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COMMENTARY

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The importance of fecal nucleic acid detection in patients with coronavirus disease (COVID-19): A systematic review and meta-analysis

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Abstract

Pooled data from 2352 hospitalized coronavirus disease 2019 (COVID-19) patients with viral RNA in feces across 46 studies were analyzed and the pooled prevalence of fecal RNA was 46.8% (95% confidence interval [CI]: 0.383–0.554). The pooled analysis showed that the occurrence of total gastrointestinal (GI) symptoms was 28.5% (95% CI: 0.125–0.44) in COVID-19 patients with fecal RNA, that of both respiratory and GI symptoms was 21.9% (95% CI: 0.09–0.346), that of only GI symptoms was 19.8% (95% CI: 0.107–0.288), and that of only respiratory symptoms was 50.5% (95% CI: 0.267–0.744). The pooled data showed no significant difference in positive fecal RNA between severe and nonsevere cases (odds ratio = 2.009, $p = 0.079$, 95% CI: 0.922–4.378). During hospital admission, after samples from the respiratory system tested negative for viral RNA, 55.4% (95% CI: 0.418–0.669) of the patients with positive fecal RNA had persistent shedding of fecal RNA and pooled results from the other 4 studies including 848 discharged patients with nucleic acid-negative stool samples indicated that the occurrence of repositive stool swabs was 18.1% (95% CI: 0.028–0.335), that of repositive respiratory swabs was 22.8% (95% CI: 0.003–0.452), that of both repositive stool and respiratory swabs was 19.1% (95% CI: 0.019–0.363), and that of only repositive stool swabs was 9.6% (95% CI: 0.010–0.203). The digestive tract may be an important organ involved in COVID-19 infection and in the excretion of the virus. Because of the potential risk of fecal–oral transmission, giving emphasis on stool swab tests can help increase the detection rate of asymptomatic carriers and reduce missed diagnoses.

KEYWORDS

COVID-19, fecal, meta-analysis, systematic review

1 | INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still an ongoing global health crisis due to the coronavirus disease 2019 (COVID-19), with severe threats to public health because of a very high transmissibility rate. Apart from respiratory symptoms, gastrointestinal (GI) manifestations are common in patients with COVID-19 and, in some cases, GI symptoms may precede the respiratory symptoms.[1–3] The positive detection of RNA from SARS-CoV-2 in feces suggests that the virus can replicate and exist in the digestive tract.[4,5] It was subsequently found that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2)

expressed in the upper esophagus and stratified epithelial cells, and absorptive enterocytes from the ileum and colon, which is the entry point for the virus to the epithelial cells.[6,7] The presence of new mutations may enable an increase in the viral tropism of the digestive tract.[8] At present, the GI symptoms in different studies are quite different in patients with COVID-19 with nucleic acid-positive stool samples,[9–11] which poses an important diagnostic challenge to clinicians on initial presentation. The presence of SARS-CoV-2 in stool samples and the potential of fecal–oral transmission is critical for our understanding of COVID-19; therefore, more attention should be given to these patients.

In addition, the recurrence of SARS-CoV-2 viral RNA in patients makes the pandemic more complex and some countries are facing a resurgence of the disease. This increases healthcare costs and the financial burden to families and societies. As viral loads in stool and perianal swabs appear to decline slower than in throat swabs,[12] the concern is the infectivity of SARS-CoV-2 in feces in the late stages of infection and recurrent viral RNA positivity in recovered COVID-19 patients. It is unclear whether patients with COVID-19 with positive long-term fecal nucleic acid tests have the risk of infection. Thus, we performed a systematic review and meta-analysis of studies reporting the disease course in patients with COVID-19 with nucleic acid-positive stool samples and recurrence of SARS-CoV-2 viral RNA in stool samples. This might help inform public health protocols for contact tracing and quarantine.

2 | METHODS

2.1 | Information sources and literature search

Three databases including PubMed, EMBASE, and the Cochrane Library were systematically searched from the inception of the databases to May 15, 2021. A principal electronic search strategy was developed for PubMed and then applied to the other databases. This search was done in two parts and the following search terms alone or matched with the Boolean operators "AND" or "OR" were used: "diarrhea," "gastrointestinal," "digestive," "feces," "fecal," "stool," "rectal swab," "anal swab," "COVID-19," "severe acute respiratory syndrome coronavirus 2," "SARS-CoV-2," "novel coronavirus," "2019-nCoV," "recurrence," "discharge," and "recovery." No language or geographic restrictions were imposed. We focused on full-text articles, but abstracts were considered if relevant. In addition, relevant review articles and references were examined for thorough assessment for existing literature. All articles were managed with Endnote X9.2 (Thompson and Reuters)/EndNote(version X9.2) and duplicates were removed.

2.2 | Election criteria

Two reviewers (ZJQ and LGX) independently screened the titles and abstracts according to these eligibility criteria. A third reviewer (HXL) subsequently reviewed the full-text articles and identified articles for inclusion. Disagreement was discussed and subsequently resolved via consensus. The inclusion criteria included the following: (1) study population: COVID-19 patients (including adult or pediatric patients and pregnant women) provided data on stool/anal/perianal viral RNA; (2) study design: case series, prospective/retrospective cohort study, case–control study, and randomized controlled trials. There was no language restriction. The exclusion criteria were small studies ($N < 5$), review articles, meta-analyses, editorials, and other forms (e.g., commentary).

2.3 | Data extraction

A data extraction sheet was created and the study characteristics, source of data, patient characteristics, and outcome of interest were collected. Two of the authors (ZJQ and LGX) independently extracted data and potential discrepancies were resolved by the third author (GHT).

Disease severity was performed according to World Health Organization interim guidance,[13] mainly on the basis of the symptoms present at diagnosis; patients with pulse oxygen saturation (SpO_2) < 90% or need of intensive care unit care, or with acute respiratory distress syndrome were classified as having severe disease.

The discharge criteria according to the discharge recommendations of the European Centre for Disease Prevention and Control:[14] (a) no fever lasting longer than 3 days, (b) resolved respiratory symptoms, (c) substantially improved acute exudative lesions on chest computed tomography (CT) images, (d) at least two consecutive negative reverse transcriptase PCR (RT-PCR) test results in respiratory samples (with samples separated by at least 1 day), and (e) appearance of specific IgG when a serological test is available.

2.4 | Data analysis

Our analysis includes cumulative descriptive statistics expressed as counts (n) and percentages (%) with a comparative analysis for the selected studies. The quantitative variables with normal distribution are presented as the mean ± SD and those with skewed distribution as median or range. We computed the odds ratios (ORs) as our effect estimate using the Mantel–Haenszel method with random effects, with a study confidence interval (CI) of 95%. Depending on the heterogeneity between studies, a fixed- or random-effects model was used to estimate the average effect and its precision. We used the I^2 statistic and Cochran's Q test to assess statistical heterogeneity. The publication bias was evaluated by the visual inspection of funnel plot and Begger's regression tests. The publication bias was done to assess the effect of each study on the pooled effect size. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the STATA software (version 15.0, Stata Corp. LP).

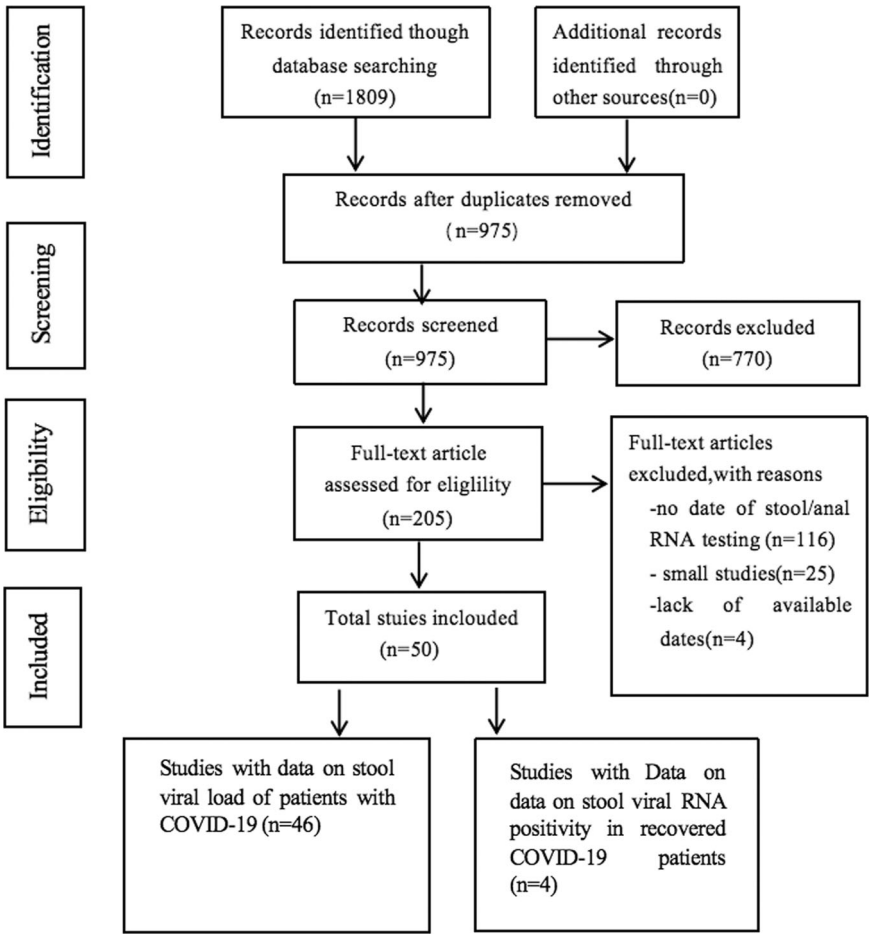

FIGURE 1 The workflow of the selection process in coronavirus disease 2019 (COVID-19) patients with the date of virus RNA in stool

Trial sequential analysis (TSA) was performed for the nucleic acid-positive stool of patients with diarrhea compared with those without diarrhea, using the TSA software 0.9.5.10 Beta (Copenhagen Trial Unit; Figure 3). The thresholds for the *Z* values using O'Brien-Fleming α-spending function were adjusted to control the risk of type 1 error. The cumulative *Z* curve represents the trial data. The risk of type 2 error was controlled using the β-spending function and futility boundaries. Random-effects modeling were applied. A two-sided CI with 95% confidence level was used to indicate statistical significance. We estimated the information size for the analyses based on the achievement of 80% power and 10% relative risk reduction between the two groups.

3 | RESULT

Our literature search identified 1809 citations from PubMed, EMBASE, and Cochrane Library database (Figure 1), of which 834 studies were removed after initial screening for duplicates. Further studies were excluded using the title and abstract review in 975 studies. A total of 205 articles were assessed for eligibility, and after excluding 116 studies, which did not provide data on stool viral RNA, 25 small studies ($N < 5$), and 4 studies that lack available dates, 50 studies were included in the final analysis (46 studies with data on stool viral load of patients with COVID-19 at the first hospitalization and 4 studies with data on stool viral RNA positivity in recovered COVID-19 patients).

3.1 | Characteristics of fecal SARS-CoV-2 RNA

The characteristics of the included studies with data of viral RNA in stool samples at the first hospitalization are shown in Table 1, including sites of patient recruitment, sample size, age, sex, SARS-CoV-2 RNA-positive result in stool sample, duration of virus shedding in stool, disease severity, and GI symptoms on presentation. There were 46 studies that reported the prevalence of fecal SARS-CoV-2 RNA in patients with COVID-19 infection confirmed by respiratory samples: 38 (82.6%) studies were from China (3 in Hong Kong) and 8 (17.4%) were from other countries (Singapore, United States, France, Germany, Italy, Korea, and India). Of the 2352 patients with COVID-19, who tested for viral RNA in stool samples from the 46 studies, 735 were reported to have positive stool specimens[4,5,11–54] (46.8% CI: 0.383–0.554; $I^2 = 96.8\%$; Figure 2 and Table 2). The median age of patients with positive fecal RNA was 41.6 ± 4.24 years and 55.4% were male.

Fourteen studies[11,19,22–25,28,30,33,34,38,39,43] including 609 patients reported the prevalence of fecal SARS-CoV-2 RNA in patients

TABLE 1 Characteristics of studies included in COVID-19 patients

Study	Design	Country	Study period	COVID-19 patients (*n*)	Positive fecal RNA of COVID-19 patients (*n*, %)	Age of positive fecal RNA patients (years)	Man in positive fecal RNA patients (*n*, %)	Positive fecal RNA of severe cases (*n*, %) vs. positive fecal RNA of nonsevere cases (*n*, %)	Positive fecal RNA patients with severe disease (*n*, %) vs. fecal virus negative patients with severe disease (*n*, %)	Positive fecal RNA patients: RNA positive in stool and negative in respiratory samples: (*n*, %)	Clinical symptoms of positive fecal RNA patients
Zhang et al.[15]	Cohort study	China	n.a.	39	4 (10.3)	n.a.	n.a.	0 (0.0) vs. 4 (8.7)	0 (0.0) vs. 3 (10.0)	n.a.	n.a.
Wang et al.[5]	Case series	China	Jan 1–Feb 17, 2020	153	44 (28.7)	n.a.	n.a.	n.a.	n.a.	1/6 (16.7)	n.a.
Young et al.[16]	Case series	Singapore	Jan 23–Feb 3, 2020	8	4 (50.0)	n.a.	n.a.	n.a.	n.a.	1/4 (25.0)	n.a.
Jiehao et al.[17]	Case series	China	Jan 19–Feb 3, 2020	6	5 (83.3)	Median: 7 (0.6–9)	2 (33.3)	n.a.	n.a.	5/5 (100.0)	5 Patients with respiratory symptoms
Ling et al.[18]	Retrospective study	China	Jan 20–Feb 10, 2020	66	54 (81.8)	Median: 44.0 (34.0–62.0)	38 (56.7)	n.a.	n.a.	43/54 (78.2)	n.a.
Han et al.[19]	Retrospective study	China	Feb 13–Feb 29, 2020	22	12 (54.5)	Mean: 43.3 (±13.8)	5 (24.0)	n.a.	n.a.	n.a.	9 Patients with respiratory symptoms, 9 patients with GI symptoms
Lei et al.[20]	Cohort study	China	Jan 22–Feb 12, 2020	7	4 (57.1)	n.a.	n.a.	n.a.	n.a.	2/4 (50.0)	n.a.
Lo et al.[21]	Case series	China	Jan 21–Feb 16, 2020	10	10 (100.0)	Median: 54 (27–64)	3 (30.0)	n.a.	n.a.	5/10 (50.0)	n.a.
Yin et al.[22]	Retrospective study	China	Jan 19–Feb 7, 2020	33	8 (24.2)	n.a.	5 (62.5)	n.a.	n.a.	n.a.	5 Patients with respiratory symptoms, 5 patients with GI symptoms
The COVID-19 Investigation Team[23]	Retrospective study	US	Jan–Feb, 2020	10	7 (70.0)	Range: 30–69	3 (60.0)	n.a.	n.a.	1/7 (14.3)	4 Patients with respiratory symptoms, 1 patient with GI symptoms

TABLE 1 (Continued)

Study	Design	Country	Study period	COVID-19 patients (*n*)	Positive fecal RNA of COVID-19 patients (*n*, %)	Age of positive fecal RNA patients (years)	Man in positive fecal RNA patients (*n*, %)	Positive fecal RNA of severe cases (*n*, %) vs. positive fecal RNA of nonsevere cases (*n*, %)	Positive fecal RNA patients with severe disease (*n*, %) vs. fecal virus negative patients with severe disease (*n*, %)	Positive fecal RNA patients: RNA positive in stool and negative in respiratory samples: (*n*, %)	Clinical symptoms of positive fecal RNA patients
Lescure et al.[24]	Case series	French	Jan 24–Jan 29, 2020	5	2 (40.0)	30, 46	0 (0.0)	n.a.	n.a.	1/2 (50.0)	2 Patients with respiratory symptoms
Xie et al.[25]	Retrospective study	China	Feb 27, 2020	9	8 (88.9)	Median: 43 (26–59)	4 (50.0)	n.a.	n.a.	n.a.	5 Patients with respiratory symptoms, 1 patient with GI symptoms
Chen et al.[26]	Retrospective study	China	Feb 26, 2020	28	11 (39.3)	n.a.	n.a.	8 (66.7) vs. 3 (18.7)	8 (72.7) vs. 4 (23.5)	n.a.	n.a.
Wu et al.[27]	Retrospective study	China	Jan 16–Mar 15, 2020	74	41 (55.4)	n.a.	n.a.	n.a.	n.a.	31/41 (75.6)	n.a.
Peng et al.[28]	Retrospective study	China	Jan 22–Feb 29, 2020	9	2 (22.2)	41, 49	2 (100.0)	n.a.	n.a.	n.a.	2 Patients with respiratory symptoms, 1 patient with GI symptoms
Zheng et al.[29]	Cohort study	China	Jan 19–Feb 15, 2020	96	55 (57.3)	n.a.	n.a.	42 (56.8) vs. 13 (59.1)	42 (76.4) vs. 32 (78.1)	n.a.	n.a.
Zhang et al.[30]	Retrospective study	China	Jan 29–Feb 10, 2020	14	5 (35.7)	n.a.	n.a.	n.a.	n.a.	3/5 (60.0)	n.a.
Xiao et al.[31]	Case series	China	Jan, 2020	28	12 (42.9)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Xiao et al.[4]	Retrospective study	China	Feb 1–Feb 14, 2020	97	39 (53.42)	Median: 49 (0.83–78)	n.a.	n.a.	n.a.	17/39 (43.6)	n.a.
Yongchen et al.[32]	Observational study	China	n.a.	15	5/15 (33.3)	n.a.	n.a.	n.a.	n.a.	3/5 (60.0)	n.a.
Wei et al.[33]	Retrospective study	China	Jan 19–Feb 7, 2020	84	28 (33.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

(Continues)

TABLE 1 (Continued)

Study	Design	Country	Study period	COVID-19 patients (*n*)	Positive fecal RNA of COVID-19 patients (*n*, %)	Age of positive fecal RNA patients (years)	Man in positive fecal RNA patients (*n*, %)	Positive fecal RNA of severe cases (*n*, %) vs. positive fecal RNA of nonsevere cases (*n*, %)	Positive fecal RNA patients with severe disease (*n*, %) vs. fecal virus negative patients with severe disease (*n*, %)	Positive fecal RNA patients: RNA positive in stool and negative in respiratory samples: (*n*, %)	Clinical symptoms of positive fecal RNA patients
Tan et al.[34]	Retrospective study	China	Jan 27–Mar 10, 2020	10	3 (33.3)	Median: 8.8 (3.6–9.4)	n.a.	n.a.	n.a.	n.a.	1 Patients with GI symptoms
Chen et al.[35]	Retrospective study	China	Jan 26–Feb 6, 2002	22	12 (54.5)	Median: 35 (29–48)	8 (66.7)	0 (0.0) vs. 12 (60.0)	0 (0.0) vs. 2 (20.0)	9/12 (75.0)	n.a.
Tan et al.[36]	Retrospective study	China	Jan 17–Feb 29, 2020	13	1 (7.7)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Wölfel et al.[37]	Case series	Germany	n.a.	9	8 (88.9)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Xu et al.[11]	Case series	China	Jan 22–Feb 20, 2020	10	8 (80.0)	n.a.	5 (62.5)	n.a.	n.a.	7/8 (87.5)	7 Patients with respiratory symptoms, 3 patients with GI symptoms
Yuan et al.[38]	Case series	China	n.a.	6	6 (100.0)	Median: 60 (range: 37–71)	3 (60.0)	n.a.	n.a.	1/6 (16.7)	4 Patients with respiratory symptoms, 1 patient with GI symptoms
Chen et al.[39]	Retrospective study	China	Jan 20–Feb 9, 2020	42	28 (66.7)	Median: 51.5 (43–62)	12 (42.86)	9 (81.8) vs 19 (61.2)	9 (32.14 vs. 2 (14.29)	11/28 (39.3)	n.a.
Lin et al.[12]	Retrospective study	China	Jan 17–Feb 25, 2020	65	31 (47.7)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Wu et al.[67]	Observation study	China	Jan 31–Feb 29, 2020	244	24 (10.0)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hua et al.[41]	Retrospective study study	China	To Feb 29, 2020	35	32 (91.4)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Chen et al.[42]	Observation study	China	Jan 17–Mar 2, 2020	97	52 (53.6)	Mean: 45.27 (±20.47)	31 (59.6)	15 (57.7) vs. 37 (57.7)	15 (59.6) vs. 11 (73.3)	n.a.	n.a.

TABLE 1 (Continued)

Study	Design	Country	Study period	COVID-19 patients (*n*)	Positive fecal RNA of COVID-19 patients (*n*, %)	Age of positive fecal RNA patients (years)	Man in positive fecal RNA patients (*n*, %)	Positive fecal RNA of severe cases (*n*, %) vs. positive fecal RNA of nonsevere cases (*n*, %)	Positive fecal RNA patients with severe disease (*n*, %) vs. fecal virus negative patients with severe disease (*n*, %)	Positive fecal RNA patients: RNA positive in stool and negative in respiratory samples: (*n*, %)	Clinical symptoms of positive fecal RNA patients
Cheung et al.[43]	Observation study	China:Hong Kong	Jan 20–Jan 29, 2020	59	9 (15.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Tong et al.[44]	Observation study	China	Feb 1–Feb 28, 2020	262	32 (12.21)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Park et al.[45]	Retrospective cohort study	Korea	Apr 4–Apr 24, 2020	46	2 (4.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Lin et al.[46]	Retrospective study	China	Jan 20–Feb 20, 2020	217	46 (21.2)	53 (41–62)		6 (37.5) vs. 40 (19.9)	6 (13.0) vs. 10 (5.8)	n.a.	n.a.
Wang et al.[47]	Observation study	China	Feb 6– Feb 22, 2020	69	20 (28.99)	Median: 43 (I31.25–51.0)	13 (35.0)	n.a.	n.a.	11/20 (55.0)	n.a.
Liu et al.[48]	Observational study	China	Jan 31–Mar 16, 2020	47	2/47 (4.3)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Li et al.[49]	Retrospective study	China	Between 9 and 28 February 2020	13	5 (38.0)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Effenberger et al.[50]	Observation study	Austria	n.a.	40	12 (25.0)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
De Ioris et al.[51]	Observation study	Italy	March 16, 2020–April 8, 2020	22	15 (68)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Huang et al.[68]	Retrospective study	China	Jan 26–Feb 25, 2020	16	11 (68.8)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
To et al.[52]	Observation study	China: Hong-Kong	Jan 22–Feb 12, 2020	23	4 (17.4)	n.a.	n.a	3 (75.0) vs. 1 (5.2)	3 (33.3) vs. 1 (7.7)	n.a.	n.a.
Xu et al.[53]	Observation study	China	Jan 13–Feb 27, 2020	51	1 (1.9)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Zuo et al.[54]				15	11 (73.3)	n.a.	n.a.	n.a.	n.a.	n.a.	

(Continues)

TABLE 1 (Continued)

Study	Design	Country	Study period	COVID-19 patients (*n*)	Positive fecal RNA of COVID-19 patients (*n*, %)	Age of positive fecal RNA patients (years)	Man in positive fecal RNA patients (*n*, %)	Positive fecal RNA of severe cases (*n*, %) vs. positive fecal RNA of nonsevere cases (*n*, %)	Positive fecal RNA patients with severe disease (*n*, %) vs. fecal virus negative patients with severe disease (*n*, %)	Positive fecal RNA patients: RNA positive in stool and negative in respiratory samples: (*n*, %)	Clinical symptoms of positive fecal RNA patients
											11 Patients with respiratory symptoms, 1 patient with GI symptoms

Abbreviations: COVID-19, coronavirus disease 2019; n.a., not applicable.

with different clinical symptoms. Pooled results indicated that 65.9% (95% CI: 0.453–0.865, $I^2 = 88.8\%$) of the 143 COVID-19 patients with GI symptoms tested positive for RNA in stool samples, whereas 33.1% (95% CI: 0.207–0.451, $I^2 = 90.1\%$) of the 469 COVID-19 patients without GI symptoms were positive for RNA in stool samples. Pooled results from 14 studies[11,12,19,21,23–25,28,33,39,42,43,47] including 560 patients indicated that the proportion of patients with COVID-19 with nucleic acid-positive stool samples was markedly increased in patients with diarrhea compared with those without diarrhea (OR = 2.961, 95% CI: 1.355–6.473, $p = 0.007$, $I^2 = 54.6\%$).

In 8 studies[15,26,29,35,39,42,46,52] including 632 COVID-19 patients, 139 patients were categorized as severe cases. Eighty-three of 139 severe cases and 129 of 416 nonsevere cases tested positive for fecal RNA. The pooled data showed no significant difference between the two groups for positive fecal RNA (OR = 2.009, $p = 0.079$, 95% CI: 0.922–4.378, $I^2 = 49.1\%$). There were 83 severe cases in the nucleic acid-positive stool group (227 patients) and 65 severe cases in the nucleic acid-negative stool group (365 patients). The pooled data showed no significant difference in the severity of illness between the two groups (OR = 1.533, $p = 0.081$, 95% CI: 0.949–2.47, $I^2 = 0.3\%$).

Eleven studies[11,17,19,22–25,28,34,38] including 69 COVID-19 patients with positive stool RNA had available data on respiratory symptoms and GI symptoms. The pooled prevalence of the total GI symptoms was 28.5% (95% CI: 0.125–0.44, $I^2 = 68.0\%$), both respiratory symptoms and GI symptoms was 21.9% (95% CI: 0.09–0.346, $I^2 = 56.9\%$), only respiratory symptoms (without GI symptoms) was 50.5% (95% CI: 0.267–0.744, $I^2 = 86.4\%$), and only GI symptoms (without respiratory symptoms) was 19.8% (95% CI: 0.107–0.288, $I^2 = 0.0\%$).

The shedding of SARS-CoV-2 RNA in feces or respiratory samples was assessed in 17 studies,[5,11,16–18,20,21,23,24,27,30–32,35,38,47] 152 of 282 patients with positive fecal RNA (pooled prevalence: 55.4%, 95% CI: 0.418–0.669, $I^2 = 79.0\%$) still presented with nucleic acid-positive stool samples after the virus was negative in their respiratory samples.

3.2 | Repositive of SARS-CoV-2 RNA

In addition, 4 studies,[55–58] including 848 discharged COVID-19 patients with negative RT-PCR tests in respiratory and stool samples, had available data on repositive tests for SARS-CoV-2 RNA. The proportion of repositive tests in stool samples was 18.1% (95% CI: 0.028–0.335, $I^2 = 88.9\%$) and persisted from 2 days to 21 days after discharge. The proportion of repositive tests in respiratory samples was 22.8% (95% CI: 0.003–0.452, $I^2 = 98.9\%$) and persisted from 2 to 19 days after discharge. By combining 3 of these studies[55,57,58] (including 229 discharged patients), the proportion of repositive tests in both stool samples and respiratory samples was 19.1% (95% CI: 0.019–0.363 , $I^2 = 94.4\%$), and the proportion of repositive tests only in stool samples was 9.6% (95% CI: 0.010–0.203, $I^2 = 76.2\%$). Most of the patients with repositive fecal RNA presented as asymptomatic or with mild-to-moderate symptoms and no severe cases were reported; there were no self-infection reports and no close contacts were found to be infected in these patients.

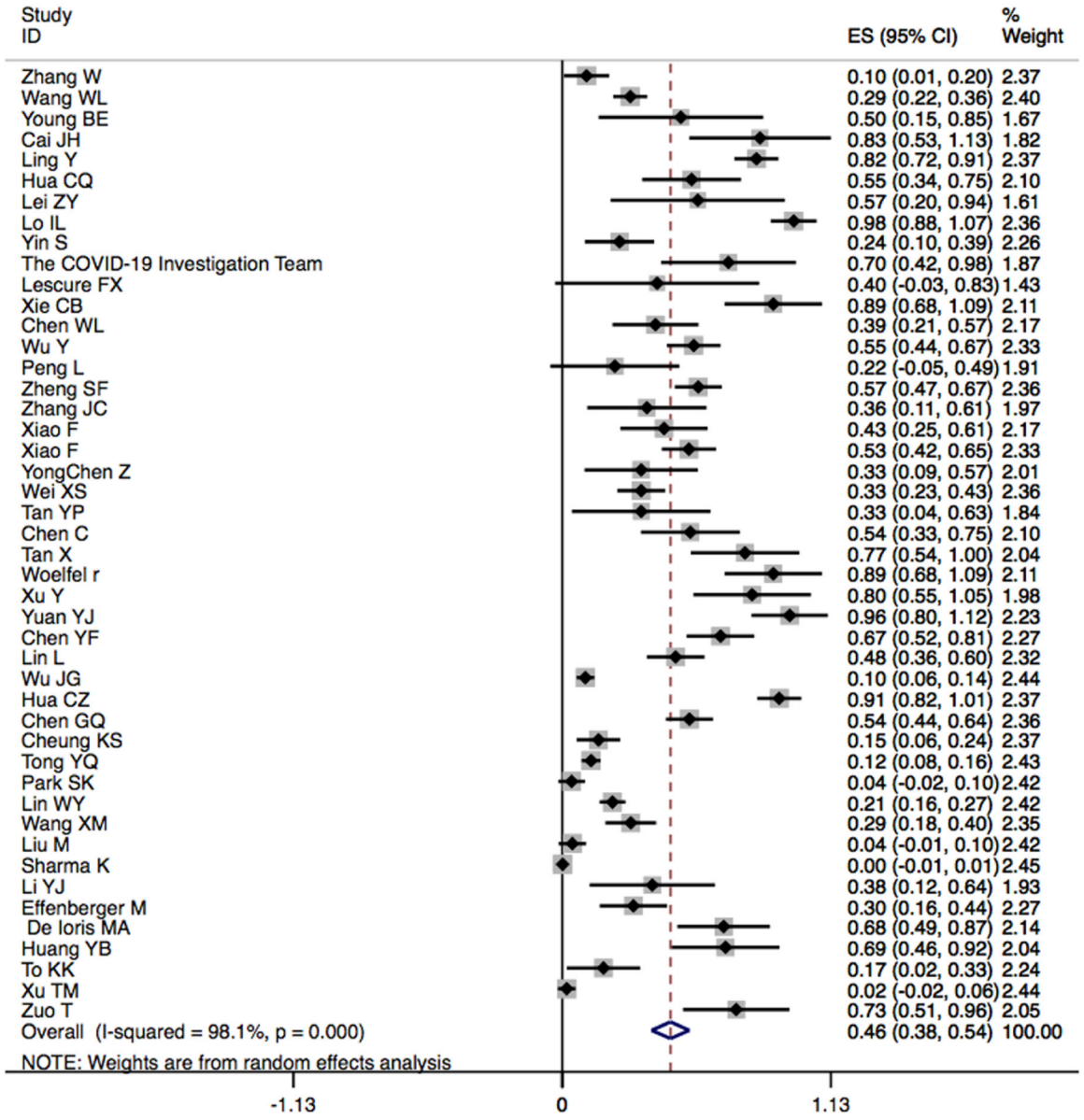

FIGURE 2 Pooled prevalence of detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in fecal samples of patients with confirmed coronavirus disease 2019 (COVID-19) infection

3.3 | Publication bias and sensitivity analysis

The funnel plot of clinical parameters is shown in Figures S1–S8 and Begger's tests are shown in Table 2. There was no publication bias in this study. In sensitivity analysis, it revealed that the study performed by Wu et al.[67] and Xu et al.[53] contributed in the significant heterogeneity observed in SARS-CoV-2 RNA-positive result in stool samples; the study by Zuo et al.[54] contributed in the significant heterogeneity observed in only respiratory symptoms of patients with positive fecal RNA; study by Lin et al.[46] contributed in the significant heterogeneity observed in patients with COVID-19 with GI symptoms tested positive for fecal RNA; study by Chen et al.[35] contributed in the significant heterogeneity observed in COVID-19 patients without GI symptoms tested positive for fecal RNA; and the study by Yuan et al.[55] contributed in the significant heterogeneity observed in repositive tests for SARS-CoV-2 RNA in both respiratory samples and in stool samples, and in repositive tests for SARS-CoV-2 RNA only in stool samples (Table 3).

3.4 | TSA

The nucleic acid-positive stool of patients with diarrhea compared with those without diarrhea: the cumulative *Z*-value curve crossed the traditional boundary value and crossed the TSA threshold line (Figure 3), which meant a positive conclusion had been reached before the expected amount of information had been reached. Patients with COVID-19 with nucleic acid-positive stool samples was

TABLE 2 Summarizing results of pooled estimates of stool virus RNA tests in COVID-19 patients

Characteristics	Number studies	Sample size		Test of association	Effect size			Heterogeneity		Publication bias
		Event	Total	Model	Estimate	95% CI	*p*	I^2	*p*	*p* (Begger's)
Positive fecal RNA of COVID-19 patients	46	735	2352	Random	0.468	0.383 −0.554	**<0.001**	96.8%	<0.001	0.338
Nucleic acid was positive in stool swabs and negative in respiratory swabs of positive fecal RNA COVID-19 patients	17	152	282	Random	0.554	0.418–0.669	0.0481	79.0%	<0.001	0.484
Positive fecal RNA of COVID-19 patients with GI symptoms	14	73	143	Random	0.659	0.453–0.865	<0.001	88.8%	<0.001	0.4243
Positive fecal RNA of COVID-19 patients without GI symptoms	14	138	446	Random	0.331	0.207–0.455	<0.001	90.10%	<0.001	0.055
Positive fecal RNA patients with total GI symptoms	11	23	70	Random	0.285	0.125–0.44	<0.001	68.0%	0.001	0.184
Positive fecal RNA patients: with both GI and respiratory symptoms	11	19	70	Random	0.219	0.09–0.346	0.001	56.9%	<0.001	0.102
Positive fecal RNA patients: only with GI symptoms	11	4	70	Fixed	0.198	0.107–0.288	0.001	0.0%	0.901	0.119
Positive fecal RNA patients: only with respiratory symptoms	11	34	70	Random	0.505	0.267–0.744	<0.001	86.4%	<0.001	0.435
				Test of association		Effect size		Heterogeneity		
Characteristics 1	Event 1/Total 1 (*n*)	Characteristics 2	Event 2/Total 2 (*n*)	Model	OR	95% CI	*p*	I^2	*p*	*P* (Egger's)
Positive fecal RNA of COVID-19 patients with diarrhea	88/179	Positive fecal RNA of COVID-19 patients without diarrhea	115/381	Random	2.961	1.355–6.473	0.007	54.6%	0.007	0.783
Positive fecal RNA of severe cases	83/139	Positive fecal RNA of nonsevere cases	129/416	Fixed	2.009	0.922–4.378	0.079	49.1%	0.056	0.902
Severe disease of positive fecal RNA patients	83/227	Severe disease of negative fecal RNA patients	65/364	Fixed	1.533	0.949–2.475	0.081	0.3%	0.862	0.711

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; GI, gastrointestinal; OR, odds ratio.

TABLE 3 Characteristics of studies in discharged COVID-19 pateints with repositive SARS-CoV-2 RNA

Study	Design	Country	Study period	COVID-19 patients (*n*)	Repositive of SARS-CoV-2 viral RNA in stool samples (%)	Repositive of SARS-CoV-2 viral RNA in respiratory samples (%)	Repositive of SARS-CoV-2 viral RNA in respiratory and stool samples (%)	Repositive of SARS-CoV-2 viral RNA only in stool samples (%)
Yuan et al.[55]	Cohort study	China	Apr, 2020	182	7 (3.8)	12 (6.6)	0 (3.1)	8 (29.6)
Lu et al.[56]	Retrospective	China	Jan 23–Feb 19, 2020	619	19/68 (27.9)[a]	87 (14.0)	n.a.	n.a.
Ma et al.[57]	Retrospective	China	Jan 30–Mar, 2020	27	8 (29.2)	0 (0.0)	0 (3.1)	7 (3.8)
Zheng et al.[58]	Observation study	China	Jan 25–Feb 26, 2020	20	3 (15.0)	2 (10.0)	2 (66.7)	1 (5.0)

Abbreviation: COVID-19, coronavirus disease 2019.

[a]A total of 68 patients tested for RNA in stool samples of which 19 were positive.

increased in patients with diarrhea compared with those without diarrhea.

4 | DISCUSSION

In the current SARS-CoV-2 pandemic, the tropism of the virus to the GI tract and its positive detection in stool are attracting increasing attention. In this meta-analysis, we noted that 46.8% of patients had detectable stool viral RNA during the course of illness and the proportion of patients with COVID-19 with nucleic acid-positive stool was markedly increased in patients with diarrhea symptoms compared with those without diarrhea, indicating that patients with COVID-19 with positive RNA in feces samples are more likely to experience GI symptoms such as diarrhea, possibly because GI epithelial cells express ACE2 and SARS-CoV-2 binds to the ACE2 before cleavage by the host transmembrane serine protease 2.[4,7,59] Virus-specific RNA and proteins can then be synthesized in the cytoplasm to assemble new virions, which can be released into the GI tract.[7,59,60] This indicates that the digestive system might be vulnerable to COVID-19 infection and fecal–oral transmission may be another route for SARS-CoV-2 spread.[7,57]

Despite the high positive rate of viral RNA in stool samples, only 28.5% of patients with nucleic acid-positive stool had GI symptoms. For most COVID-19 patients, respiratory symptoms were the main complaints at admission instead of GI symptoms. In our meta-analysis, 50.5% of patients with nucleic acid-positive stool samples had only respiratory symptoms but no GI symptoms. Therefore, fecal nucleic acid examinations may be missed in two-thirds of patients without GI symptoms. Notably, it has been found that SARS-CoV-2 detection was positive in the fecal swabs but negative in respiratory swabs of patients during the visit. Li et al.[61] presented a case on mild SARS-CoV-2 infection in a baby with PCR-negative oropharyngeal/nasopharyngeal (OP/NP) swabs and normal chest CT, but her anal swabs remained positive for 8 days. Therefore, patients who only have positive RT-PCR tests in stool samples may be clinically ignored. Pauci-symptomatic and asymptomatic individuals represent a major concern for diagnosis and viral transmission. Furthermore, false-negative results of OP/NP swabs ranged from 1% to 30% in previous studies.[62,63] To reduce the rate of missed diagnosis, it is proposed to perform SARS-CoV-2 RT-PCR testing on fecal samples as part of routine analyses for the detection of SARS-CoV-2.[64]

SARS-CoV-2 RNA can be detected not only in fecal samples from severe cases but also in fecal samples from nonsevere cases. The pooled data showed no significant difference in positive fecal RNA between the two groups; therefore, fecal SARS-CoV-2 RNA tests are also important for patients with mild disease.

The elimination of SARS-CoV-2 from the digestive system may be much later and harder than that from the respiratory system, as ACE2 is abundantly expressed in gastric, duodenal, and rectal epithelia in patients with COVID-19, which may lead to virus internalization and accumulation in these organs.[4,7] In our

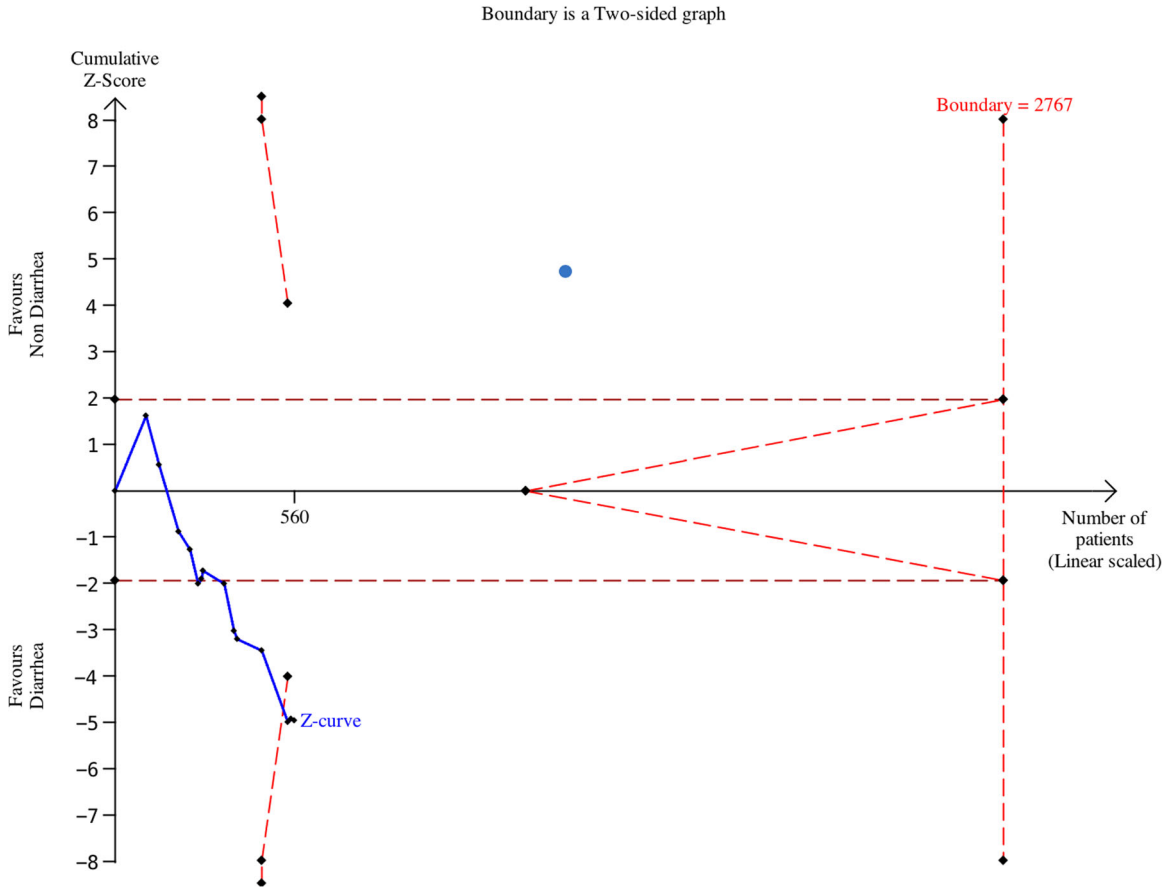

FIGURE 3 Trial sequential analysis for the nucleic acid-positive stool of patients with diarrhea compared with those without diarrhea

meta-analysis, 55.4% of patients with positive stool RNA still had persistent positive viral RNA in the feces after the pharyngeal swabs turned negative. The potential recurrence of the disease in discharged patients with two sequential negative OP swab tests collected 24 h apart from the clearance of viral RNA in patient stool samples is delayed.[65,66] In our meta-analysis, we noted that some patients with COVID-19 (18.1%) tested positive for SARS-CoV-2 RNA in fecal samples after discharge. To reduce the number of false negatives, it is important to consider a combined assessment of both fecal and respiratory specimens for patients, especially at the time of discharge and during convalescence.[39,65]

Furthermore, even if viral nucleic acid examinations in stool were negative at discharge, there is still a possibility of repositive tests for SARS-CoV-2 RNA. It is still uncertain whether the recurrence of SARS-CoV-2 RNA among discharged COVID-19 patients could be contagious.[66] In our analysis, 9.6% of discharged patients tested positive again for SARS-CoV-2 RNA in stool samples but negative in respiratory samples; the possibility cannot be excluded that the virus may be transmitted through the digestive tract. Therefore, to prevent the spread of the pandemic, it is important to monitor patients, and respiratory and fecal samples should be tested regularly after discharge.[66] Patients need to pay close attention to hand hygiene and try to avoid sharing toilets with family members after discharge. Attention should be paid to standard and transmission-based precautions for patients until the negative conversion of SARS-CoV-2 RNA in feces.[39]

In conclusion, the detection of fecal SARS-CoV-2 RNA in patients with COVID-19 is common, and the repositive tests of viral RNA are not unusual in discharged patients. As the respiratory RNA test results may not be consistent with those from stool samples, giving emphasis on stool swab tests can help increase the detection rate of asymptomatic carriers and reduce the number of false negatives. In addition, the possibility of fecal–oral transmission is unclear and the virus may be transmitted through the digestive tract; therefore, quarantine and other such policies should be maintained during convalescence even after discharge.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS CONTRIBUTIONS

Jin-Qiu Zhou, Gong-Xiang Liu, Xiao-Li Huang, and Hua-Tian Gan wrote the manuscript and participated in the literature review. Jin-Qiu Zhou analyzed the data, wrote the manuscript, and participated in literature review. Gong-Xiang Liu participated in the literature review. Xiao-Li Huang and Hua-Tian Gan supervised, designed, and checked the quality of the study. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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