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...
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.

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

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 (PaO₂)/fraction of inspiration oxygen (FiO₂) ≤ 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. 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 (SDs) of each arm were extracted. Other statistical variable data, like median and interquartile range (IQR), were converted to means and SDs. 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 I² statistics. Articles were considered to have significant heterogeneity between studies when the p value less than .1 or I² greater than 50%. 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.

3 RESULTS

3.1 Characteristics of included studies

Systematic search as depicted in Figure 1A yield 125 eligible publications, including 25,252 participants. 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). Of these, 26 studies compared severe/critical COVID-19 patients versus mild cases, four articles compared between hospitalized patients and those not required hospitalization, five studies compared ICU admitted patients versus floor hospitalization, and 11 publications compared between those who died with those who survived.
negative fecal shedding,\textsuperscript{36,65,130} and of the remaining 14 studies comparing cohorts with and without GI symptoms.\textsuperscript{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 co-morbid 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).

3.3 | Differential outcomes of patients presenting with gastrointestinal manifestations

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 \( p < .001 \)).

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, mean ± SD | Sex (% male) | GI symptoms (number) |
|--------------|-----------------|----------------|---------|-------------------------|--------------|-------------|----------------|--------------|---------------------|
| Aghemo A     | 11-May          | Milan          | Italy   | European                | Retrospective| 292         | 65.0 ± 14.1   | 68.15        | 69 11 - - - - - -   |
| Ai J         | 9-Jun           | Xiangyang      | China   | Asian                   | Retrospective| 7           | 54.1 ± 15.5   | 57.14        | 6 2 4 6 7          |
| Annweiler C  | 18-Jun          | d’Angers       | France  | European                | Retrospective| 353         | 84.7 ± 7.0    | 45.33        | 77 22 22 - - - -   |
| Barillari M  | 25-Jul          | Multiple       | Italy   | European                | Observational multicenter | 294         | 42.1 ± 123    | 50.00        | 81 42 42 37 84     |
| Cai Q        | 18-Mar          | Shenzhen       | China   | Asian                   | Open-Label nonrandomized Control | 80          | 47.9 ± 18.7   | 43.75        | 1 - - - - - -      |
| Cavaliere K  | 20-Apr          | New York       | USA     | American                | Retrospective| 6           | 67.8 ± 12.4   | 50.00        | - - - - - - - -    |
| Chang D      | 17-Mar          | Beijing        | China   | Asian                   | Retrospective| 13          | 38.7 ± 10.4   | 76.92        | 1 - - - - - -      |
| Chang D      | 20-Jun          | Beijing        | China   | Asian                   | Retrospective| 67          | 46.6 ± 15.8   | 56.72        | 6 - - - - - -      |
| Chen A       | 16-May          | Maryland       | USA     | American                | Prospective Case-Control | 101         | 48.3 ± 14.7   | 40.59        | 51 14 30 26 54     |
| Chen F       | 8-Jul           | Wuhan          | China   | Asian                   | Retrospective| 681         | 63.7 ± 133    | 53.16        | 119 - - - - - -    |
| Chen J       | 19-Mar          | Shanghai       | China   | Asian                   | Retrospective| 249         | 50.3 ± 20.7   | 50.60        | 8 - - - - - - 8    |
| Chen L       | 13-May          | Guangdong      | China   | Asian                   | Retrospective| 51          | 59.5 ± 13.6   | 66.67        | 3 - - - - - -      |
| Chen M       | 13-May          | Hubei          | China   | Asian                   | Retrospective| 11          | 48.4 ± 14.1   | 72.73        | 2 - 3 - - - -      |
| Chen N       | 30-Jan          | Wuhan          | China   | Asian                   | Retrospective| 99          | 55.5 ± 13.1   | 67.68        | 2 1 1 - - - -      |
| Chen R       | 11-May          | Multiple       | China   | Asian                   | Retrospective| 548         | 56.0 ± 145    | 57.12        | 14 18 - - - - - - |
| Chen X       | 30-Jun          | Guangzhou      | China   | Asian                   | Retrospective| 267         | 48.3 ± 20.7   | 45.32        | 19 7 14 - 47      |
| Chen Y       | 3-Apr           | Wuhan          | China   | Asian                   | Retrospective| 42          | 51.9 ± 143    | 35.71        | 7 3 4 - - - - -    |
| Cholankeril G| 10-Jun          | California     | USA     | American                | Retrospective| 207         | 49.3 ± 22.9   | 50.24        | 22 22 22 14 - -    |
| Cholankeril G| 10-Apr          | California     | USA     | American                | Retrospective| 116         | 50.7 ± 23.7   | 53.45        | 12 12 12 10 22     |
| Deng W       | 19-Jun          | Chongqing      | China   | Asian                   | Retrospective| 61          | 54.8 ± 129    | 40.98        | 3 - - - - - - - -   |
| 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 X39     | 26-May           | Luoyang        | China   | Asian                   | Retrospective| 25          | 52.0 ± 19.3          | 60.00       | 2                    | 1        | 1        | 1      | -        | 3       |
| Effenberger M40 | 20-Apr         | Innsbruck      | Austria | European                | Retrospective| 40          | 65.4 ± 15.1          | 60.00       | 22                   | 5        | 11       | -      | -        | -       |
| Fang Z41     | 21-Mar           | Xiangtan       | China   | Asian                   | Retrospective| 32          | 43.0 ± 14.8          | 50.00       | 3                    | -        | -        | -      | -        | -       |
| Ferm S42     | 1-Jun            | New York       | USA     | American                | Retrospective| 892         | 59.3 ± 18.5          | 59.87       | 177                  | 91       | 148      | 70     | 105      | -       |
| Fu J43       | 6-May            | Suzhou         | China   | Asian                   | Retrospective| 75          | 46.0 ± 14.0          | 60.00       | 6                    | -        | -        | -      | -        | -       |
| Guan W44     | 28-Feb           | Multi provinces| China   | Asian                   | Retrospective| 1099        | 46.7 ± 17.1          | 57.96       | 42                   | 55       | 55       | -      | -        | -       |
| Hajifathalian K45 | 8-May           | New York       | USA     | American                | Retrospective| 1059        | 61.1 ± 18.3          | 57.70       | 234                  | 91       | 168      | 72     | 240      | -       |
| Han C46      | 15-Apr           | Wuhan          | China   | Asian                   | Retrospective| 206         | 60.5 ± 48.1          | 44.17       | 67                   | 24       | -        | 9      | 70       | -       |
| Han J47      | 25-Jun           | Tianjin        | China   | Asian                   | Retrospective| 185         | 44.0 ± 17.9          | 51.35       | 11                   | -        | -        | -      | -        | -       |
| Hong L48     | 24-Jun           | Zhejiang       | China   | Asian                   | Retrospective| 127         | 45.7 ± 51.1          | 55.91       | 13                   | 5        | 5        | -      | 38       | -       |
| Hu J49       | 28-May           | Zhejiang       | China   | Asian                   | Retrospective| 884         | 46.0 ± 14.0          | 51.47       | 71                   | 31       | 31       | -      | -        | -       |
| Huang C50    | 24-Jan           | Wuhan          | China   | Asian                   | Retrospective| 41          | 49.3 ± 12.6          | 73.17       | 1                    | -        | -        | -      | -        | -       |
| Huang M51    | 1-Jun            | Jiangsu        | China   | Asian                   | Retrospective| 60          | 60.0 ± 52.6          | 58.33       | 4                    | 2        | 2        | -      | -        | -       |
| Jehi L52     | 10-Jun           | Cleveland      | USA     | American                | Prospective  | 1108        | 52.3 ± 19.9          | 49.91       | 185                  | 129      | -        | -      | 216      | -       |
| Jin A53      | 12-May           | Beijing        | China   | Asian                   | Retrospective| 45          | 58.8 ± 20.1          | 40.00       | -                    | 1        | 2        | -      | 5        | -       |
| Jin X54      | 24-Mar           | Zhejiang       | China   | Asian                   | Retrospective| 651         | 45.1 ± 14.4          | 50.84       | -                    | -        | -        | -      | -        | -       |
| Kaafarani H55| 1-May            | Massachusetts  | USA     | American                | Retrospective| 141         | 58.0 ± 17.1          | 65.25       | 42                   | 31       | 31       | 21     | -        | -       |
| Lapostolle F56| 30-May           | Paris          | France  | European                | Prospective  | 1452        | 42.9 ± 18.1          | 48.21       | 352                  | 168      | 288      | -      | 305      | -       |
| Lei Z57      | 9-Apr            | Guangzhou      | China   | Asian                   | Retrospective| 119         | 53.4 ± 13.2          | 64.71       | 7                    | 4        | 4        | -      | -        | -       |
| Leung C58    | 27-Apr           | Multi provinces| China   | Asian                   | Retrospective| 154         | 72.2 ± 8.5           | 57.79       | 7                    | 2        | 2        | -      | -        | -       |
| Li J59       | 19-May           | Wuhan          | China   | Asian                   | Retrospective| 54          | 53.3 ± 47.4          | 16.67       | 4                    | 6        | 52       | -      | -        | -       |
| Li J60       | 1-Jun            | Wuhan          | China   | Asian                   | Retrospective| 74          | 64.3 ± 12.6          | 59.46       | 6                    | -        | -        | -      | 41       | -       |
| Li K18       | 29-Feb           | Chongqing      | China   | Asian                   | Retrospective| 83          | 45.5 ± 12.3          | 53.01       | 7                    | -        | -        | -      | 7        | -       |

(Continues)
| 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 | 17-Apr | Hubei | China | Asian | Retrospective | 105 | 47.7 ± 11.8 | 57.14 | 2 | 3 | 3 | – | 6 |
| Li X | 12-Apr | Wuhan | China | Asian | Retrospective | 548 | 59.0 ± 15.5 | 50.91 | 179 | 45 | – | 16 | – |
| Liang Y | 29-Jun | Guangdong | China | Asian | Prospective | 86 | 29.5 ± 37.8 | 51.16 | 6 | 4 | – | – | 15 |
| Lin L | 2-Apr | Zuhai | China | Asian | Retrospective | 95 | 45.3 ± 18.3 | 47.37 | 23 | 4 | 17 | – | 17 |
| Lin W | 16-Jul | Guangzhou | China | Asian | Retrospective | 217 | 49.7 ± 20.0 | 49.77 | 17 | 4 | 9 | 3 | 38 |
| Liu B | 3-Jun | Wuhan | China | Asian | Prospective | 68 | 44.3 ± 16.4 | 36.76 | 5 | 4 | 4 | – | – |
| Liu J | 14-Apr | Wuhan | China | Asian | Retrospective | 140 | 64.3 ± 13.8 | 35.00 | 5 | – | 3 | 3 | 9 |
| Liu F | 17-Jun | Wuhan | China | Asian | Retrospective | 17 | 57.0 ± 9.6 | 76.47 | 4 | – | – | – | – |
| Liu F | 12-Mar | Zhejiang | China | Asian | Prospective | 10 | 42.0 ± 11.8 | 40.00 | – | – | 3 | – | – |
| Liu J | 18-Apr | Wuhan | China | Asian | Retrospective | 40 | 48.7 ± 13.9 | 37.50 | 3 | 1 | 3 | 1 | – |
| Liu k | 9-Feb | Shenzhen | China | Asian | Retrospective | 137 | 53.3 ± 46.7 | 44.53 | 11 | – | – | – | – |
| Liu y | 15-Mar | Macau | China | Asian | Retrospective | 12 | 53.7 ± 18.0 | 66.67 | 2 | 2 | 2 | – | – |
| Lo I | 18-Apr | Hong Kong | China | Asian | Prospective | 11 | 56.7 ± 20.7 | 63.64 | 2 | – | – | – | – |
| Liu G | 20-Mar | Hubei | China | Asian | Retrospective | 183 | 53.8 ± NA | 55.74 | 68 | 119 | 134 | 45 | 180 |
| Mao B | 14-May | Shanghai | China | Asian | Retrospective | 188 | 46.0 ± 24.0 | 50.00 | 6 | 1 | 1 | – | 24 |
| Mo P | 16-Mar | Wuhan | China | Asian | Retrospective | 155 | 54.0 ± 17.8 | 55.48 | 7 | 3 | 3 | 3 | 26 |
| Nobel Y | 12-Apr | New York | USA | American | Retrospective case-control | 278 | NA | 52.16 | 56 | 63 | 63 | – | – |
| Noh J | 21-May | Gyeong-sangbuk | Korea | Asian | Prospective | 199 | 38.0 ± 13.1 | 34.67 | 9 | – | – | – | 1 |
| Ortiz-Brizuela E | 14-May | Mexico City | Mexico | Mexican | Prospective | 309 | 43.3 ± 15.6 | 59.22 | 94 | 30 | – | 39 | – |
| Pan L | 14-Apr | Hubei | China | Asian | Retrospective | 204 | 52.9 ± 15.9 | 52.45 | 35 | 4 | – | 2 | 81 |
| Park S | 10-Jun | North Gyeongsang | Korea | Asian | Prospective | 46 | 33.7 ± 28.9 | 45.65 | 7 | – | 1 | 1 | 5 |
| Peng S | 10-Apr | Wuhan | China | Asian | Retrospective | 11 | 60.3 ± 13.3 | 72.73 | 3 | – | 6 | – | 6 |
| Poggiali E | 26-Mar | Piacenza | Italy | European | Retrospective | 10 | 50.0 ± 18.0 | 60.00 | 6 | 3 | – | 1 | – |
| Qi L | 17-May | Hunan | China | Asian | Retrospective | 147 | 43.7 ± 14.1 | 45.58 | – | – | – | – | – |
| First author      | Publication date | Study location | Country     | Geographic distribution | Study design | Sample size | Age, years, mean ± SD | Sex (% male) | GI symptoms (number) |    |    |    |    |    |    |    |    |
|------------------|------------------|----------------|-------------|-------------------------|--------------|-------------|-----------------------|--------------|----------------------|----|----|----|----|----|----|----|----|
| Ramachandran P   | 29-Jun           | New York       | USA         | American                | Retrospective| 150         | 62.1 ± 15.1           | 55.33        | 15 6 6 3              |    |    |    |    |    |    |    |    |
| Redd W           | 22-Apr           | Massachusetts  | USA         | American                | Retrospective| 318         | 63.4 ± 16.6           | 54.72        | 107 49 84 46          | 110 |    |    |    |    |    |    |    |
| Remes-Troche J   | 21-May           | Veracruz       | Mexico      | Mexican                 | Retrospective| 112         | 43.7 ± 15.0           | 72.32        | 20 8 – 11             |    |    |    |    |    |    |    |    |
| Rivera-Izquierdo M | 16-Jun         | Granada        | Spain       | European                | Prospective  | 76          | 45.8 ± 11.4           | 30.26        | 31 7 17 21            | 12 |    |    |    |    |    |    |    |
| Shi H            | 24-Feb           | Wuhan          | China       | Asian                   | Retrospective| 81          | 49.5 ± 11.0           | 51.85        | 3 4 – 1               |    |    |    |    |    |    |    |    |
| Sun H            | 8-May            | Wuhan          | China       | Asian                   | Retrospective| 244         | 70.0 ± 8.1            | 54.51        | 72 – 10               |    |    |    |    |    |    |    |    |
| Tabata S         | 12-Jun           | Tokyo          | Japan       | Asian                   | Retrospective| 71          | 62.0 ± 22.9           | 54.93        | 8 – 8 – 8             |    |    |    |    |    |    |    |    |
| To K             | 23-Mar           | Hong Kong      | China       | Asian                   | Retrospective| 23          | 57.7 ± 27.5           | 56.52        | 2 – 1 – 1             |    |    |    |    |    |    |    |    |
| Tomlins J        | 27-Apr           | Bristol        | UK          | European                | Retrospective| 95          | 72.0 ± 17.1           | 63.16        | 11 13 13              | 5  |    |    |    |    |    |    |    |
| Wan Y            | 15-Apr           | Guangdong, Hubei, Jiangxi | China       | Asian                   | Retrospective| 230         | 47.8 ± 16.2           | 56.09        | 49 – 3 – 3            |    |    |    |    |    |    |    |    |
| Wang D           | 7-Feb            | Wuhan          | China       | Asian                   | Retrospective| 138         | 55.3 ± 19.3           | 54.35        | 14 5 14 3             | 55 |    |    |    |    |    |    |    |
| Wang K           | 23-Mar           | Hubei          | China       | Asian                   | Retrospective| 114         | 51.3 ± 40.7           | 50.88        | 3 – 3 – 3             |    |    |    |    |    |    |    |    |
| Wang R           | 11-Apr           | Anhui          | China       | Asian                   | Retrospective| 125         | 38.8 ± 13.8           | 56.80        | 50 24 24              |    |    |    |    |    |    |    |    |
| Wang X           | 3-Apr            | Wuhan          | China       | Asian                   | Retrospective| 1012        | 49.0 ± 14.1           | 51.78        | 152 36 37             |    |    |    |    |    |    |    |    |
| Wang Z           | 12-Mar           | Wuhan          | China       | Asian                   | Retrospective| 69          | 46.3 ± 20.0           | 46.38        | 10 3 – 3              |    |    |    |    |    |    |    |    |
| Wei X            | 18-Apr           | Wuhan          | China       | Asian                   | Retrospective| 84          | 45.0 ± 37.0           | 33.33        | 26 6 16              | 2  |    |    |    |    |    |    |    |
| Wei Y            | 17-Apr           | Anhui          | China       | Asian                   | Retrospective| 167         | 42.3 ± 15.3           | 56.89        | 56 17 17              |    |    |    |    |    |    |    |    |
| Wu J             | 29-Feb           | Jiangsu        | China       | Asian                   | Retrospective| 80          | 46.1 ± 15.4           | 48.75        | 1 1 1 – 1             |    |    |    |    |    |    |    |    |
| Xie J            | 6-Jun            | Zhejiang       | China       | Asian                   | Retrospective| 104         | 54.0 ± 15.6           | 60.58        | 13 3 6 2              |    |    |    |    |    |    |    |    |
| Xiong Y          | 3-Mar            | Hubei          | China       | Asian                   | Retrospective| 42          | 49.5 ± 14.1           | 59.52        | 10 – 10              |    |    |    |    |    |    |    |    |
| Xu K             | 9-Apr            | Hangzhou & Shenzhen | China       | Asian                   | Retrospective| 113         | 52.7 ± 14.8           | 58.41        | – – – –               |    |    |    |    |    |    |    |    |
| Xu X             | 28-Feb           | Guangzhou      | China       | Asian                   | Retrospective| 90          | 51.3 ± 50.4           | 43.33        | 5 2 5 – 5             |    |    |    |    |    |    |    |    |
| Xu X             | 19-Feb           | Zhejiang       | China       | Asian                   | Retrospective case series | 62          | 41.7 ± 14.8           | 56.45        | 3 – 3 – 3             |    |    |    |    |    |    |    |    |
| 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      | 26-Feb          | Wenzhou        | China   | Asian                   | Retrospective| 149         | 45.1 ± 13.3         | 54.36       | 11 2 2              | -       | -        | -      | -        | -       |
| Yang X      | 21-Feb          | Wuhan          | China   | Asian                   | Retrospective| 52          | 59.7 ± 13.3         | 67.31       | – 2 –               | -       | -        | -      | -        | -       |
| Yang Y      | 29-Apr          | Shenzhen       | China   | Asian                   | Retrospective| 50          | 54.0 ± 41.5         | 58.00       | 4 – –               | -       | -        | -      | -        | -       |
| Yin S       | 30-Apr          | Hunan          | China   | Asian                   | Retrospective| 33          | 47.5 ± 24.8         | 48.48       | 5 – –               | -       | -        | -      | -        | -       |
| Yoshimura Y | 12-Jun          | Yokohama       | Japan   | Asian                   | Retrospective| 17          | 69.0 ± 10.0         | 47.06       | 1 4 4               | -       | -        | -      | -        | -       |
| Young B     | 3-Mar           | Singapore      | Singapore| Asian                   | Retrospective| 18          | 50.3 ± 31.1         | 50.00       | 3 – –               | -       | -        | -      | -        | -       |
| Zayet S     | 16-Jun          | Grand Est region | France | European                | Retrospective & observational | 70          | 56.7 ± 19.3         | 41.43       | 28 2 22 14         | -       | -        | -      | -        | -       |
| Zeng Q      | 12-Jun          | Henan & Shaanxi provinces | China   | Asian                   | Retrospective & observational| 149         | 42.3 ± 18.5         | 61.07       | 11 4 8              | -       | -        | -      | 20       | -       |
| Zhang G     | 9-Apr           | Wuhan          | China   | Asian                   | Retrospective| 221         | 53.5 ± 20.4         | 48.87       | 25 – –              | -       | -        | -      | 5 80      | -       |
| Zhang H     | 23-Jun          | Wuhan          | China   | Asian                   | Retrospective| 107         | 66.7 ± 45.9         | 56.07       | 15 – –              | -       | -        | -      | -        | -       |
| Zhang J     | 15-Apr          | Wuhan          | China   | Asian                   | Retrospective| 663         | 56.2 ± 18.5         | 48.42       | 61 17 31 5         | -       | -        | -      | -        | -       |
| Zhang J     | 6-Jun           | Wuhan          | China   | Asian                   | Retrospective| 135         | 62.3 ± 10.4         | 57.78       | 18 15 15 2         | 12      | -        | -      | -        | -       |
| Zhang J     | 28-Apr          | Wuhan          | China   | Asian                   | Retrospective| 111         | 42.3 ± 18.5         | 41.44       | 10 – –              | -       | -        | -      | -        | -       |
| Zhang J     | 19-Feb          | Wuhan          | China   | Asian                   | Retrospective| 140         | 56.3 ± 45.9         | 50.71       | 18 7 24 8          | 17      | -        | -      | -        | -       |
| Zhang L     | 29-Jun          | Wuhan          | China   | Asian                   | Retrospective| 409         | 64.0 ± 11.1         | 57.21       | 91 42 50 28        | -       | -        | -      | -        | -       |
| Zhang L     | 1-Apr           | Anhui          | China   | Asian                   | Retrospective| 80          | 44.1 ± 17.1         | 58.75       | 33 17 17           | -       | -        | -      | -        | -       |
| Zhang L     | 26-Mar          | Wuhan          | China   | Asian                   | Retrospective| 28          | 63.7 ± 10.4         | 60.71       | 3 – –               | -       | -        | -      | -        | -       |
| Zhang P     | 5-Jun           | Wuhan          | China   | Asian                   | Retrospective| 136         | 67.7 ± 14.8         | 63.24       | 28 – –              | -       | -        | -      | -        | -       |
| Zhang X     | 20-Mar          | Zhejiang       | China   | Asian                   | Retrospective| 645         | 45.3 ± 13.9         | 50.85       | 53 22 22           | -       | -        | -      | -        | -       |
| Zhao D      | 12-Mar          | Anhui          | China   | Asian                   | Comparative  | 19          | 43.7 ± 21.5         | 57.89       | 1 – –               | -       | -        | -      | -        | -       |
| Zhao F      | 16-May          | Shenzhen       | China   | Asian                   | Retrospective| 401         | 46.7 ± 20.0         | 47.38       | 25 1 1             | -       | -        | -      | -        | -       |
| Zhao W      | 3-Mar           | Shenzhen       | China   | Asian                   | Retrospective| 101         | 44.4 ± 12.3         | 55.45       | 3 2 2              | -       | -        | -      | -        | -       |
| Zheng S     | 21-Apr          | Zhejiang       | China   | Asian                   | Retrospective| 96          | 54.7 ± 15.2         | 60.42       | 10 2 5             | -       | -        | -      | -        | -       |
| Zheng Y     | 8-Jun           | Wuhan          | China   | Asian                   | Retrospective| 1320        | 49.0 ± 12.6         | 43.86       | 107 57 11          | 62      | -        | -      | -        | -       |
| Zheng Y     | 30-Apr          | Shiyian        | China   | Asian                   | Retrospective| 73          | 46.7 ± 40.7         | 54.79       | 1 – –              | -       | -        | -      | 3        | -       |
Further, 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 (\( p = .012 \; \text{Table S2} \)).

### 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.\(^{145} \) Regarding the outcome, Asian patients

\[ p < .001 \]
| First author | Year  | DOP       | Journal name                     | City    | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex(F/M) |
|--------------|-------|-----------|----------------------------------|---------|---------|-----------|-------------|------------------------|-----------|
| Chen L       | 2020  | 13-May    | Journal of Infection             | Guangdong | China   | Asian     | 20          | 62.5 ± 13.3            | 6/14 11/20 |
| Fu J         | 2020  | 6-May     | Thrombosis Research              | Suzhou   | China   | Asian     | 16          | 51.8 ± 12.8            | 6/10 24/35 |
| Guan W       | 2020  | 28-Feb    | New England Journal of Medicine   | Multiple | China   | Asian     | 173         | 52.3 ± 18.5            | 73/100 386540 |
| Han J        | 2020  | 25-Jun    | Epidemiol Infect                  | Tianjin  | China   | Asian     | 30          | 61.6 ± 12.4            | 13/17 77/78 |
| Huang M      | 2020  | 1-Jun     | The Am Jof the Medical Sciences   | Jiangsu  | China   | Asian     | 8           | NA                     | NA NA     |
| Jin A        | 2020  | 12-May    | Biosafety and Health              | Beijing  | China   | Asian     | 20          | 74.7 ± 10.7            | 10/10 17/8 |
| Li K         | 2020  | 29-Feb    | Invest Radiol                     | Chongqing | China | Asian     | 25          | 53.7 ± 12.3            | 10/15 29/29 |
| Li X         | 2020  | 12-Apr    | J of Allergy & Clinical Immunol   | Wuhan    | China   | Asian     | 269         | 63.7 ± 13.3            | 116/153 153/126 |
| Liu F        | 2020  | 14-Apr    | Journal of Clinical Virolgy       | Wuhan    | China   | Asian     | 33          | 76.7 ± 16.3            | 25/8 66/41 |
| Liu J        | 2020  | 18-Apr    | EBioMedicine                      | Wuhan    | China   | Asian     | 13          | 59.7 ± 10.1            | 6/7 19/8 |
| Lo F         | 2020  | 15-Mar    | Int J Biol Sci                    | Macau    | China   | Asian     | 4           | 61.0 ± 5.0             | 3/1 4/2 |
| Lui G        | 2020  | 18-Apr    | Journal of Infection              | Hong Kong | China | Asian     | 5           | 65.7 ± 5.9             | 1/4 3/3 |
| Mo P         | 2020  | 16-Mar    | Clin Infect Dis                   | Wuhan    | China   | Asian     | 85          | 60.7 ± 14.1            | 30/55 39/31 |
| Tabata S     | 2020  | 12-Jun    | The Lancet Infectious Diseases    | Tokyo    | Japan   | Asian     | 28          | 68.3 ± 16.3            | 11/17 21/22 |
| First author | Year | DOP | Journal name | City         | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex(F/M) |
|--------------|------|-----|--------------|--------------|---------|-----------|-------------|------------------------|----------|
| To K         | 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       | 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       | 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        | 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       | 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      | 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      | 2020 | 23-Jun | Cancer | Wuhan     | China   | Asian     | 56   | 51   | 67.7 ± 45.9 | 59.7 ± 30.4 | 19/37 | 28/23  |
| Zhang J      | 2020 | 15-Apr | Clinical Microbiology and Inf | Wuhan     | China   | Asian     | 315  | 254  | 52.2 ± 18.5 | 48.7 ± 18.5 | 166/149 | 138/116 |
| Zhang J      | 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      | 2020 | 19-Feb | Allergy | Wuhan     | China   | Asian     | 58   | 82   | 58.7 ± 45.9 | 51.8 ± 38.5 | 25/33 | 44/38  |
| Zheng S      | 2020 | 21-Apr | BMJ | Zhejiang   | China   | Asian     | 74   | 22   | 56.8 ± 13.7 | 46.9 ± 14.4 | 25/49 | 13/9   |
| Zhu Z        | 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    | 2020 | 10-Jun | Am J Gastroenterol | California | USA | American | 60 | 147 | 60.7 ± 25.2 | 44.0 ± 20.0 | 28/32 | 75/72 |
| Hajifathalian K  | 2020 | 8-May | Gastroenterology | New York | USA | American | 768 | 291 | 64.7 ± 17.1 | 51.6 ± 17.8 | 302/466 | 146/145 |
| First author         | Year  | DOP       | Journal name                  | City       | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex (F/M) |
|---------------------|-------|-----------|------------------------------|------------|---------|-----------|--------------|-----------------------|-----------|
| Ortiz-Brizuela E    | 2020  | 14-May    | Rev Invest Clin              | Mexico     | Mexico  | Mexican   | 140          | 169                   | 55/85     |
|                     |       |           |                              |            |         |           |              |                       | 71/98     |
| Rivera-Izquierdo M  | 2020  | 16-Jun    | Int J Environ Res Public Health | Granada   | Spain   | European | 11           | 65                    | NA        |
|                     |       |           |                              |            |         |           |              |                       | NA        |
|                     |       |           |                              |            |         |           |              |                       | NA        |
|                     |       |           |                              |            |         |           |              |                       | NA        |
| Huang C             | 2020  | 24-Jan    | Lancet                       | Wuhan      | China   | Asian     | 13           | 28                    | 50.3 ± 14.8 |
|                     |       |           |                              |            |         |           |              |                       | 49.2 ± 12.2 |
|                     |       |           |                              |            |         |           |              |                       | 2/11      |
|                     |       |           |                              |            |         |           |              |                       | 9/20      |
|                     |       |           |                              |            |         |           |              |                       | 46/65     |
| Ortiz-Brizuela E    | 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              | 2020  | 7-Feb     | Jama                         | Wuhan      | China   | Asian     | 36           | 102                   | 67.0 ± 15.6 |
|                     |       |           |                              |            |         |           |              |                       | 50.0 ± 18.5 |
|                     |       |           |                              |            |         |           |              |                       | 14/22     |
|                     |       |           |                              |            |         |           |              |                       | 49/53     |
| Zeng Q              | 2020  | 12-Jun    | Transbound Emerg Dis         | Henan      | China   | Asian     | 27           | 122                   | 57.3 ± 20.0 |
|                     |       |           |                              |            |         |           |              |                       | 39.0 ± 17.0 |
|                     |       |           |                              |            |         |           |              |                       | NA        |
|                     |       |           |                              |            |         |           |              |                       | NA        |
| Cholankeril G       | 2020  | 10-Jun    | Am J Gastroenterol           | California | USA     | American | 17           | 43                    | 55.7 ± 20.7 |
|                     |       |           |                              |            |         |           |              |                       | 62.3 ± 23.7 |
|                     |       |           |                              |            |         |           |              |                       | 7/10      |
|                     |       |           |                              |            |         |           |              |                       | 21/22     |
| Chen F              | 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              | 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             | 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                | 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              | 2020  | 10-Apr    | J of Thoracic and CV Surgery | Wuhan      | China   | Asian     | 3            | 8                     | NA        |
|                     |       |           |                              |            |         |           |              |                       | NA        |
|                     |       |           |                              |            |         |           |              |                       | 1/2       |
|                     |       |           |                              |            |         |           |              |                       | 2/6       |
| First author | Year | DOP   | Journal name                          | City     | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex(F/M) |
|--------------|------|-------|--------------------------------------|----------|---------|-----------|--------------|------------------------|---------|
| Sun H        | 2020 | 8-May | J of American Geriatrics Society     | Wuhan    | China   | Asian     | 121          | 72.0 ± 8.9             | 67.7/5.9 | 39/82    | 72/51    |
| Tomlins J    | 2020 | 27-Apr| Journal of Infection                 | Bristol  | UK      | European  | 20           | 78.0 ± 9.6             | 70.7/19.3| 8/12    | 72/48    |
| Yang X       | 2020 | 21-Feb| Lancet Respir Med                    | Wuhan    | China   | Asian     | 32           | 64.6 ± 11.2            | 51.9/12.9| 11/21   | 6/14     |
| Zhang G      | 2020 | 9-Apr | Journal of Clinical Virology         | Wuhan    | China   | Asian     | 9            | 71.7 ± 17.8            | 60.7/16.3| 2/7     | 8/15     |
| Zhang L      | 2020 | 29-Jun| Gastroenterology                     | Wuhan    | China   | Asian     | 102          | 66.3 ± 10.4            | 62.3/14.1| 30/72   | 145/162  |
| Zhou F       | 2020 | 9-Mar | Lancet                               | Wuhan    | China   | Asian     | 54           | 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

| First author | Year | DOP   | Journal name                          | City     | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex(F/M) |
|--------------|------|-------|--------------------------------------|----------|---------|-----------|--------------|------------------------|---------|
| Chen Y       | 2020 | 3-Apr | J Med Virol                          | Wuhan    | China   | Asian     | 28           | 52.2 ± 14.1            | 48.7/12.1| 16/12   | 11/3     |
| Lin W        | 2020 | 16-Jul| J Med Virol                          | Guangzhou| China   | Asian     | 46           | 52.0 ± 15.6            | 48.3/21.5| 20/26   | 89/82    |
| Zhao F       | 2020 | 16-May| Gastroenterology                     | Shenzhen | T       | China     | 80           | 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

| First author | Year | DOP   | Journal name                          | City     | Country | Ethnicity | Sample size | Age, years (mean ± SD) | Sex(F/M) |
|--------------|------|-------|--------------------------------------|----------|---------|-----------|--------------|------------------------|---------|
| Cao C        | 2020 | 15-Jun| Critical Care                        | China    | Asian   | Retrospective | 63           | 51.9 ± 14.9            | 47.5/14.0| 39/24   | 44/50    |
| Effenberger M| 2020 | 20-Apr| Gut                                  | Austria  | European| Retrospective | 9            | 78.3 ± 13.8            | 58.4/17.1| 3/6     | 9/9      |
| Ferm S       | 2020 | 1-Jun | Clin Gastroenterol Hepatol           | USA      | American| Retrospective | 219          | NA                     | NA        | NA      | NA       |
| Han C        | 2020 | 15-Apr| Am J Gastroenterol                   | China    | Asian   | Retrospective | 48           | 62.5 ± 44.4            | 61.0/47.4| 35/13   | 41/48    |
| Jin X        | 2020 | 24-Mar| Gut                                  | China    | Asian   | Retrospective | 74           | 46.1 ± 14.2            | 45.1/14.4| 37/37   | 283/294  |

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

Pandemics have historically come in waves with differing severities and lengths of time between them. 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 | Estimate      | 95% CI    | p value | I² | p value | p value |
| A. Demographic characteristics   |                |             |                     |              |               |          |         |    |         |         |
| Age, years                       | 59             | 14200       | 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/m²                       | 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   |
| PaO₂ (mm/Hg)                     | 4              | 392         | 97                  | 313          | IV SMD        | Random   | -0.442  | -1.343 to -0.460 | .337 | 91.45% | <.001 | .107   |
| PaCO₂ (mm/Hg)                    | 4              | 392         | 97                  | 313          | IV SMD        | Random   | -0.465  | -0.824 to -0.106 | .011 | 47.55% | .126  | .034   |
| PaO₂:FiO₂ ratio (mm/Hg)          | 4              | 451         | 105                 | 346          | IV SMD        | Random   | -1.067  | -1.428 to -0.705 | <.001 | 52.14% | .099  | .678   |
| SpO₂ (%)                         | 8              | 2080        | 479                 | 1601         | IV SMD        | Random   | -1.039  | -1.340 to -0.738 | <.001 | 82.42% | <.001 | .907   |
| Characteristics | Number studies | Sample size | Poor prognosis | Good prognosis | Test of association | Effect size | Heterogeneity | Pub bias |
|-----------------|----------------|-------------|----------------|----------------|---------------------|-------------|--------------|---------|
|                 |                | Total       |                |                | Statistical method  | Effect measure | Analysis model | p value |
| Highest         | 15             | 4411        | 1268           | 3143           | IV SMD             | Random      |              |         |
| temperature °C  |                |             |                |                |                     |             |              |         |
| C. General clinical presentations | | | | | | | | |
| Fever (≥ 37.3°C) | 51             | 13373       | 4076           | 9297           | MH OR              | Random      |              |         |
| Dry cough       | 49             | 13,142      | 3964           | 9178           | MH OR              | Random      |              |         |
| Expectoration   | 22             | 7759        | 1765           | 5994           | MH OR              | Random      |              |         |
| Chest pain      | 18             | 4622        | 1543           | 3079           | MH OR              | Random      |              |         |
| Dizziness       | 10             | 2152        | 960            | 1192           | MH OR              | Random      |              |         |
| Rhinorrhea      | 14             | 2966        | 806            | 2160           | MH OR              | Random      |              |         |
| Anosmia         | 6              | 1997        | 1163           | 834            | MH OR              | Random      |              |         |
| Dyspnea         | 42             | 11,927      | 3524           | 8403           | MH OR              | Random      |              |         |
| Headache        | 30             | 8667        | 2188           | 6479           | MH OR              | Random      |              |         |
| Sore throat     | 30             | 8747        | 2060           | 6687           | MH OR              | Random      |              |         |
| Myalgia         | 41             | 11,027      | 3497           | 7530           | MH OR              | Random      |              |         |
| Fatigue         | 33             | 9903        | 3189           | 6714           | MH OR              | Random      |              |         |
| Nasal congestion| 8              | 4431        | 674            | 3757           | MH OR              | Random      |              |         |
| D. Comorbidities |                |             |                |                |                     |             |              |         |
| Hypertension    | 44             | 10,807      | 3351           | 7456           | MH OR              | Random      |              |         |
| Diabetes mellitus| 48             | 11722       | 3779           | 7943           | MH OR              | Random      |              |         |
| Cardiovascular disease | 34 | 8702 | 3224 | 5478 | MH OR | Random |              |         |
| Cerebrovascular disease | 15 | 4328 | 1123 | 3205 | MH OR | Random |              |         |
| Chronic liver disease| 23 | 5666 | 2124 | 3542 | MH OR | Random |              |         |
| Chronic kidney disease | 24 | 7313 | 2452 | 4861 | MH OR | Random |              |         |

(Continues)
| Characteristics | Number of studies | Sample size Total | Poor prognosis | Good prognosis | Test of association | Effect size | Heterogeneity | Pub bias |
|-----------------|------------------|-------------------|----------------|----------------|---------------------|------------|--------------|---------|
|                 |                  |                   |                |                | Statistical method | Analysis model | Estimate 95% CI | p value | I² | 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

|                  |                  |                   |                |                | Statistical method | Analysis model | Estimate 95% CI | p value | I² | p value | p value |
|------------------|------------------|-------------------|----------------|----------------|---------------------|------------|----------------|--------|----|--------|--------|
| WBCs (×10⁹/L)    | 44               | 10913             | 3020          | 7893           | IV SMD Random       | 0.325      | 0.174-0.476 | <.001  | 88.64% | <.001 | .286 |
| Neutrophils count (×10⁹/L) | 30         | 7072              | 2024          | 5048           | IV SMD Random       | 0.589      | 0.372-0.807 | <.001  | 91.31% | <.001 | .115 |
| Lymphocytes count (×10⁹/L) | 45       | 10169             | 2979          | 7190           | IV SMD Random       | -0.533     | -0.659 to -0.408 | <.001  | 82.21% | <.001 | .108 |
| NLR (×10⁹/L)     | 7                | 1242              | 235           | 1007           | IV SMD Random       | 1.064      | 0.476-1.653 | <.001  | 92.18% | <.001 | .294 |
| Monocytes count (×10⁹/L) | 9       | 1566              | 452           | 1114           | IV SMD Random       | -0.217     | -0.334 to -0.100 | <.001  | 0.0%   | .462  | .282 |
| Platelets count, (×10⁹/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 |
| Characteristics            | Number studies | Sample size | Total | Poor prognosis | Good prognosis | Test of association | Statistical method | Effect measure | Analysis model | Effect size | 95% CI          | p value  | Heterogeneity | Pub bias |
|-----------------------------|----------------|-------------|-------|----------------|----------------|---------------------|--------------------|---------------|---------------|------------|----------------|----------|---------------|----------|
| ALP (U/L)                   | 4              | 1540        | 1002  | 538            |                | IV SMD             | Random             |               |               | 0.076      | -0.034 to 0.187 | .177     | 0.0%          | .630     |
| Creatinine (μmol/L)         | 29             | 4358        | 1211  | 3147           |                | IV SMD             | Random             |               |               | 0.295      | 0.121-0.470    | .001     | 80.94%        | <.001    |
| BUN (mmol/L)                | 15             | 2183        | 589   | 1594           |                | IV SMD             | Random             |               |               | 0.449      | 0.138-0.760    | .005     | 87.67%        | <.001    |
| Sodium (mmol/L)             | 12             | 2964        | 659   | 2305           |                | IV SMD             | Random             |               |               | -0.228     | -0.436 to -0.020 | .031     | 74.78%        | <.001    |
| Potassium (mmol/L)          | 9              | 2548        | 555   | 1993           |                | IV SMD             | Random             |               |               | -0.302     | -0.768 to 0.164 | .204     | 93.89%        | <.001    |
| Lactate (mmol/L)            | 7              | 883         | 343   | 540            |                | IV SMD             | Random             |               |               | 0.202      | -0.113 to 0.516 | .208     | 72.35%        | .001     |
| Fasting blood glucose (mmol/L) | 4             | 1123        | 190   | 933            |                | IV SMD             | Random             |               |               | 0.423      | -0.094 to 0.941 | .109     | 88.62%        | <.001    |
| Lactate dehydrogenase (U/L) | 26             | 4953        | 1697  | 3256           |                | IV SMD             | Random             |               |               | 0.773      | 0.471-1.076    | <.001    | 93.76%        | <.001    |
| Troponin (ng/L)             | 13             | 2656        | 1250  | 1406           |                | IV SMD             | Random             |               |               | 0.661      | 0.329-0.992    | <.001    | 90.84%        | <.001    |
| NT-proBNP (pg/ml)           | 4              | 763         | 346   | 417            |                | IV SMD             | Random             |               |               | 0.488      | -0.116 to 1.092 | .113     | 91.55%        | <.001    |
| Creatine kinase (U/L)       | 20             | 3861        | 1496  | 2365           |                | IV SMD             | Random             |               |               | 0.260      | 0.082-0.438    | .004     | 77.93%        | <.001    |
| Creatine kinase-MB (U/L)    | 10             | 1697        | 408   | 1289           |                | IV SMD             | Random             |               |               | 0.613      | 0.077-1.148    | .025     | 93.89%        | <.001    |
| Myoglobin (ng/mL)           | 3              | 304         | 64    | 240            |                | IV SMD             | Random             |               |               | 0.947      | 0.652-1.242    | <.001    | 0.0%          | .411     |
| Serum amyloid A (mg/L)      | 4              | 853         | 199   | 654            |                | IV SMD             | Random             |               |               | 0.868      | 0.175-1.561    | .014     | 91.98%        | <.001    |
| International Normalized Ratio | 5          | 2142        | 1064  | 1078           |                | IV SMD             | Random             |               |               | 0.084      | -0.186 to 0.354 | .543     | 77.96%        | .001     |
| Prothrombin time (s)        | 15             | 2028        | 596   | 1432           |                | IV SMD             | Random             |               |               | 0.370      | 0.201-0.539    | <.001    | 58.80%        | .002     |
| APTT (s)                    | 15             | 3347        | 1502  | 1845           |                | IV SMD             | Random             |               |               | 0.085      | 0.004-0.166    | .040     | 4.63%         | .400     |

(Continues)
### Table 3 (Continued)

| Characteristics                        | Number of studies | Sample size | Test of association | Effect size | Heterogeneity | Pub bias |
|----------------------------------------|-------------------|-------------|---------------------|-------------|---------------|----------|
| o-dimer (ng/ml)                        | 24                | 4694        | IV, SMD, Random     | 0.548       | 87.59%        | .280     |
| CRP (mg/L)                             | 33                | 7834        | IV, SMD, Random     | 0.812       | 92.63%        | .067     |
| Ferritin (ng/ml)                       | 10                | 2812        | IV, SMD, Random     | 0.709       | 93.82%        | .342     |
| Fibrinogen (g/L)                       | 8                 | 923         | IV, SMD, Random     | 0.913       | 89.50%        | .068     |
| ESR (mm/h)                             | 9                 | 2230        | IV, SMD, Random     | 0.491       | 83.96%        | .694     |
| Procalcitonin (ng/ml)                  | 22                | 4591        | IV, SMD, Random     | 0.810       | 93.09%        | .098     |
| Interleukin-6 (pg/ml)                  | 14                | 3653        | IV, SMD, Random     | 1.098       | 93.39%        | .399     |
| CD3+ T lymphocyte (Cells/μL)           | 2                 | 1229        | IV, SMD, Random     | -0.998      | 0.0%          | NA       |
| CD4+ T lymphocyte (Cells/μL)           | 5                 | 1531        | IV, SMD, Random     | -0.864      | 0.0%          | .722     |
| CD8+ T lymphocyte (Cells/μL)           | 5                 | 1531        | IV, SMD, Random     | -0.931      | 1.75%         | .283     |
| Oxygen therapy                         | 10                | 2620        | MH, OR, Random      | 1.971       | 89.86%        | .344     |
| High-flow nasal cannula                | 8                 | 1698        | MH, OR, Random      | 0.440       | 94.96%        | .859     |
| Mechanical ventilation: IMV            | 18                | 3815        | MH, OR, Random      | 35.46       | 43.79%        | .322     |
| Mechanical ventilation: NIV            | 15                | 3502        | MH, OR, Random      | 15.56       | 81.96%        | .002     |
| ACE/ARB inhibitor                      | 5                 | 992         | MH, OR, Random      | 1.173       | 0.0%          | .639     |
| Antibiotics                            | 19                | 6429        | MH, OR, Random      | 1.892       | 69.59%        | .494     |
| Antifungal                             | 4                 | 2035        | MH, OR, Random      | 4.015       | 0.0%          | .793     |
| Antiviral                              | 17                | 4480        | MH, OR, Random      | 1.040       | 15.80%        | .583     |
| Antiviral: Oseltamivir                 | 5                 | 2954        | MH, OR, Random      | 1.092       | 80.83%        | .919     |
| Antiviral: Ganciclovir                 | 2                 | 755         | MH, OR, Random      | 1.791       | 0.0%          | .328     |

F. Medications

| Medication                              | Number of studies | Sample size | Test of association | Effect size | Heterogeneity | Pub bias |
|-----------------------------------------|-------------------|-------------|---------------------|-------------|---------------|----------|
| Oxygen therapy                          | 10                | 2620        | MH, OR, Random      | 1.971       | 89.86%        | .344     |
| High-flow nasal cannula                 | 8                 | 1698        | MH, OR, Random      | 0.440       | 94.96%        | .859     |
| Mechanical ventilation: IMV             | 18                | 3815        | MH, OR, Random      | 35.46       | 43.79%        | .322     |
| Mechanical ventilation: NIV             | 15                | 3502        | MH, OR, Random      | 15.56       | 81.96%        | .002     |
| ACE/ARB inhibitor                       | 5                 | 992         | MH, OR, Random      | 1.173       | 0.0%          | .639     |
| Antibiotics                             | 19                | 6429        | MH, OR, Random      | 1.892       | 69.59%        | .494     |
| Antifungal                              | 4                 | 2035        | MH, OR, Random      | 4.015       | 0.0%          | .793     |
| Antiviral                               | 17                | 4480        | MH, OR, Random      | 1.040       | 15.80%        | .583     |
| Antiviral: Oseltamivir                  | 5                 | 2954        | MH, OR, Random      | 1.092       | 80.83%        | .919     |
| Antiviral: Ganciclovir                  | 2                 | 755         | MH, OR, Random      | 1.791       | 0.0%          | .328     |
TABLE 3 (Continued)

| Characteristics                  | Number studies | Sample size | Poor prognosis | Good prognosis | Test of association | Effect size | Heterogeneity | Pub bias |
|----------------------------------|----------------|-------------|----------------|----------------|---------------------|-------------|---------------|----------|
|                                  |                |             | Total           |                | Statistical method  | Effect measure | Analysis model | i2       | p value | p value | p value |
|                                 |                |             | 480            | 1169           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 516            | 887            | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 713            | 1445           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 266            | 1115           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 713            | 1445           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 1068           | 689            | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 2367           | 5395           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 1543           | 4565           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 621            | 1969           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 672            | 1714           | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 799            | 410            | MH                  | OR           | Random        |          |         |         |         |
|                                 |                |             | 3734           | 2802           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2737           | 1941           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1008           | 604            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1111           | 915            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2761           | 2002           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 3734           | 2802           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2737           | 1941           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1008           | 604            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1111           | 915            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2761           | 2002           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 3734           | 2802           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2737           | 1941           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1008           | 604            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1111           | 915            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2761           | 2002           | MH                  | RR           | Random        |          |         |         |         |
| G. Complications                 |                |             |                |                |                     |              |               |          |         |         |         |
| ARDS                             | 13             | 3734         | 932            | 2802           | MH                  | RR           | Random        |          |         |         |         |
| Acute cardiac injury             | 13             | 2737         | 796            | 1941           | MH                  | RR           | Random        |          |         |         |         |
| Arrhythmia                       | 7              | 1008         | 404            | 604            | MH                  | RR           | Random        |          |         |         |         |
| Acute liver injury               | 3              | 1111         | 196            | 915            | MH                  | RR           | Random        |          |         |         |         |
| Acute kidney injury              | 10             | 2761         | 759            | 2002           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 3734           | 2802           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 2737           | 1941           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1008           | 604            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1111           | 915            | MH                  | RR           | Random        |          |         |         |         |
| H. Clinical classification       |                |             |                |                |                     |              |               |          |         |         |         |
| Mild                             | 6              | 1026         | 299            | 727            | MH                  | RR           | Random        |          |         |         |         |
| Severe/critical                  | 38             | 7713         | 2078           | 5832           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 1026           | 727            | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 7713           | 5832           | MH                  | RR           | Random        |          |         |         |         |
| I. Clinical outcome              |                |             |                |                |                     |              |               |          |         |         |         |
| Hospitalized                     | 14             | 5183         | 1788           | 3395           | MH                  | RR           | Random        |          |         |         |         |
| Length of hospital stay (days)   | 16             | 5370         | 1173           | 4197           | IV                  | MD           | Random        |          |         |         |         |
| ICU admission                    | 18             | 5838         | 1346           | 4492           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 5183           | 3395           | MH                  | RR           | Random        |          |         |         |         |
|                                 |                |             | 5370           | 4197           | IV                  | MD           | Random        |          |         |         |         |
|                                 |                |             | 5838           | 4492           | MH                  | RR           | Random        |          |         |         |         |

(Continues)
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 subgroup 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.

### TABLE 3 (Continued)

| Characteristics          | Sample size | Test of association | Effect size | Heterogeneity | Pub bias |
|--------------------------|-------------|---------------------|-------------|---------------|----------|
|                          | Number studies | Statistical method | Effect measure | Analysis model | Estimate | 95% CI  | p value | I² | p value | p value |
| Mechanical ventilation   | 7           | MH                  | OR          | Random        | 2.363    | 0.972–5.742 | .058    | 76.75% | <.001  | .042    |
| Length of ICU stay (days)| 3           | IV                  | MD          | Random        | 0.017    | −3.717 to 3.750 | .993    | 86.53% | .001    | .943    |
| Discharged               | 14          | MH                  | RR          | Random        | 0.714    | 0.604–0.844 | <.001  | 83.78% | .001    | .029    |
| Mortality                | 25          | MH                  | RR          | Random        | 2.017    | 1.186–3.431 | <.001  | 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, activated 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; 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; OR, odds ratio; PaCO₂, The partial pressure of carbon dioxide; PaO₂, The partial pressure of oxygen; PaO₂:FIO₂ 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; SpO₂, 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.
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 predominantly 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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### 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

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**FIGURE 4** Subgroup analysis for pooled pairwise comparison analysis of coronavirus disease-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.
M. Elshazli, Mohammad H. Hussein, Eman A. Toraih, Manal S. Fawzy, and Emad Kandi, 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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