17-Apr	Anhui	China	Asian	Retrospective	167	42.3 ± 15.3	56.89	56	17	17	–	–
Wu J[103]	29-Feb	Jiangsu	China	Asian	Retrospective	80	46.1 ± 15.4	48.75	1	1	1	–	–
Xie J[104]	6-Jun	Zhejiang	China	Asian	Retrospective	104	54.0 ± 15.6	60.58	13	3	6	2	–
Xiong Y[105]	3-Mar	Hubei	China	Asian	Retrospective	42	49.5 ± 14.1	59.52	10	–	–	–	–
Xu K[106]	9-Apr	Hangzhou & Shenzhen	China	Asian	Retrospective	113	52.7 ± 14.8	58.41	–	–	–	–	–
Xu X[107]	28-Feb	Guangzhou	China	Asian	Retrospective	90	51.3 ± 50.4	43.33	5	2	5	–	–
Xu X[108]	19-Feb	Zhejiang	China	Asian	Retrospective case series	62	41.7 ± 14.8	56.45	3	–	–	–	–

(Continues)

TABLE 1 (Continued)

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Yang W[109]	26-Feb	Wenzhou	China	Asian	Retrospective	149	45.1 ± 13.3	54.36	11	2	2	–	–
Yang X[110]	21-Feb	Wuhan	China	Asian	Retrospective	52	59.7 ± 13.3	67.31	–	2	–	–	–
Yang Y[111]	29-Apr	Shenzhen	China	Asian	Retrospective	50	54.0 ± 41.5	58.00	4	–	–	–	–
Yin S[112]	30-Apr	Hunan	China	Asian	Retrospective	33	47.5 ± 24.8	48.48	5	–	–	–	–
Yoshimura Y[113]	12-Jun	Yokohama	Japan	Asian	Retrospective	17	69.0 ± 10.0	47.06	1	4	4	–	–
Young B[114]	3-Mar	Singapore	Singapore	Asian	Retrospective	18	50.3 ± 31.1	50.00	3	–	–	–	–
Zayet S[115]	16-Jun	Grand Est region	France	European	Retrospective & observational	70	56.7 ± 19.3	41.43	28	2	22	14	–
Zeng Q[116]	12-Jun	Henan & Shaanxi Provinces	China	Asian	Retrospective &observational	149	42.3 ± 18.5	61.07	11	4	8	–	20
Zhang G[117]	9-Apr	Wuhan	China	Asian	Retrospective	221	53.5 ± 20.4	48.87	25	–	–	5	80
Zhang H[118]	23-Jun	Wuhan	China	Asian	Retrospective	107	66.7 ± 45.9	56.07	15	–	–	–	–
Zhang J[119]	15-Apr	Wuhan	China	Asian	Retrospective	663	56.2 ± 18.5	48.42	61	17	31	5	–
Zhang J[120]	6-Jun	Wuhan	China	Asian	Retrospective	135	62.3 ± 10.4	57.78	18	15	15	2	12
Zhang J[121]	28-Apr	Wuhan	China	Asian	Retrospective	111	42.3 ± 18.5	41.44	10	–	–	–	–
Zhang J[122]	19-Feb	Wuhan	China	Asian	Retrospective	140	56.3 ± 45.9	50.71	18	7	24	8	17
Zhang L[123]	29-Jun	Wuhan	China	Asian	Retrospective	409	64.0 ± 11.1	57.21	91	42	50	28	–
Zhang L[124]	1-Apr	Anhui	China	Asian	Retrospective	80	44.1 ± 17.1	58.75	33	17	17	–	–
Zhang L[125]	26-Mar	Wuhan	China	Asian	Retrospective	28	63.7 ± 10.4	60.71	3	–	–	–	–
Zhang P[126]	5-Jun	Wuhan	China	Asian	Retrospective	136	67.7 ± 14.8	63.24	28	–	–	–	–
Zhang X[127]	20-Mar	Zhejiang	China	Asian	Retrospective	645	45.3 ± 13.9	50.85	53	22	22	–	–
Zhao D[129]	12-Mar	Anhui	China	Asian	Comparative	19	43.7 ± 21.5	57.89	1	–	–	–	–
Zhao F[130]	16-May	Shenzhen	China	Asian	Retrospective	401	46.7 ± 20.0	47.38	25	1	1	–	–
Zhao W[131]	3-Mar	Hunan	China	Asian	Retrospective	101	44.4 ± 12.3	55.45	3	2	2	–	–
Zheng S[132]	21-Apr	Zhejiang	China	Asian	Retrospective	96	54.7 ± 15.2	60.42	10	2	5	–	–
Zheng T[133]	8-Jun	Wuhan	China	Asian	Retrospective	1320	49.0 ± 12.6	43.86	107	57	57	11	62
Zheng Y[134]	30-Apr	Shiyan	China	Asian	Retrospective	73	46.7 ± 40.7	54.79	1	–	–	–	3

TABLE 1 (Continued)

First author	Publication date	Study location	Country	Geographic distribution	Study design	Sample size	Age, years, mean ± SD	Sex (% male)	GI symptoms (number)				
									Diarrhea	Vomiting	Nausea	Abd pain	Anorexia
Zhong Q[135]	28-Mar	Wuhan	China	Asian	Retrospective	49	31.3 ± 3.7	14.29	–	3	–	–	–
Zhou B[136]	17-Apr	Tongji	China	Asian	Retrospective	41	56.0 ± 10.4	53.66	–	–	–	–	
Zhou F[137]	9-Mar	Wuhan	China	Asian	Retrospective	191	56.3 ± 15.6	62.30	9	7	7	–	–
Zhou Z[138]	19-Mar	Wuhan	China	Asian	Retrospective	254	50.3 ± 21.5	45.28	46	15	21	3	–
Zhu H[139]	7-Jun	Zhejiang	China	Asian	Retrospective	98	49.6 ± 15.7	32.65	8	–	–	–	–
Zhu Z[140]	22-Apr	Zhejiang	China	Asian	Retrospective	127	50.9 ± 15.3	35.43	43	–	57	4	59
Zou X[141]	14-Jun	Shanghai	China	Asian	Retrospective	105	61.0 ± 14.1	52.38	19	4	–	–	–
Zuo T[128]	26-Jun	Hong Kong	China	Asian	Retrospective	30	46.0 ± 25.2	53.33	4	11	–	–	–

Note: All articles were published in 2020.

Abbreviations: GI, gastrointestinal; NA, not applicable.

$p < .001$), acute cardiac injury (RR = 5.36; 95% CI = 3.47–8.27, $p < .001$), and AKI (RR = 5.52; 95% CI = 2.83–10.76, $p < .001$). Furthermore, GI cohorts showed a higher risk of ICU admission (RR = 2.56; 95% CI = 1.62–1.04, $p < .001$), and mortality (RR = 2.01; 95% CI = 1.18–3.43, $p = .010$).

Subgroup analysis by date of publication showed that affected cohorts in the first wave had a higher risk of being hospitalized (RR = 1.60; 95% CI = 1.15–2.22, $p = .005$), requiring ventilation (RR = 11.6; 95% CI = 5.08–26.9, $p < .001$), and ICU admission (RR = 3.0; 95% CI = 1.58–5.68, $p < .001$). However, patients in the second wave were less associated with hospitalization, ICU admission, mechanical ventilation, or mortality, although not reach significant levels (Figure 4). Meta-regression analysis revealed that heterogeneity in mechanical ventilation parameters was partly related to geographical region ($p = .012$; Table S2).

4 | DISCUSSION

SARS-CoV-2 has been found to infect multiple organ systems and is not exclusively a respiratory virus, as initially thought. Gastrointestinal symptoms have previously been reported to worsen outcomes in COVID-19 patients, although it remains unclear as contradictory research also exists.[7]

This relatively wide scoped meta-analysis showed that GI symptoms were present in about one-fifth of the study population and were associated with higher rates of adverse outcomes such as ICU admission and/or mortality. Furthermore, patients with GI symptoms were more likely to develop AKIs associated with worse outcomes in COVID-19 patients.[143,144] Similarly, GI symptoms correlated with a greater risk of cardiac injury, another poor prognostic factor for hospitalized patients with COVID-19.[145,146] The strong correlation between GI symptoms and the most unfavorable COVID-19 outcomes in such a large population underscores the clinical importance of what was once considered incidental symptoms of the disease. Focused research should be conducted to understand the mechanism of how GI pathology may lead to severe and worse outcomes. With this knowledge, health care providers can more closely monitor and treat these symptoms, which may lower mortality. Of note, the fecal shedding rate of SARS-CoV-2 was more common than the rate of manifested GI symptoms of COVID-19, suggesting that some patients with colonized GI tracts may be asymptomatic. While this is consistent with previous studies, the significance of this viral shedding is still unclear.[147,148] Future research should be conducted to evaluate the usefulness of viral stool studies in the workup of acutely ill patients with COVID-19.

Regarding the geographical distribution, European patients had a greater GI symptoms rate than all other regions studied, which could be attributed to differences in reporting or different genetic variants between continents. Islam et al. report that the mutation rate in the SARS-CoV-2 genomic sequence is higher in Europe compared with Asia and North America.[149] Regarding the outcome, Asian patients

TABLE 2 Characteristics of the included studies in the pairwise meta-analysis

First author	Year	DOP	Journal name	City	Country	Ethnicity	Sample size		Age, years (mean ± *SD*)		Sex(F/M)	
(1) Comparison between severe versus non-severe groups							**Severe**	**Non-severe**	**Severe**	**Non-severe**	**Severe**	**Non-severe**
Chen L[31]	2020	13-May	Journal of Infection	Guangdong	China	Asian	20	31	62.5 ± 13.3	57.6 ± 13.7	6/14	11/20
Fu J[43]	2020	6-May	Thrombosis Research	Suzhou	China	Asian	16	59	51.8 ± 12.8	45.1 ± 14.0	6/10	24/35
Guan W[44]	2020	28-Feb	New England Journal of Medicine	Multiple	China	Asian	173	926	52.3 ± 18.5	45.3 ± 17.0	73/100	386540
Han J[47]	2020	25-Jun	Epidemiol Infect	Tianjin	China	Asian	30	155	61.6 ± 12.4	40.6 ± 16.8	13/17	77/78
Huang M[51]	2020	1-Jun	The Am Jof the Medical Sciences	Jiangsu	China	Asian	8	52	NA	NA	NA	NA
Jin A[53]	2020	12-May	Biosafety and Health	Beijing	China	Asian	20	25	74.7 ± 10.7	46.0 ± 17.0	10/10	17/8
Li K[18]	2020	29-Feb	Invest Radiol	Chongqing	China	Asian	25	58	53.7 ± 12.3	41.9 ± 10.6	10/15	29/29
Li X[62]	2020	12-Apr	J of Allergy & Clinical Immunol	Wuhan	China	Asian	269	279	63.7 ± 13.3	55.3 ± 16.3	116/153	153/126
Liu F[67]	2020	14-Apr	Journal of Clinical Virology	Wuhan	China	Asian	33	107	76.7 ± 16.3	61.0 ± 12.6	25/8	66/41
Liu J[70]	2020	18-Apr	EBioMe-dicine	Wuhan	China	Asian	13	27	59.7 ± 10.1	43.2 ± 12.3	6/7	19/8
Lo I[73]	2020	15-Mar	Int J Biol Sci	Macau	China	Asian	4	6	61.0 ± 5.0	37.0 ± 19.0	3/1	4/2
Lui G[74]	2020	18-Apr	Journal of Infection	Hong Kong	China	Asian	5	6	65.7 ± 5.9	49.2 ± 14.8	1/4	3/3
Mo P[77]	2020	16-Mar	Clin Infect Dis	Wuhan	China	Asian	85	70	60.7 ± 14.1	45.7 ± 15.6	30/55	39/31
Tabata S[92]	2020	12-Jun	The Lancet Infectious Diseases	Tokyo	Japan	Asian	28	43	68.3 ± 16.3	57.0 ± 22.9	11/17	21/22

TABLE 2 (Continued)

First author	Year	DOP	Journal name	City	Country	Ethnicity	Sample size		Age, years (mean ± *SD*)		Sex(F/M)	
To K[93]	2020	23-Mar	The Lancet Infectious Diseases	Hong Kong	China	Asian	10	13	60.0 ± 26.7	56.0 ± 28.1	4/6	6/7
Wang R[98]	2020	11-Apr	Int Journal of Infectious Diseases	Anhui	China	Asian	25	100	49.4 ± 13.6	39.5 ± 14.8	9/16	45/55
Wang X[99]	2020	3-Apr	Clin Microbiol Infect	Wuhan	China	Asian	100	912	54.8 ± 11.1	48.7 ± 14.8	38/62	450/462
Wei Y[101]	2020	17-Apr	Journal of Infection	Anhui	China	Asian	30	137	49.0 ± 12.6	40.8 ± 15.5	10/20	62/75
Yang Y[111]	2020	29-Apr	J Allergy Clin Immunol	Shenzhen	China	Asian	25	14	58.3 ± 26.7	50.5 ± 41.5	11/14	7/7
Zhang G[117]	2020	9-Apr	Journal of Clinical Virology	Wuhan	China	Asian	55	166	62.7 ± 16.3	50.4 ± 20.9	20/35	93/73
Zhang H[118]	2020	23-Jun	Cancer	Wuhan	china	Asian	56	51	67.7 ± 45.9	59.7 ± 30.4	19/37	28/23
Zhang J[119]	2020	15-Apr	Clinical Micro-biology and Inf	Wuhan	china	Asian	315	254	52.2 ± 18.5	48.7 ± 18.5	166/149	138/116
Zhang J[121]	2020	28-Apr	Journal of Clinical Virology	Wuhan	china	Asian	18	93	63.3 ± 24.4	38.2 ± 12.2	4/14	61/32
Zhang J[122]	2020	19-Feb	Allergy	Wuhan	china	Asian	58	82	58.7 ± 45.9	51.8 ± 38.5	25/33	44/38
Zheng S[132]	2020	21-Apr	BMJ	Zhejiang	china	Asian	74	22	56.8 ± 13.7	46.9 ± 14.4	25/49	13/9
Zhu Z[140]	2020	22-Apr	Int Journal of Infectious Diseases	Zhejiang	China	Asian	16	111	57.5 ± 11.7	49.9 ± 15.5	7/9	38/73
(2) Comparison between hospitalized and nonhospitalized cohorts							**Hosp**	**None**	**Hosp**	**None**	**Hosp**	**Non**
Cholankeril G[142]	2020	10-Jun	Am J Gastroen-terol	California	USA	American	60	147	60.7 ± 25.2	44.0 ± 20.0	28/32	75/72
Hajifathalian K[45]	2020	8-May	Gastroenter-ology	New York	USA	American	768	291	64.7 ± 17.1	51.6 ± 17.8	302/466	146/145

(Continues)

TABLE 2 (Continued)

First author	Year	DOP	Journal name	City	Country	Ethnicity	Sample size		Age, years (mean ± *SD*)		Sex(F/M)	
Ortiz-Brizuela E[80]	2020	14-May	Rev Invest Clin	Mexico	Mexico	Mexican	140	169	49.7 ± 16.5	39.3 ± 14.1	55/85	71/98
Rivera-Izquierdo M[89]	2020	16-Jun	Int J Environ Res Public Health	Granada	Spain	European	11	65	NA	NA	NA	NA
(3) Comparison between ICU admission and general hospital ward							**ICU**	**Floor**	**ICU**	**Floor**	**ICU**	**Floor**
Huang C[50]	2020	24-Jan	Lancet	Wuhan	China	Asian	13	28	50.3 ± 14.8	49.2 ± 12.2	2/11	9/19
Ortiz-Brizuela E[80]	2020	14-May	Rev Invest Clin	Mexico	Mexico	Mexican	29	111	52.3 ± 17.8	49.2 ± 15.9	9/20	46/65
Wang D[96]	2020	7-Feb	Jama	Wuhan	China	Asian	36	102	67.0 ± 15.6	50.0 ± 18.5	14/22	49/53
Zeng Q[116]	2020	12-Jun	Transbound Emerg Dis	Henan	China	Asian	27	122	57.3 ± 20.0	39.0 ± 17.0	NA	NA
Cholankeril G[142]	2020	10-Jun	Am J Gastroenterol	California	USA	American	17	43	55.7 ± 20.7	62.3 ± 23.7	7/10	21/22
(4) Comparison between patients who expired and those survived							**Died**	**Alive**	**Died**	**Alive**	**Died**	**Alive**
Chen F[29]	2020	8-Jul	Journal of Critical Care	Wuhan	China	Asian	104	577	72.8 ± 11.7	61.7 ± 13.3	39/65	280/297
Chen R[34]	2020	11-May	J of Allergy & Clinical Immunol	Multiple	China	Asian	103	445	66.9 ± 12.1	53.5 ± 13.9	34/69	201/244
Leung C[58]	2020	27-Apr	Mechanisms of Ageing and Devel	Multiple	China	Asian	89	65	74.3 ± 10.4	69.3 ± 5.9	36/53	29/36
Li J[60]	2020	1-Jun	Am J of the medical sciences	Wuhan	China	Asian	14	60	72.3 ± 5.9	61.7 ± 12.6	3/11	27/33
Peng S[83]	2020	10-Apr	J of Thoracic and CV Surgery	Wuhan	China	Asian	3	8	NA	NA	1/2	2/6

TABLE 2 (Continued)

First author	Year	DOP	Journal name	City	Country	Ethnicity	Sample size		Age, years (mean ± *SD*)		Sex(F/M)	
Sun H[91]	2020	8-May	J of American Geriatrics Society	Wuhan	China	Asian	121	123	72.0 ± 8.9	67.7 ± 5.9	39/82	72/51
Tomlins J[94]	2020	27-Apr	Journal of Infection	Bristol	UK	European	20	75	78.0 ± 9.6	70.7 ± 19.3	8/12	27/48
Yang X[110]	2020	21-Feb	Lancet Respir Med	Wuhan	China	Asian	32	20	64.6 ± 11.2	51.9 ± 12.9	11/21	6/14
Zhang G[117]	2020	9-Apr	Journal of Clinical Virology	Wuhan	China	Asian	9	23	71.7 ± 17.8	60.7 ± 16.3	2/7	8/15
Zhang L[123]	2020	29-Jun	Gastroenterology	Wuhan	China	Asian	102	307	66.3 ± 10.4	62.3 ± 14.1	30/72	145/162
Zhou F[137]	2020	9-Mar	Lancet	Wuhan	China	Asian	54	137	69.3 ± 9.6	51.7 ± 9.6	16/38	56/81
(5) Comparison between positive and negative fecal RNA for SARS-COV-2 groups							**Positive**	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**
Chen Y[36]	2020	3-Apr	J Med Virol	Wuhan	China	Asian	28	14	52.2 ± 14.1	48.7 ± 12.1	16/12	11/3
Lin W[65]	2020	16-Jul	J Med Virol	Guangzhou	China	Asian	46	171	52.0 ± 15.6	48.3 ± 21.5	20/26	89/82
Zhao F[130]	2020	16-May	Gastroenterology	Shenzhen T	China	Asian	80	321	37.3 ± 25.2	37.7 ± 42.9	48/32	163/158
(6) Rest of studies comparing cohorts with and without GI symptoms but lacking outcomes data							**GI**	**Non-GI**	**GI**	**Non-GI**	**GI**	**Non-GI**
Cao C[24]	2020	15-Jun	Critical Care	China	Asian	Retrospective	63	94	51.9 ± 14.9	47.5 ± 14.0	39/24	44/50
Effenberger M[40]	2020	20-Apr	Gut	Austria	European	Retrospective	9	18	78.3 ± 13.8	58.4 ± 17.1	3/6	9/9
Ferm S[42]	2020	1-Jun	Clin Gastroenterol Hepatol	USA	American	Retrospective	219	658	NA	NA	NA	NA
Han C[46]	2020	15-Apr	Am J Gastroenterol	China	Asian	Retrospective	48	89	62.5 ± 44.4	61.0 ± 47.4	35/13	41/48
Jin X[54]	2020	24-Mar	Gut	China	Asian	Retrospective	74	577	46.1 ± 14.2	45.1 ± 14.4	37/37	283/294

(Continues)

TABLE 2 (Continued)

First author	Year	DOP	Journal name	City	Country	Ethnicity	Sample size		Age, years (mean ± *SD*)		Sex(F/M)	
Lin L[64]	2020	2-Apr	Gut	China	Asian	Retrospective	58	37	48.0 ± 17.1	41.1 ± 19.5	31/27	19/18
Pan L[81]	2020	14-Apr	Am J Gastroenterol	China	Asian	Retrospective	103	101	52.2 ± 15.9	53.6 ± 16.1	48/55	49/52
Ramachandran P[86]	2020	29-Jun	Dig Dis	USA	American	Retrospective	31	119	57.6 ± 17.2	63.3 ± 14.6	12/19	55/64
Redd W[87]	2020	22-Apr	Gastroenterology	USA	American	Retrospective	195	123	62.3 ± 15.9	65.0 ± 17.6	93/102	51/72
Wan Y[95]	2020	15-Apr	Lancet Gastroenterol Hepatol	China	Asian	Retrospective	49	181	53.3 ± 18.5	46.3 ± 15.6	22/27	79/102
Wei X[101]	2020	18-Apr	Cl Gastroenterology and Hepatol	China	Asian	Retrospective	26	58	47.2 ± 33.3	42.7 ± 31.8	18/8	38/20
Zhang L[124]	2020	1-Apr	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	China	Asian	Retrospective	33	47	45.1 ± 16.5	43.4 ± 17.5	11/22	22/25
Zheng T[133]	2020	8-Jun	Journal Medical Virology	China	Asian	Retrospective	192	1128	48.0 ± 13.3	50.0 ± 12.6	102/90	639/489
Zhou Z[138]	2020	19-Mar	Gastroenterology	China	Asian	Retrospective	66	188	50.6 ± 11.3	51.4 ± 12.8	44/22	95/93

Abbreviations: DOP, publication date; ICU, intensive care unit; NA, not applicable.

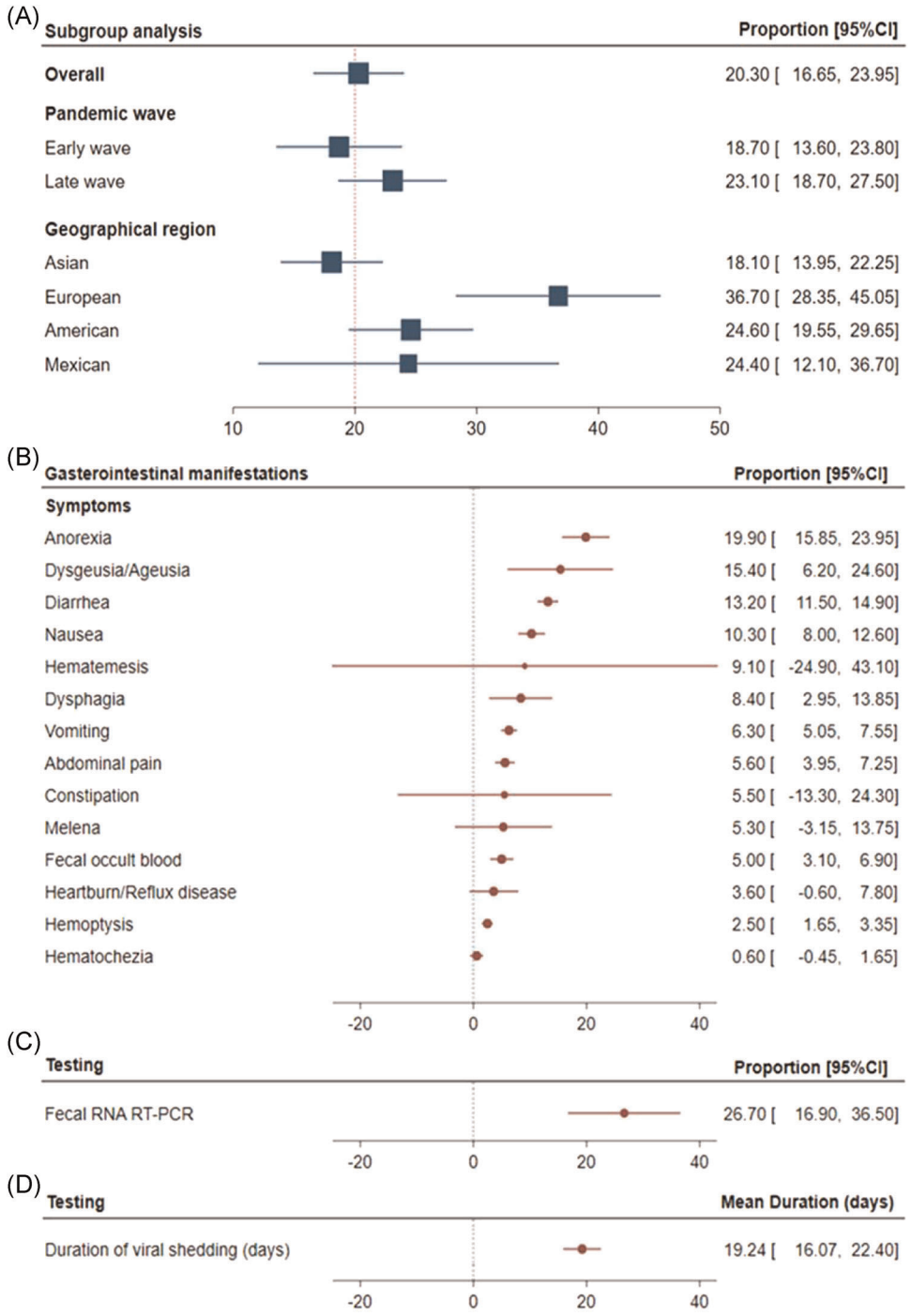

FIGURE 2 Prevalence of gastrointestinal manifestations. (A) The proportion of patients with COVID-19 presenting with gastrointestinal symptoms. One-arm meta-analysis was applied. Overall proportion and confidence intervals are shown. Subgroup analysis was performed stratifying studies by the date of publication (during the first wave; < May 15, or during the second wave; > May 15) and by geographical regions (Asia, Europe, America, and Mexico). (B) The proportion of gastrointestinal symptoms in COVID-19 cohorts. (C) Prevalence of fecal shedding confirmed by fecal RNA RT-PCR. (D) Duration of viral shedding (days). CI, confidence interval; COVID-19, coronavirus disease 2019; RT-PCR, reverse-transcription polymerase chain reaction

were ventilated less often than non-Asians. However, this might be due to the differences in medical practices between these geographic areas. Despite the discrepancy in ventilation rates, there were no differences in ARDS, AKI, or acute cardiac injury rates. Admission outcomes, including mortality, were likewise equal among Asian versus nonAsian patients.

Pandemics have historically come in waves with differing severities and lengths of time between them.[150] Consequentially, it is

TABLE 3 Summary for pairwise comparison in the meta-analysis

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
A. Demographic characteristics													
Age, years	59	14,200	4342	9858	IV	SMD	Random	**0.531**	**0.413–0.649**	**<.001**	86.68%	<.001	.070
Sex: (Male)	59	14,062	4318	9744	MH	OR	Random	**1.292**	**1.144–1.460**	**<.001**	43.90%	<.001	.488
Sex: (Female)	59	14,062	4318	9744	MH	OR	Random	**0.774**	**0.685–0.874**	**<.001**	43.90%	<.001	.488
BMI, kg/m^2	13	3731	1673	2058	IV	SMD	Random	0.124	−0.047 to 0.295	.154	77.37%	<.001	.790
Race/Ethnicity: (Asian)	4	1476	876	600	MH	OR	Random	1.124	0.782–1.617	.527	0.0%	.795	.628
Race/Ethnicity: (White)	4	1476	876	600	MH	OR	Random	0.786	0.456–1.356	.387	51.27%	.104	.935
Race/Ethnicity: (Black)	4	1476	876	600	MH	OR	Random	**0.705**	**0.499–0.997**	**.048**	0.0%	.735	.196
Race/Ethnicity: (Hispanic)	3	417	108	309	MH	OR	Random	1.137	0.370–3.499	.823	61.51%	.074	.991
Cigarette smoking	26	6123	1719	4404	MH	OR	Random	**1.594**	**1.312–1.937**	**<.001**	0.0%	.665	.439
B. Vital signs at presentations													
pH	3	341	59	282	IV	SMD	Random	**0.290**	**0.008–0.573**	**.044**	0.0%	.963	.342
PaO_2 (mm/Hg)	4	392	97	313	IV	SMD	Random	−0.442	−1.343 to 0.460	.337	91.45%	<.001	.107
$PaCO_2$ (mm/Hg)	4	392	97	313	IV	SMD	Random	**−0.465**	**−0.824 to −0.106**	**.011**	47.55%	.126	.034
PaO_2:FiO_2 ratio (mm/Hg)	4	451	105	346	IV	SMD	Random	**−1.067**	**−1.428 to −0.705**	**<.001**	52.14%	.099	.678
SpO_2 (%)	8	2080	479	1601	IV	SMD	Random	**−1.039**	**−1.340 to −0.738**	**<.001**	82.42%	<.001	.907

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
Highest temperature (°C)	15	4411	1268	3143	IV	SMD	Random	**0.231**	**0.120–0.342**	**<.001**	54.64%	.006	.440
C. General clinical presentations													
Fever (≥ 37.3°C)	51	13,373	4076	9297	MH	OR	Random	**1.364**	**1.081–1.722**	**.009**	68.64%	<.001	.075
Dry cough	49	13,142	3964	9178	MH	OR	Random	**1.207**	**1.043–1.396**	**.011**	46.50%	<.001	.369
Expectoration	22	7759	1765	5994	MH	OR	Random	**1.470**	**1.125–1.920**	**.005**	67.91%	<.001	.967
Chest pain	18	4622	1543	3079	MH	OR	Random	1.374	0.866–2.182	.178	70.67%	<.001	.326
Dizziness	10	2152	960	1192	MH	OR	Random	1.703	0.979–2.962	.060	31.60%	.156	.191
Rhinorrhea	14	2966	806	2160	MH	OR	Random	1.166	0.750–1.814	.494	36.72%	.082	.050
Anosmia	6	1997	1163	834	MH	OR	Random	0.898	0.435–1.854	.771	55.58%	.047	.956
Dyspnea	42	11,927	3524	8403	MH	OR	Random	**3.368**	**2.584–4.388**	**<.001**	76.68%	<.001	.181
Headache	30	8667	2188	6479	MH	OR	Random	1.130	0.809–1.580	.473	59.55%	<.001	.253
Sore throat	30	8747	2060	6687	MH	OR	Random	1.063	0.820–1.378	.646	41.47%	.010	.598
Myalgia	41	11,027	3497	7530	MH	OR	Random	**1.307**	**1.048–1.630**	**.017**	60.67%	<.001	.581
Fatigue	33	9903	3189	6714	MH	OR	Random	**1.604**	**1.288–1.999**	**<.001**	70.47%	<.001	.260
Nasal congestion	8	4431	674	3757	MH	OR	Random	1.154	0.738–1.806	.530	5.87%	.385	.240
D. Comorbidities													
Hypertension	44	10,807	3351	7456	MH	OR	Random	**2.126**	**1.764–2.561**	**<.001**	58.54%	<.001	.625
Diabetes mellitus	48	11,722	3779	7943	MH	OR	Random	**2.061**	**1.661–2.557**	**<.001**	54.60%	<.001	.911
Cardiovascular disease	34	8702	3224	5478	MH	OR	Random	**2.264**	**1.748–2.933**	**<.001**	51.94%	<.001	.192
Cerebrovascular disease	15	4328	1123	3205	MH	OR	Random	**2.249**	**1.482–3.414**	**<.001**	20.79%	.222	.362
Chronic liver disease	23	5666	2124	3542	MH	OR	Random	**1.513**	**1.143–2.003**	**.004**	0.0%	.499	.325
Chronic kidney disease	24	7313	2452	4861	MH	OR	Random	**1.787**	**1.213–2.634**	**.003**	29.83%	.085	.538

(Continues)

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
Coronary heart disease	16	3626	928	2698	MH	OR	Random	**2.637**	**1.416–4.912**	**.002**	64.35%	<.001	.775
Hyperlipidemia	4	653	304	349	MH	OR	Random	0.931	0.635–1.366	.715	0.0%	0.751	.930
COPD	39	9344	3165	6179	MH	OR	Random	**1.977**	**1.457–2.682**	**<.001**	23.94%	.093	.025
Asthma	10	4077	1504	2573	MH	OR	Random	1.223	0.874–1.711	.241	0.0%	.875	.352
Endocrine disease	6	839	417	422	MH	OR	Random	1.081	0.670–1.743	.750	0.0%	.483	.540
Tuberculosis	5	959	454	505	MH	OR	Random	1.125	0.402–3.149	.822	7.04%	.367	.606
Immunosuppression	11	3560	1422	2138	MH	OR	Random	1.494	0.895–2.494	.125	0.0%	.931	.247
Malignancy	30	7911	2771	5140	MH	OR	Random	**1.447**	**1.118–1.871**	**.005**	0.0%	.997	.030
E. Laboratory findings													
WBCs ($\times 10^9$/L)	44	10913	3020	7893	IV	SMD	Random	**0.325**	**0.174–0.476**	**<.001**	88.64%	<.001	.286
Neutrophils count ($\times 10^9$/L)	30	7072	2024	5048	IV	SMD	Random	**0.589**	**0.372–0.807**	**<.001**	91.31%	<.001	.115
Lymphocytes count ($\times 10^9$/L)	45	10169	2979	7190	IV	SMD	Random	**−0.533**	**−0.659 to −0.408**	**<.001**	82.21%	<.001	.108
NLR ($\times 10^9$/L)	7	1242	235	1007	IV	SMD	Random	**1.064**	**0.476–1.653**	**<.001**	92.18%	<.001	.294
Monocytes count ($\times 10^9$/L)	9	1566	452	1114	IV	SMD	Random	**−0.217**	**−0.334 to −0.100**	**<.001**	0.0%	.462	.282
Platelets count, ($\times 10^9$/L)	34	8624	2545	6079	IV	SMD	Random	**−0.143**	**−0.274 to −0.013**	**.031**	80.10%	<.001	.926
Hemoglobin (g/L)	24	6406	1437	4969	IV	SMD	Random	**−0.156**	**−0.254 to −0.059**	**.002**	45.88%	.008	.748
ALT (U/L)	32	6240	2259	3981	IV	SMD	Random	**0.228**	**0.112 to 0.343**	**<.001**	69.18%	<.001	.432
AST (U/L)	29	5756	2149	3607	IV	SMD	Random	**0.473**	**0.290–0.657**	**<.001**	86.92%	<.001	.183
Albumin (g/L)	18	3829	1519	2310	IV	SMD	Random	**−0.532**	**−0.756 to −0.308**	**<.001**	86.44%	<.001	.775
Total bilirubin (μmol/L)	17	3408	1375	2033	IV	SMD	Random	**0.234**	**0.098–0.370**	**.001**	54.24%	.004	.318

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
ALP (U/L)	4	1540	1002	538	IV	SMD	Random	0.076	−0.034 to 0.187	.177	0.0%	.630	.553
Creatinine (μmol/L)	29	4358	1211	3147	IV	SMD	Random	**0.295**	**0.121–0.470**	**.001**	80.94%	<.001	.353
BUN (mmol/L)	15	2183	589	1594	IV	SMD	Random	**0.449**	**0.138–0.760**	**.005**	87.67%	<.001	.175
Sodium (mmol/L)	12	2964	659	2305	IV	SMD	Random	**−0.228**	**−0.436 to −0.020**	**.031**	74.78%	<.001	.554
Potassium (mmol/L)	9	2548	555	1993	IV	SMD	Random	−0.302	−0.768 to 0.164	.204	93.89%	<.001	.993
Lactate (mmol/L)	7	883	343	540	IV	SMD	Random	0.202	−0.113 to 0.516	.208	72.35%	.001	.007
Fasting blood glucose (mmol/L)	4	1123	190	933	IV	SMD	Random	0.423	−0.094 to 0.941	.109	88.62%	<.001	.231
Lactate dehydrogenase (U/L)	26	4953	1697	3256	IV	SMD	Random	**0.773**	**0.471–1.076**	**<.001**	93.76%	<.001	.235
Troponin (ng/L)	13	2656	1250	1406	IV	SMD	Random	**0.661**	**0.329–0.992**	**<.001**	90.84%	<.001	.060
NT-proBNP (pg/ml)	4	763	346	417	IV	SMD	Random	0.488	−0.116 to 1.092	.113	91.55%	<.001	.628
Creatine kinase (U/L)	20	3861	1496	2365	IV	SMD	Random	**0.260**	**0.082–0.438**	**.004**	77.93%	<.001	.405
Creatine kinase-MB (U/L)	10	1697	408	1289	IV	SMD	Random	**0.613**	**0.077–1.148**	**.025**	93.89%	<.001	.011
Myoglobin (ng/ml)	3	304	64	240	IV	SMD	Random	**0.947**	**0.652–1.242**	**<.001**	0.0%	.411	.477
Serum amyloid A (mg/L)	4	853	199	654	IV	SMD	Random	**0.868**	**0.175–1.561**	**.014**	91.98%	<.001	.183
International Normalized Ratio	5	2142	1064	1078	IV	SMD	Random	0.084	−0.186 to 0.354	.543	77.96%	.001	.349
Prothrombin time (s)	15	2028	596	1432	IV	SMD	Random	**0.370**	**0.201–0.539**	**<.001**	58.80%	.002	.414
APTT (s)	15	3347	1502	1845	IV	SMD	Random	**0.085**	**0.004–0.166**	**.040**	4.63%	.400	.579

(Continues)

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
D-dimer (ng/ml)	24	4694	1904	2790	IV	SMD	Random	**0.548**	**0.345–0.751**	**<.001**	87.59%	<.001	.280
CRP (mg/L)	33	7834	2411	5423	IV	SMD	Random	**0.812**	**0.593–1.032**	**<.001**	92.63%	<.001	.067
Ferritin (ng/ml)	10	2812	1343	1469	IV	SMD	Random	**0.709**	**0.322–1.095**	**<.001**	93.82%	<.001	.342
Fibrinogen (g/L)	8	923	295	628	IV	SMD	Random	**0.913**	**0.395–1.431**	**.001**	89.50%	<.001	.068
ESR (mm/h)	9	2230	1149	1081	IV	SMD	Random	**0.491**	**0.214–0.767**	**<.001**	83.96%	<.001	.694
Procalcitonin (ng/ml)	22	4591	1717	2874	IV	SMD	Random	**0.810**	**0.522–1.097**	**<.001**	93.09%	<.001	.098
Interleukin-6 (pg/ml)	14	3653	1468	2185	IV	SMD	Random	**1.098**	**0.754–1.443**	**<.001**	93.39%	<.001	.399
CD3+ T lymphocyte (Cells/μL)	2	1229	207	1022	IV	SMD	Random	**−0.998**	**−1.153 to −0.843**	**<.001**	0.0%	.919	NA
CD4+ T lymphocyte (Cells/μL)	5	1531	336	1195	IV	SMD	Random	**−0.864**	**−0.999 to −0.729**	**<.001**	0.0%	.722	.550
CD8+ T lymphocyte (Cells/μL)	5	1531	336	1195	IV	SMD	Random	**−0.931**	**−1.069 to −0.793**	**<.001**	1.75%	.396	.283
F. Medications													
Oxygen therapy	10	2620	717	1903	MH	OR	Random	1.971	0.797–4.874	.142	89.86%	<.001	.344
High-flow nasal cannula	8	1698	514	1184	MH	OR	Random	0.440	0.114–1.699	.234	94.96%	<.001	.859
Mechanical ventilation: IMV	18	3815	1047	2768	MH	OR	Random	**35.46**	**16.87–74.51**	**<.001**	43.79%	.025	.322
Mechanical ventilation: NIV	15	3502	873	2629	MH	OR	Random	**15.56**	**7.01–34.59**	**<.001**	81.96%	<.001	.002
ACE/ARB inhibitor	5	992	386	606	MH	OR	Random	1.173	0.777–1.769	.448	0.0%	.639	.183
Antibiotics	19	6429	1465	4964	MH	OR	Random	**1.892**	**1.276–2.804**	**.002**	69.59%	<.001	.494
Antifungal	4	2035	400	1635	MH	OR	Random	**4.015**	**2.429–6.635**	**<.001**	0.0%	.793	.343
Antiviral	17	4480	1158	3322	MH	OR	Random	1.040	0.775–1.396	.792	15.80%	.269	.583
Antiviral: Oseltamivir	5	2954	694	2260	MH	OR	Random	1.092	0.696–1.712	0.703	80.83%	<.001	.919
Antiviral: Ganciclovir	2	755	118	637	MH	OR	Random	**1.791**	**1.056–3.038**	**.031**	0.0%	.328	NA

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association			Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
Antiviral:Ribavirin	4	1649	480	1169	MH	OR	Random	1.101	0.505–2.399	.808	70.75%	.017	.745
Antiviral:Lopinavir/Ritonavir	5	1403	516	887	MH	OR	Random	1.081	0.587–1.992	.803	72.86%	.005	.751
Antiviral: Arbidol	4	1381	266	1115	MH	OR	Random	0.718	0.327–1.578	.410	69.99%	.019	.179
Nebulized α-interferon	9	2158	713	1445	MH	OR	Random	1.561	0.972–2.508	.066	69.39%	.001	.240
Anticoagulants	3	1757	1068	689	MH	OR	Random	1.490	0.471–4.707	.497	82.98%	.003	.532
Corticosteroids	25	7762	2367	5395	MH	OR	Random	**2.814**	**1.943–4.077**	**<.001**	78.95%	<.001	.720
Intravenous immunoglobulin	21	6108	1543	4565	MH	OR	Random	**2.852**	**1.846–4.407**	**<.001**	80.86%	<.001	.351
ECMO	13	2590	621	1969	MH	OR	Random	**9.155**	**4.167–20.11**	**<.001**	0.0%	.623	.038
CRRT	9	2386	672	1714	MH	OR	Random	**15.72**	**6.321–39.09**	**<.001**	0.0%	.856	.441
NSAID	2	1209	799	410	MH	OR	Random	1.321	0.613–2.846	.478	53.03%	.145	NA
G. Complications													
ARDS	13	3734	932	2802	MH	RR	Random	**8.161**	**4.777–13.94**	**<.001**	80.66%	<.001	.673
Acute cardiac injury	13	2737	796	1941	MH	RR	Random	**5.361**	**3.473–8.275**	**<.001**	53.64%	.011	.766
Arrhythmia	7	1008	404	604	MH	RR	Random	**3.646**	**1.081–12.30**	**.037**	84.94%	<.001	.234
Acute liver injury	3	1111	196	915	MH	RR	Random	**2.547**	**1.565–4.145**	**<.001**	41.67%	.180	.370
Acute kidney injury	10	2761	759	2002	MH	RR	Random	**5.524**	**2.836–10.76**	**<.001**	65.85%	.002	.060
H. Clinical classification													
Mild	6	1026	299	727	MH	RR	Random	0.895	0.747–1.072	.227	76.27%	.001	.020
Severe/critical	38	7713	2078	5832	MH	RR	Random	0.97	0.66, 1.288	.545	93.46%	<0.001	.247
I. Clinical outcome													
Hospitalized	14	5183	1788	3395	MH	RR	Random	**1.943**	**1.392–2.711**	**<.001**	95.30%	<.001	.018
Length of hospital stay (days)	16	5370	1173	4197	IV	MD	Random	0.447	−1.223 to 2.118	.600	94.91%	<.001	.328
ICU admission	18	5838	1346	4492	MH	RR	Random	**2.560**	**1.622–4.041**	**<.001**	85.34%	<.001	.289

(Continues)

TABLE 3 (Continued)

Characteristics	Number studies	Sample size			Test of association		Effect size			Heterogeneity		Pub bias
		Total	Poor prognosis	Good prognosis	Statistical method	Effect measure	Analysis model	Estimate	95% CI	*p* value	I^2	*p* value	*p* value
Mechanical ventilation	7	1872	493	1379	MH	OR	Random	2.363	0.972–5.742	.058	76.75%	<.001	.042
Length of ICU stay (days)	3	427	166	261	IV	MD	Random	0.017	−3.717 to 3.750	.993	86.53%	.001	.943
Discharged	14	5231	1154	4077	MH	RR	Random	**0.714**	**0.604–0.844**	**<.001**	83.78%	<.001	.029
Mortality	25	6786	1923	4863	MH	RR	Random	**2.017**	**1.186–3.431**	**.010**	90.89%	<.001	.093

Note: The random-effects model was applied.

Abbreviations: ACE/ARB, angiotensin-converting enzyme and an angiotensin receptor blocker; ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, ativated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CD, cluster of differentiation; CI, confidence interval; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; COPD, chronic obstructive pulmonary disease; Duration of viral shedding, The time from diagnosis date to the day before first negative conversion of two consecutive negative results of RT-PCR; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; GGT, Gamma-Glutamyl transferase; I^2, the ratio of true heterogeneity to total observed variation; IMV, invasive mechanical ventilation; IV, inverse variance; MD, mean difference; MH, Mantel–Haenszel; pub bias, publication bias assessed by Egger's test; NIV, noninvasive mechanical ventilation; NLR, neutrophil-to-Lymphocyte ratio; NSAID, nonsteroidal anti-inflammatory drugs; NT-proBNP, N-terminal-pro hormone B-type natriuretic peptide; OR, odds ratio; $PaCO_2$, The partial pressure of cardon dioxide; PaO_2, The partial pressure of oxygen; PaO_2:FiO_2 ratio, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; pH, a measure of hydrogen ion concentration, the acidity or alkalinity of blood; RR, relative risk; RBCs, red blood cells or erythrocytes; RT-PCR, reverse transcription-polymerase chain reaction; SMD, standardized mean difference; SpO_2, oxygen saturation; WBCs, white blood cells or leukocytes;.

FIGURE 3 Subgroup analysis for pooled one-arm meta-analysis of COVID-19 outcomes by the pandemic wave. Odds ratio and 95% confidence intervals were reported. *p* values comparing the first and second waves were estimated using Student's *t*-test. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019

important to evaluate the success of the initial treatment interventions compared with the more recent treatment innovations; this can be done by comparing the outcomes of critically ill patients. A comparison between the early wave and subsequent wave of COVID-19 infections was achieved by a sub-group analysis of the enrolled studies. The second wave of cases showed more GI manifestations than first wave cases; however, this was not statistically significant. Pooled prevalence comparisons between early and late wave cases showed mixed results regarding outcome events. Early wave patients experienced greater rates of acute cardiac injury and ICU admission, and late wave patients had higher ARDS, AKI, mechanical ventilation, and mortality rates. This may be due to more patients in the second wave presenting with GI symptoms indicating severe disease. To directly compare patients with GI symptoms in each wave, a pairwise comparison analysis of patients with and without GI symptoms was performed. Second wave patients with GI symptoms were less likely to have acute cardiac injuries, be admitted to the ICU, receive mechanical ventilation, or die due to COVID-19,

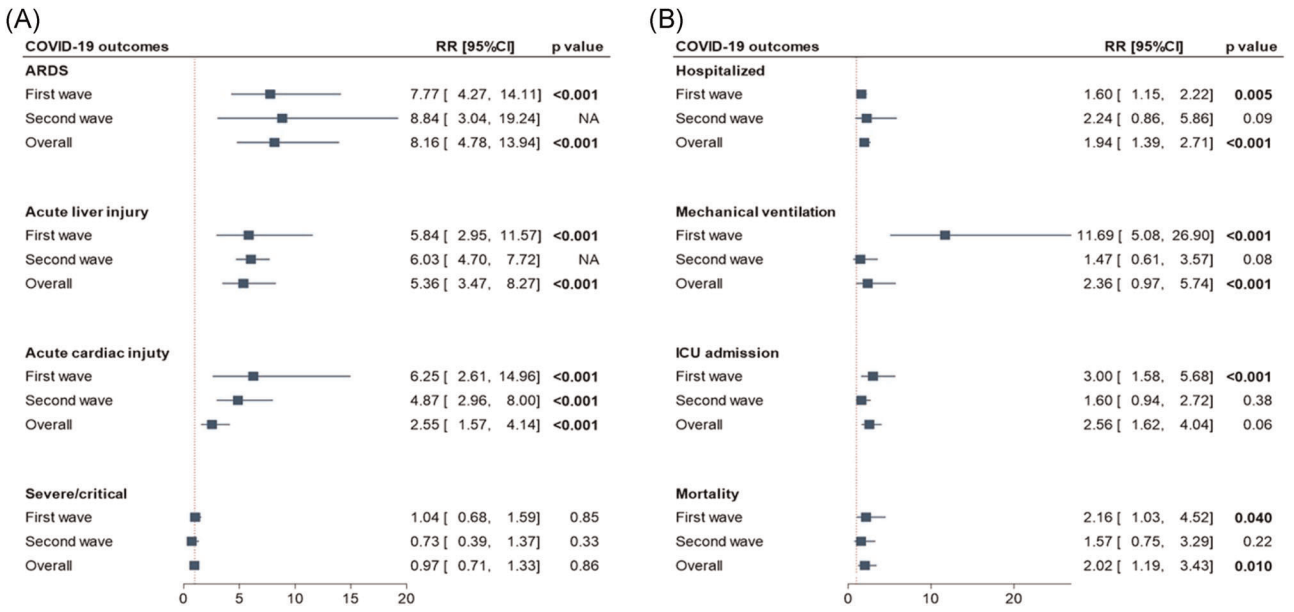

FIGURE 4 Subgroup analysis for pooled pairwise comparison analysis of coronavirus diease-2019 outcomes by the pandemic wave. (A) Clinical outcomes. (B) Admission outcomes were compared between cohorts presented with versus without gastrointestinal manifestations. CI, confidence interval

compared with first wave patients with GI symptoms. This particular analytic method allowed a comparison between the more acutely ill patients showing GI symptoms, which demonstrated more accurate results than the pooled prevalence results.

Fan et al.[15] found that mortality rates in the second wave of the pandemic decreased sharply even among countries that saw a greater caseload than the first wave. In the studies analyzed for this meta-analysis, there was an overall lower rate of complications and mortality in the GI symptom-positive cohort of the second wave providing evidence of improved management of patients with COVID-19, which agrees with the findings of Fan et al.[15] This meta-analysis is further evidence of the decrease in mortality outcome that might be due to an improvement in the clinical handling of the disease. While many treatments have proven effective at improving the disease course in smaller trials, it is reassuring to see a large-scale improvement in morbidity and mortality in severe cases. This is most likely due to the combined efforts of medical providers and public health officials in identifying severe COVID-19 cases earlier and intervening appropriately. Also, likely contributing factors are the improvements in therapeutics, treatment algorithms, and familiarity with the disease course.

A limitation of this meta-analysis was that it reviewed predominately retrospective studies making randomization impossible. Since not all studies had the primary goal of evaluating GI symptoms' impact on COVID-19 outcomes, differences in the recording of symptoms between studies could be potentially present. While including studies throughout the world was beneficial for increasing the findings' generalizability, doing so might affect the data collected from differently impacted countries. This limitation was addressed by controlling analysis for a geographic area.

5 | CONCLUSIONS

The findings of this meta-analysis suggest that there is an association between gastrointestinal symptoms in patients with COVID-19 and worse disease outcomes, especially in the first wave of infection. These symptoms were found to be common, appearing in approximately one-fifth of studied patients. Screening patients for GI symptoms is quick and may benefit providers by offering a simple method for stratifying patient risk levels. By grouping the studies in the first wave and second wave categories, the analysis showed overall improved outcomes for patients who have more recently been treated for COVID-19 regardless of their GI affection.

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This work is dedicated to the soul of our beloved Professor Dr. Akram El Awady, the president and godfather of Horus University – Egypt, who passed away on February 3rd, 2021. We will miss you and love you always. Your love will light our way and your memory will be forever in our hearts. We will grasp you in our hearts till we can cuddle you again in Heaven.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Rami M. Elshazli and Eman A. Toraih study design; Rami M. Elshazli, Abdelaziz Elgaml, Mohamed H. Aboutaleb, Mohamed M. Salim, Mahmoud Omar, Ruhul Munshi, Nicholas Mankowski, and Abdallah S. Attia: study identification and data extraction; Rami M. Elshazli, Mohammad H. Hussein, and Eman A. Toraih, statistical analysis; Rami

M. Elshazli, Mohammad H. Hussein, Eman A. Toraih, Manal S. Fawzy, and Emad Kandil, data interpretation; Rami M. Elshazli, Adam Kline, and Eman A. Toraih, AS, Manal S. Fawzy, original draft preparation. All authors revised and approved the final version of the manuscript

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the manuscript and the supplementary materials.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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