Gastrointestinal and Hepatic Manifestations of COVID-19 in Children: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Children with COVID-19 may present with gastrointestinal (GI) symptoms and liver dysfunction.

Objective. To determine the type and prevalence of gastrointestinal (GI) and hepatic manifestations of COVID-19 in children and its association with severity of illness.

Methods. A systematic literature search was done from inception until January 4, 2021 using PubMed, Cochrane Library, Google Scholar and prepublication repositories with no language restrictions. Studies that reported the demographic and clinical features of children with COVID-19 and provided data on their GI and hepatic signs and symptoms were included. Prevalence of GI and hepatic manifestations were pooled using Stata14.

Results. We included 58 studies with total of 4497 participants. Overall, one-third of children with COVID-19 presented with at least one GI symptom (33.8%; 95% confidence interval (CI) 23.0, 45.4; I^2 97.5%; 42 studies, 3327 participants) with abdominal pain, nausea or vomiting, and diarrhea each occurring in approximately 20%. Children with severe COVID-19 were more likely to present with GI symptoms (odds ratio 2.59; 95% CI 1.35, 4.99; I^2 24%; 4 studies, 773 participants). The pooled prevalence of elevated transaminases was 11% for both AST (11.3%, 95% CI 4.9, 19.3; I^2 74.7%; 11 studies, 447 participants) and ALT (11.2%, 95% CI 7.1, 16.0; I^2 40.8%; 15 studies, 513 participants). Hepatic findings such as jaundice (2-17%), hepatomegaly (2%) or behavioral changes (2%) from hepatic encephalopathy were variably reported by a few studies.

The degree of heterogeneity was not improved on exclusion of studies with poor quality, but markedly improved on subgroup analysis according to geographical region and presence of MIS-C. Studies from China showed that children with COVID-19 had significantly lower pooled prevalence for any of the GI symptoms with low degree of heterogeneity, particularly for diarrhea, nausea/vomiting, and abdominal pain, all of which had I^2 of 0%. Those with multisystem inflammatory syndrome in children (MIS-C) had significantly more common GI symptoms and increased transaminases than those without.

Conclusion. One-third of children with COVID-19 exhibit at least one GI symptom and more likely present in those with severe disease. Elevated transaminases were present in 10%. Prevalence of GI and hepatic manifestations were higher among children with MIS-C.

Keywords: COVID-19, gastrointestinal, liver disease, pediatric multisystem inflammatory disease, COVID-19 related

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
GI	Gastrointestinal
MIS-C	Multisystem inflammatory syndrome in children
OR	Odds ratio
PIMS-TS	Pediatric multisystem inflammatory syndrome temporally associated with COVID-19
RT-PCR	Reverse transcriptase polymerase chain reaction

INTRODUCTION

The COVID-19 pandemic started with an unusual clustering of severe pneumonia cases of unknown cause in December 2019, initially among those with history of exposure to the Huanan seafood market in Wuhan, Hubei province of China.[1] Its causative agent, now known as SARS-CoV-2 has been confirmed in more than 470 million cases and 6 million deaths have been reported globally.[2] Although phylogenetic data point to a zoonotic origin,[3] person-to-person transmission appears to be the principal route of ongoing rapid spread, mainly via airborne or direct contact with respiratory droplets and indirect contact through fomites contaminated with infectious respiratory secretions.[4] Fecal-oral transmission is also considered as possible route of transmission.[5]

Gastrointestinal and hepatic involvement were first recognized among adults with COVID-19.[6–8] Children with COVID-19 are considered to have a milder course of illness with fewer alterations in radiologic and laboratory parameters.[5] Systematic reviews which included patients during the early months of the pandemic reported lower prevalence of GI symptoms (5-12%),[9,10] as compared to a more recent review (20%)[11] which included children with multisystem inflammatory syndrome in children (MIS-C) or pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS). MIS-C or PIMS-TS were initially recognized in April 2020 among children who had a more severe clinical course, multiorgan involvement (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic), and elevated inflammatory markers.[12] We performed this systematic review to further elucidate on the prevalence of gastrointestinal and hepatic manifestations of COVID-19 among children and determine whether the presence of gastrointestinal and/or hepatic involvement is associated with a more severe course of illness and poor prognosis.

METHODS

Search Strategy and Selection Criteria

Systematic literature search was done following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines from inception of database until January 4, 2021. We searched Medline and Cochrane Library using a combined MeSH and free text terms "novel coronavirus", "nCoV", "COVID-19", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "gastrointestinal tract", "gastrointestinal diseases", "liver" and "child". Grey literature and preprints were also searched using Google Scholar, biorvix and medrvix. Screening of reference lists of included studies and previously published systematic reviews were also done. We used Google Translate to translate articles that were published in languages other than English. Records were managed using Zotero (version 5.0.89) to exclude duplicates.

Independent screening of titles and abstracts were performed by two reviewers) according to the following eligibility criteria: studies which enrolled children (0-18 y) with confirmed COVID-19 using an RT-PCR (reverse transcriptase polymerase chain reaction) test or antibody test, and reported their epidemiological and clinical features, particularly gastrointestinal or hepatic findings, were included. The following studies were excluded: (1)>20% of participants had no microbiologic (nasopharyngeal swab or fecal RT-PCR) and/or serologic evidence (IgG or IgM) of SARS-CoV-2 infection; (2) did not report gastrointestinal symptoms or hepatic abnormalities; (3) small case series (<10 cases); (4) duplicate publications, reviews, and editorials.

Two reviewers independently rated the quality of included studies using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort, Cross-Sectional and Cases Series Studies, whichever were applicable. Disagreements were discussed with a third author and resolved through a consensus.

Data Extraction

To minimize inclusion of same patients who were also enrolled in other studies, we adopted a two-step hierarchical model of data extraction.[13] First, data on study and patient characteristics were extracted, then we identified studies for full data extraction based on study location and total number of patients. We selected the study with most number of participants reported if there were multiple studies done in similar institutions with overlapping dates of study inclusion.

Two reviewers independently extracted data using Microsoft Excel and disagreements were resolved via consensus with a third reviewer. We corresponded with study authors to clarify study data, as necessary. The following data were extracted from included studies: author, date of publication, study design, site of study (hospital name, city, province or state, country), time period of enrollment, number of included participants; patient characteristics including age (mean, median, interquartile interval or range), number of males/females and GI comorbidities; prevalence of gastrointestinal symptoms (diarrhea, nausea / vomiting, abdominal pain, bloody stools, loss of appetite) including onset (in relation to other non-gastrointestinal symptoms), severity and duration; prevalence of liver function abnormalities (presence of

increased AST, ALT, total and direct bilirubin, coagulopathy and hypoalbuminemia) including its onset and duration; and prevalence and duration of viral stool shedding. Disease severity followed the definitions used by the studies, with reference to the WHO Clinical Management of COVID-19 Interim Guidance.[13] Admission to the ICU was considered severe illness, unless otherwise specified. Lastly, only participants with complete clinical data (i.e. reported presence or absence of GI symptoms or hepatic abnormalities) were included in the analysis.

Data Synthesis and Statistical Analysis

Statistical analyses were performed using Stata14[14] for pooling single armed outcome (i.e., pooled prevalence of GI and hepatic manifestations) and Review Manager (version 5.4)[15] for pooling dichotomous outcome (i.e., severity of illness). Continuous variables (e.g., age, duration of stool shedding, etc.) were expressed as mean ± standard deviation or as median (interquartile range). The prevalence of GI and hepatic manifestations from individual studies were computed by dividing the number of children reported to have specific GI symptom or liver dysfunction by the total number of children with confirmed COVID-19. Prevalence from individual studies were subsequently pooled using random effects model and reported as pooled prevalence and 95% confidence interval, and presented as forest plots. I^2 statistic was used to measure heterogeneity of studies, with values of <25%, 25-75% and >75% indicative of low, moderate, and high heterogeneity, respectively. We performed a subgroup analysis according to presence of MIS-C or PIMS-TS by separating the studies that enrolled children with COVID 19 with any symptoms and those that reported only children who satisfied the MIS-C or PIMS-TS criteria. p-value of >0.05 between groups was considered significant difference. For the purpose of this study, we used the term MIS-C to include children who satisfied the case definition for MIS-C or PIMS-TS by the World Health Organization (WHO),[16] Centers for Disease Control and Prevention (CDC)[17] or the Royal College of Pediatrics and Child Health (RCPH).[18]

RESULTS

A total of 958 records were identified through database search and other sources (Appendix Supplementary Table 1). After removal of duplicates, titles and abstracts of 581 records were screened and 185 full-text articles were assessed for eligibility (Figure 1). After exclusion of society guidelines, review articles, case reports and small case series with less than 10 participants, 100 potentially relevant reports were reviewed for detailed assessment. Fifteen (15) studies were excluded due to high likelihood of duplicate participants enrolled from similar institutions with overlapping inclusion period; 24 studies were further excluded because GI and hepatic manifestations were not reported; and three studies[19–21]

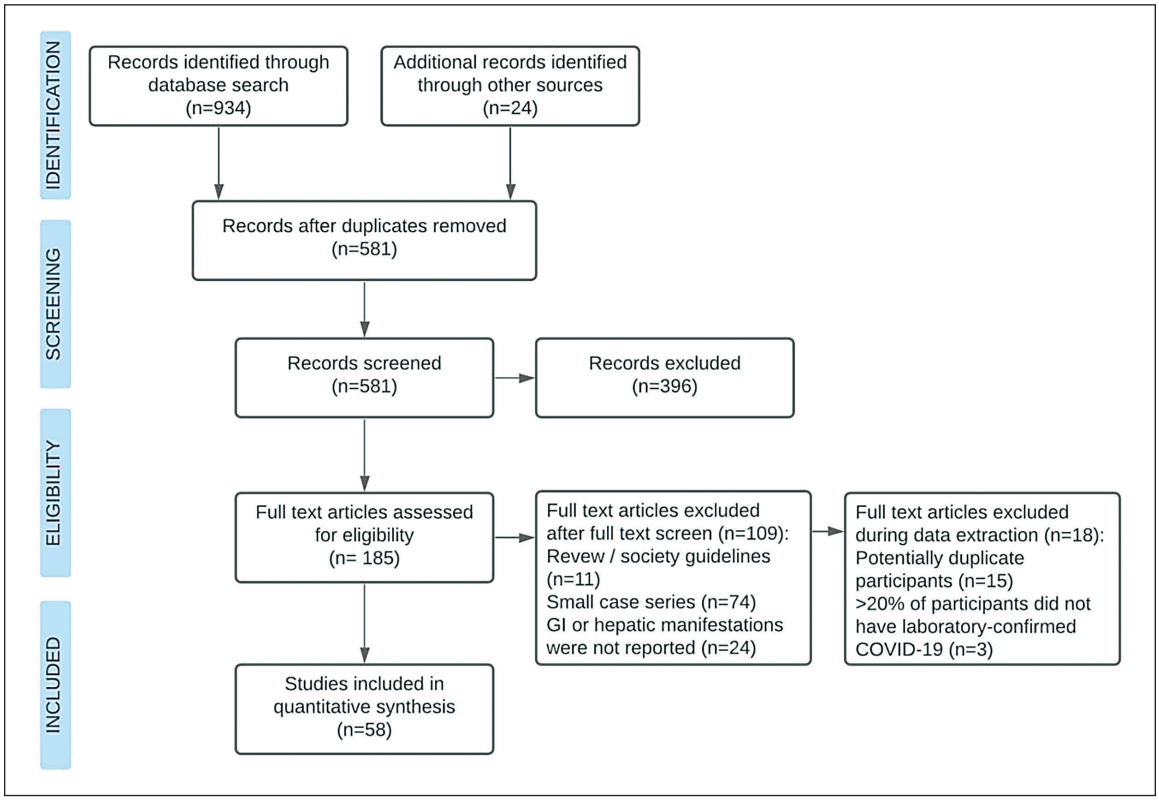

Figure 1. Study flow diagram.

were excluded because >20% of participants did not have microbiologic (RT-PCR) or serologic (IgG/IgM) evidence of COVID-19. For three studies,[22–24] only participants with microbiologic or serologic evidence for COVID-19 infection were included in the analysis, since the authors reported their clinical data separately. Thus, 58 studies[22–79] including 7165 participants with demographic data, of whom 4497 had data on GI or hepatic manifestations were analyzed in our review.

Study and Patient Characteristics

The characteristics of the 58 studies included in our analysis are summarized in Appendix Supplementary Table 2. Majority of study participants were reported from retrospective cohort studies (1947 participants or 43%, 41 studies) and review of surveillance databases (1890 participants or 42%, 8 studies). The rest of the studies were ambispective cohort studies (518 participants or 11.5%, 4 studies), prospective cohort studies (122 participants or 3%, 3 studies) and case series (20 participants or 0.5%, 2 studies). Most studies included children 0-18 years old (55 studies) and three studies[22–24] included participants up to 21 years old. However, we were not able to stratify the patients according to age due to different cut-offs used across studies. A total of 3912 out of 7165 participants with demographic data (55%) were males.

Location

The initial studies mostly came from China (650 participants or 14%, 20 studies) but the majority of participants included in our analysis came from the US (1501 participants or 33%, 11 studies) and Europe (1421 participants or 32%, 16 studies).

Treatment Center

Most studies reported on hospitalized (48 studies, 2420 participants) or combination of outpatient and hospitalized patients (9 studies, 836 of 1495 participants, 56% were hospitalized); One study[43] with 582 participants did not specify if the participants were hospitalized or outpatients. In total, 3256 out of 3915 children (83%, range: 16-100%) were hospitalized. However, reasons for hospitalization were not necessarily due to severe disease. In studies which included only hospitalized patients and with disease severity stratification (42 studies, 1593 participants), 181 (11%) were asymptomatic, 891 (56%) had mild to moderate disease and 521 (33%) had severe or critical illness.

Risk of Bias

The overall certainty of evidence was very low because all the included studies were observational studies and pooled prevalence across all GI and hepatic manifestations had high heterogeneity. Risk of bias assessment of individual studies is reported in Appendix Supplementary Tables 3 and 4. Most of the studies were prone to selection bias because they did not specify if all eligible subjects were consecutively included and majority of the subjects were hospitalized patients who may have more severe disease. The studies are also prone to detection bias due to possibly different RT-PCR cycle threshold used in detecting SARS-CoV-2. Furthermore, there may be some misclassification bias, because some studies (particularly those on MIS-C) included participants without laboratory confirmed COVID-19 but satisfied clinical criteria and had epidemiologic link. To minimize this bias, we only included studies with >80% laboratory confirmed COVID-19 via RT-PCR or serology, and only included participants with positive RT-PCR or serology if their clinical data were reported separately. The sample size was not computed in all studies and outcomes were mostly not adjusted according to presence of confounders (e.g., co-morbidities, treatment given).

Gastrointestinal Manifestations of COVID-19 in Children

A total of 42 studies,[1,22,23,25–28,30,31,34–36,38–41,43–45,47–50,53,54,56,57,59–63,65,68–72,74,75,78,79] including 3327 children reported on the presence of at least one gastrointestinal symptom (i.e., diarrhea, nausea/vomiting or abdominal pain). In 16 studies, the number of children with GI symptoms was not reported but only reported the GI symptoms that were observed. Analysis of these 42 studies demonstrated that the pooled prevalence of the presence of any GI symptom was 33.8% (95% CI 23.0, 45.4) with high heterogeneity (I^2 97.5) (Figure 2). The degree of heterogeneity was not improved on exclusion of studies with poor quality, but markedly improved on subgroup analysis according to geographical region. Studies from China showed that children with COVID-19 had significantly lower pooled prevalence for any of the GI symptoms with low degree of heterogeneity, particularly for diarrhea, nausea/vomiting, and abdominal pain, all of which had I^2 of 0% (Figures 2-4).

By combining 40 studies,[22–25,27,29–39,41,42,44–47,49–53,55,58,60,63,64,66,67,71,72,74,76,77,79] the estimated pooled prevalence of diarrhea among 3392 children with COVID-19 was 17.2% (95% CI 12.1, 22.8) but with high heterogeneity (I^2 92.9%) (Figure 3). Very few studies described diarrhea with regard to onset, duration, and character. Chen et al.[30] reported that the median time from exposure to onset of diarrhea was 11 days among four patients, only one of whom had diarrhea at the onset along with low grade fever and cough; the other three patients developed diarrhea three to four days after hospitalization. Furthermore, diarrhea had a more delayed onset compared to fever and cough, with median time from exposure to onset of 8 and 10 days, respectively. The character of stools was yellow and loose, occurring 2-6 times a day, typical of a nonspecific viral gastroenteritis.[71,72] None of the studies reported on the duration of diarrhea.

A total of 32 studies[22–24,29,32–39,41,42,45–47,51–53,55,58,60,63,65–67,71,72,74,76,77] including 2823 children with COVID-19 reported on presence of nausea or vomiting, with estimated pooled prevalence of 19.5% (95% CI 12.1, 28.0), again with high heterogeneity (I^2 96%) (Figure 4). Twenty-three (23)

studies[23,24,32,34,35,38,39,41,42,45–47,52,53,55,60,63–65,67,72,74,77] including a total of 2167 participants reported on presence of abdominal pain, with pooled prevalence of 21.8% (95% CI 11.4, 33.8) with high heterogeneity (I^2 97.1%) as well (Figure 5). The onset and duration of nausea, vomiting, and abdominal pain were not described in any of the included studies.

There were four studies[38,41,43,74] which explicitly reported GI symptoms in the absence of respiratory symptoms among children with COVID-19. In these studies, the prevalence of GI symptoms not associated with respiratory symptoms ranged from 6-28%. In the study by Götzinger et al.[43] of 582 children from Europe, 40 children (7%) had GI symptoms without respiratory symptoms, 26 (65%) of whom presented with fever. Zachariah et al.[74] from the US reported that three out of 50 children (6%) had abdominal pain and vomiting only, hence triggering an evaluation for appendicitis.

GI symptoms and association with severe disease

We were able to pool four studies[22,38,43,74] including 773 children, that stratified the participants according to presence of any GI symptom and severity of illness (non-severe versus severe/critical). Our analysis showed that children with severe COVID-19 are 2.5 times more likely to present with gastrointestinal symptom(s) (Odds ratio 2.59, [95% CI 1.35-4.99]; I^2 24%) compared with children with non-severe disease (Figure 6).

GI imaging findings in pediatric COVID-19

Two studies[35,53] reported on abdominal imaging findings in children with COVID-19, both of whom enrolled children with MIS-C from New York, USA. Dufort et al.[35] reported that 34 out of 44 children (77%) who underwent any abdominal imaging (ultrasound, computed tomography scan or magnetic resonance imaging) had abnormal findings. The most common findings were abnormal fluid collection (ascites, pleural effusion or pelvic fluid) in 36%, bowel inflammation in 34%, mesenteric lymphadenopathy in 18%, hepatosplenomegaly in 18%, and gallbladder inflammation in 11%. Similarly, Miller et al. reported abnormal findings in 12 out of 15 children with MIS-C (80%) and the most common findings were ascites (50%), biliary sludge or acalculous cholecystitis (50%), bowel wall thickening (25%), and mesenteric lymphadenopathy (17%).[53]

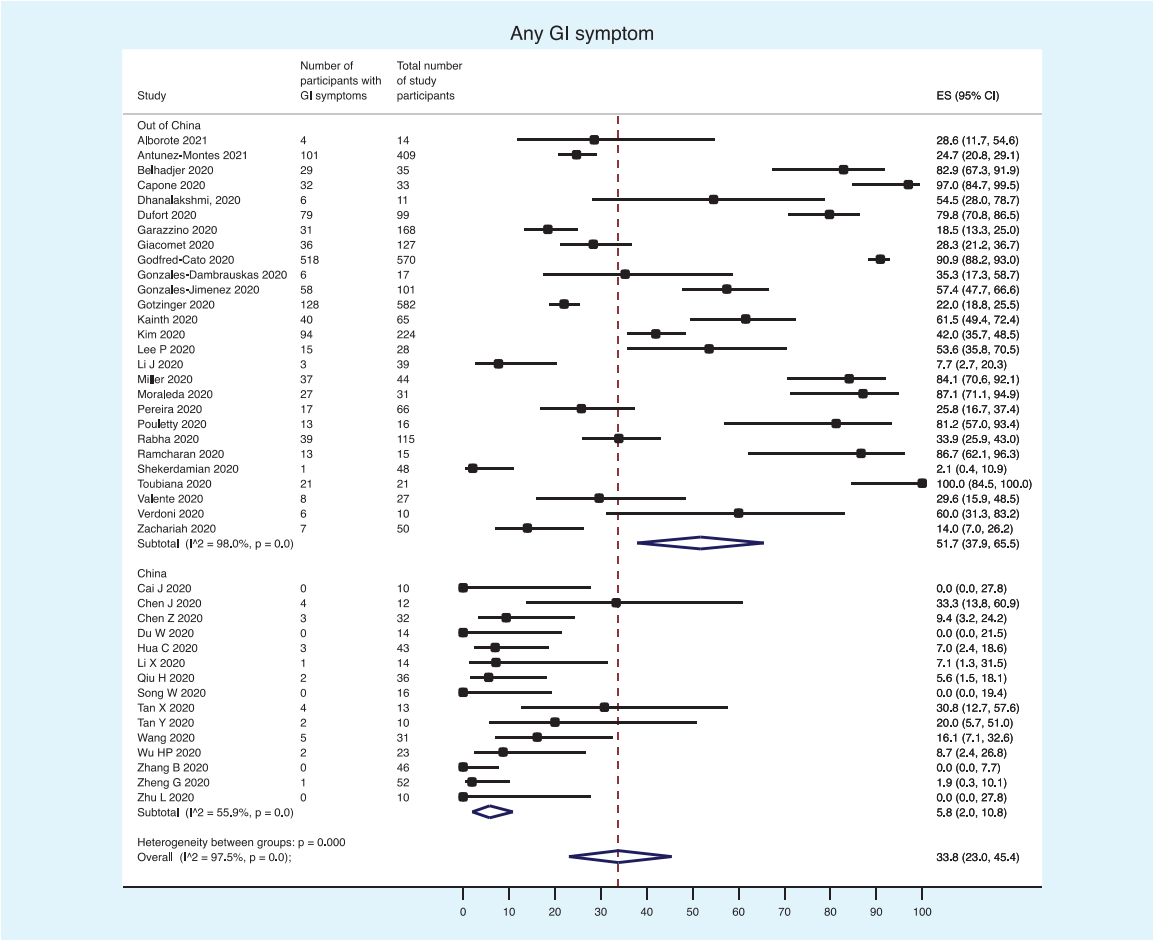

Figure 2. Pooled estimate of the overall prevalence of gastrointestinal symptoms in children with COVID-19.

Virologic studies in stool or anal swab

Six studies[5,26,27,31,44,49] reported data on the detection of SARS-CoV-2 in stool or anal swab. The estimated pooled prevalence of SARS-CoV-2 viral RNA positivity in fecal or anal swab samples was 50.7% (95% CI 12.2, 88.7) with high heterogeneity (I^2 95%) (Figure 7). In a study by Chen et al.,[31] 17 children who were tested for viral RNA in feces or anal swab, the average duration of fecal shedding was 28.9 ± 11.81 days, which was longer than the duration of viral RNA in respiratory samples (15.8 days, range 1-29 days). The longest duration of fecal shedding was 65 days in a 3-month-old. The average duration of fecal shedding decreased with age (39.8 days in infants and preschool children, 27.5 days in school-age children, and 20.4 days in adolescents (p value <0.05).

Hepatic Manifestations of COVID-19 in Children

Out of 58 included studies, only 15 studies[23,27,28,34,42,49,51,59,59,65,66,70,72,73,79] including 513 children, reported on the presence of liver injury based on increased ALT level. The estimated pooled prevalence of increased ALT was 11.2% (95% CI 7.1,16.0) with moderate heterogeneity (I^2 40.8%) (Figure 8). However, there were different cut-offs used across studies: nine studies[5,23,30,34,51,59,65,66,79] used above upper limit of normal (normal value 40-50 IU/L), three studies[27,28,70] used twice the upper limit of normal, one study[42] used three times of upper limit of normal and two studies[49,72] did not specify the cut-off.

Increased AST was reported by 11 studies[27,34,42,49,51,59,65,66,70,72,73] including 447 children. The estimated pooled prevalence for increased AST was 11.3% (95% CI 4.9, 19.3) with moderate heterogeneity (I^2 74.7%) (Figure 9). Similar to ALT, different cut-offs were used across studies. Seven studies[5,34,51,59,65,66,70] used above upper limit of normal (normal value 37-50 IU/L), two studies[27,42] used three times the upper limit of normal and two studies[49,72] did not specify the cut-off. Other components of the liver function test such as total bilirubin, direct bilirubin or prothrombin time could not be pooled because values were only reported as means and the actual number of patients with deranged parameters were not routinely reported in any of the included studies.

Three of the included studies reported presence of jaundice (2-17%), hepatomegaly (2%), and behavioral

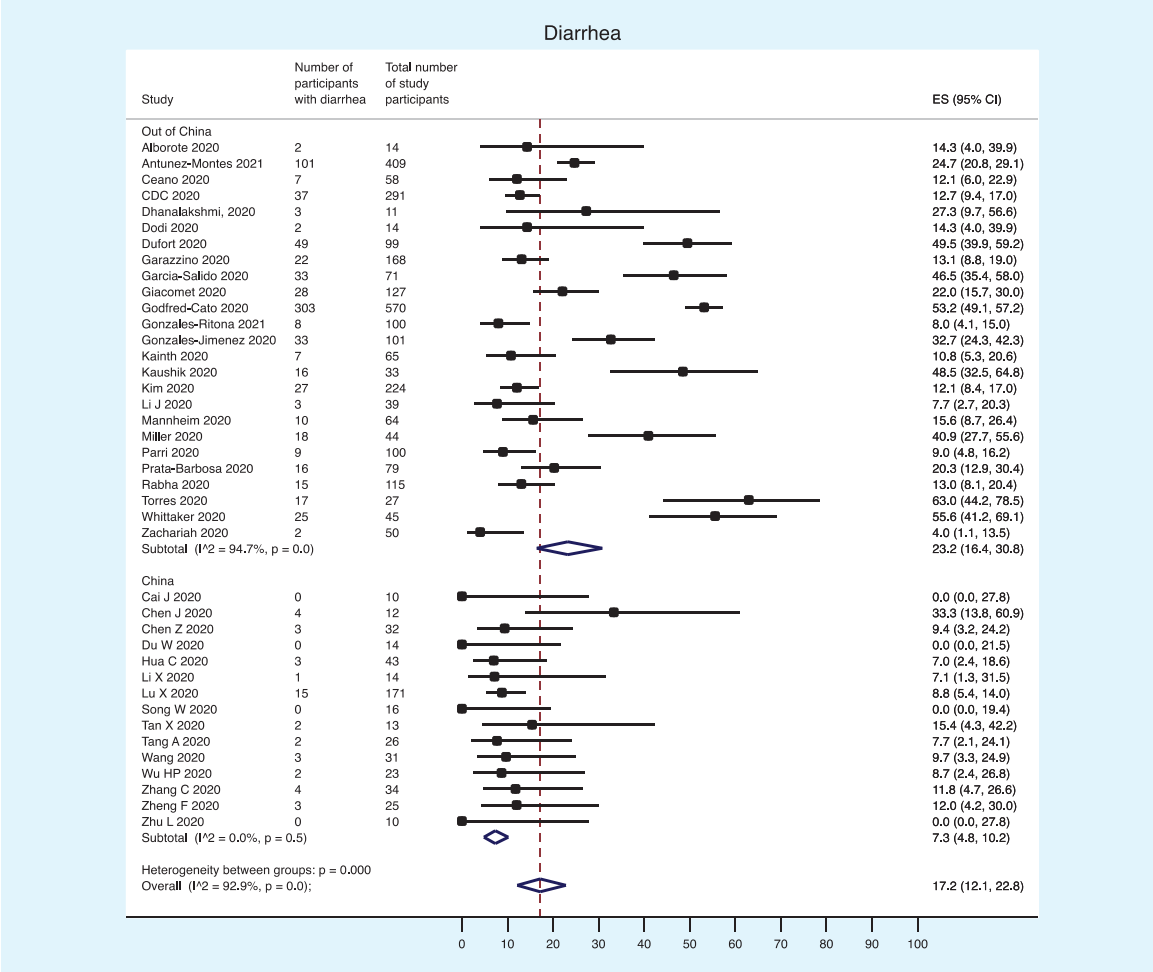

Figure 3. Pooled estimate of the prevalence of diarrhea in children with COVID-19.

changes (2%) among children with hepatic involvement from COVID-19.[19,42,60] In particular, all three children with hepatomegaly were hospitalized and none of the 93 children who did not require hospitalization had hepatomegaly (p 0.006).[60] On work-up, elevated liver enzymes were noted by both Dooki[19] and Gonzales-Ritona[42]. Markedly increased aminotransferase levels (>50x) associated with cholestasis, coagulopathy, and hyperammonemia were reported in two children who were eventually diagnosed with pediatric acute liver failure (PALF). All of these children are not known to have liver disease in the past and were not exposed to hepatotoxic drugs. Tests for known causes of hepatitis such as viral infection, Wilson disease, and autoimmune hepatitis (if clinically warranted) were negative.

Multisystem inflammatory syndrome in children (MIS-C)

We performed a subgroup analysis according to the presence of MIS-C (Table 1). A total of 1179 children (26%) who satisfied the criteria for MIS-C or PIMS-TS by CDC, RCPH or WHO were included in our analysis. Fifteen studies[23,24,26,28,35,39,46,48,53,54,57,61,67,68,70] reported only children with MIS-C and five studies[25,37,42,56,58] reported data for children with MIS-C separately. The estimated point prevalence of the presence of any GI symptoms and elevated transaminase levels were significantly higher in children who satisfied the criteria for MIS-C as compared to children who did not. No heterogeneity was noted on the presence of increased ALT levels in the MIS-C subgroup.

Publication bias

The funnel plots on the pooled prevalence of diarrhea, nausea or vomiting, abdominal pain, and increased ALT showed that our meta-analysis may be affected by publication bias due to the asymmetry of the scatter plot. All funnel plots characteristically had gaps in the right lower portion, which may represent unpublished studies with smaller sample size (Figure 10).

DISCUSSION

We have shown that one third of children with COVID-19 may present with gastrointestinal symptoms, the most common of which is abdominal pain (21.4%), followed by nausea/vomiting (20.7%), and diarrhea (18.5%). Hepatic involvement is less observed, with increased transaminases (11%) as the most commonly reported hepatic manifestation.

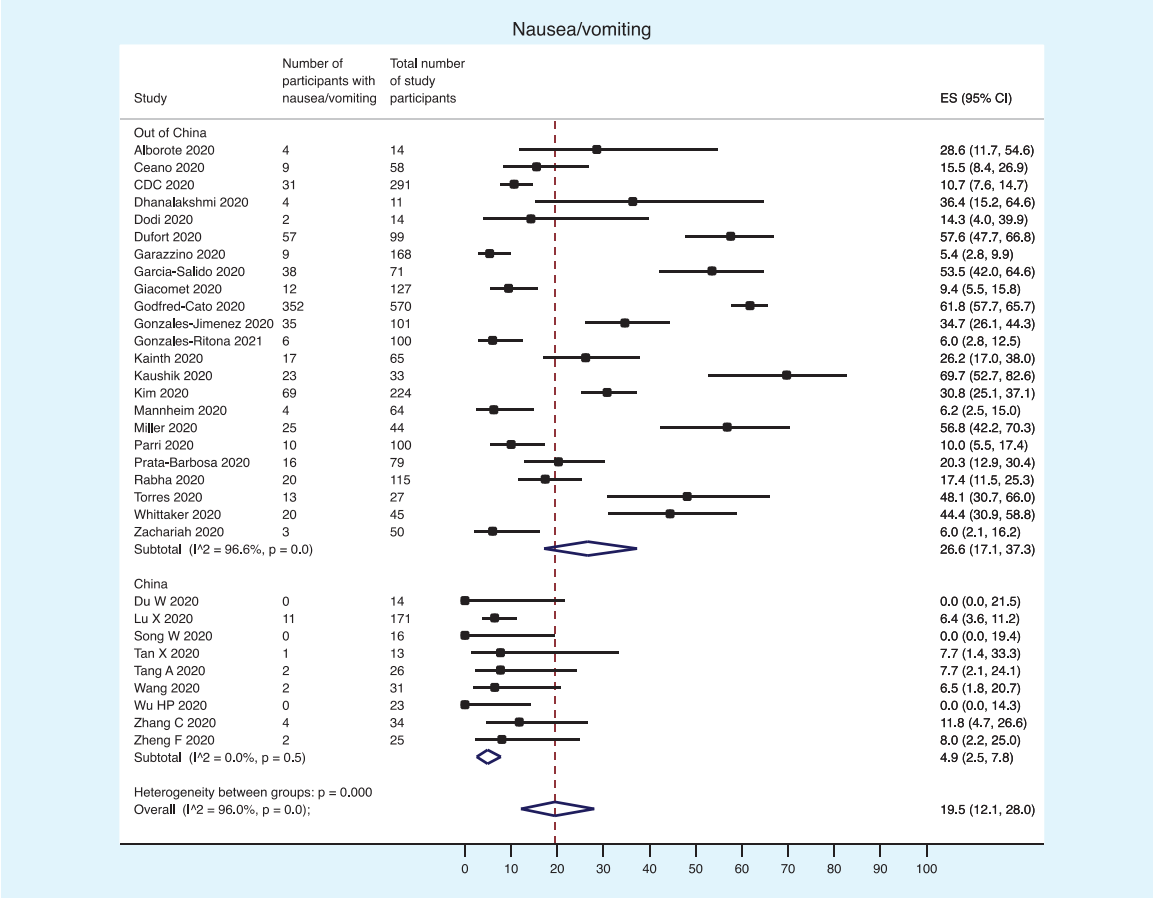

Figure 4. Pooled estimate of the prevalence of nausea or vomiting in children with COVID-19.

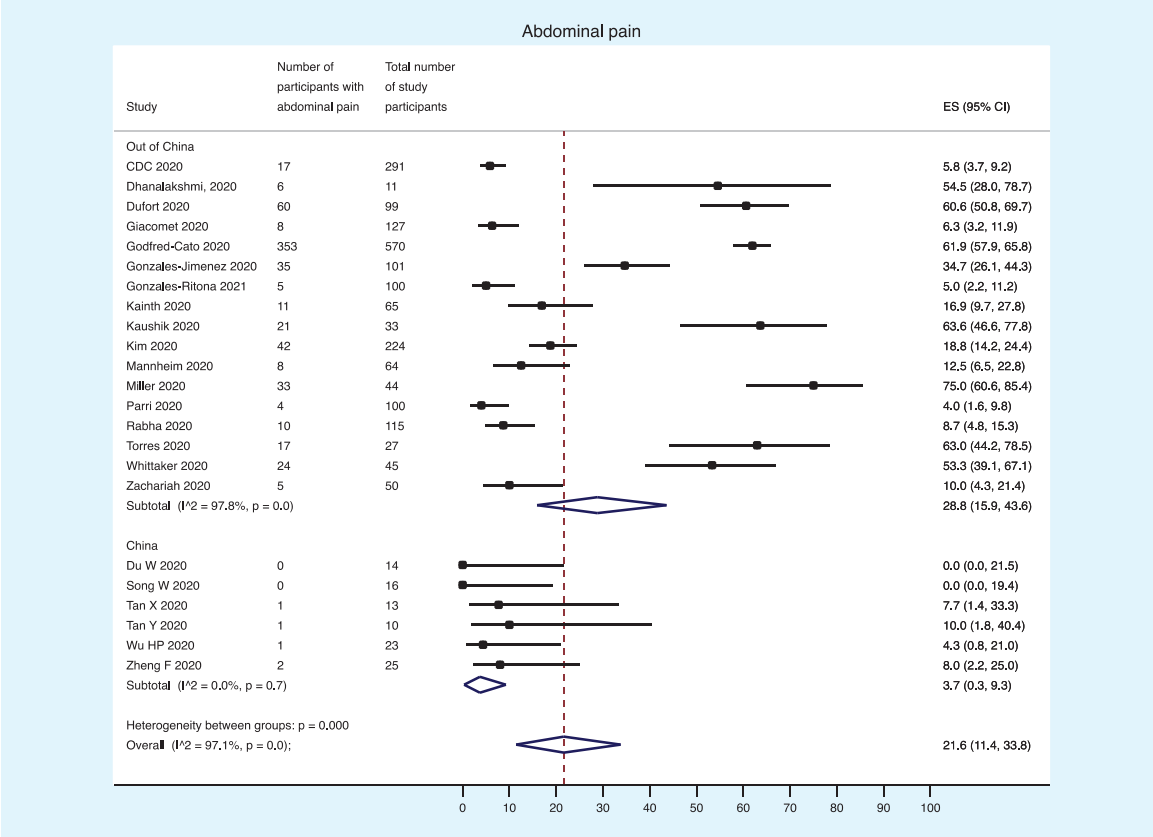

Figure 5. Pooled estimate of the prevalence of abdominal pain in children with COVID-19.

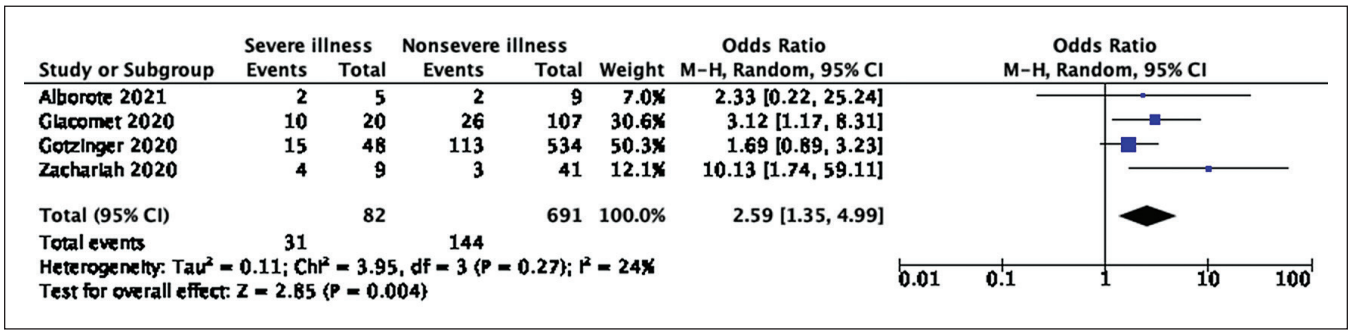

Figure 6. Gastrointestinal symptoms according to COVID-19 severity (severe vs non-severe).

Viruses which belong to the Coronaviridae family have long been known to cause disease among humans, and in the last two decades, three highly pathogenic and deadly human coronaviruses (HCoV) have emerged, namely Severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and SARS-CoV-2 in 2019 which is presently the cause of the COVID 19 pandemic.[80] SARS-CoV-2's impact is by far the most serious and extensive, having affected more than 470 million individuals and caused more than 6 million deaths, and the numbers continue to increase as new variants emerge.[2] The clinical manifestations of COVID-19 are predominantly similar with SARS and MERS, mainly presenting with fever and mild upper respiratory tract symptoms. The involvement of the gastrointestinal tract and liver in COVID-19 is mainly due to the characteristic distribution of Angiotensin I converting enzyme 2 (ACE2). ACE2 is the target entry receptor for both SARS-CoV and SARS-CoV-2, and is mainly expressed in lung alveolar type 2 cells, epithelial cells of the esophagus, stomach, ileum, colon and rectum, liver cholangiocytes, and renal proximal tubules.[81]

Comparing with previously published meta-analyses, Akobeng[10] and Wang[9] included participants mostly from China who were diagnosed with COVID-19 during the

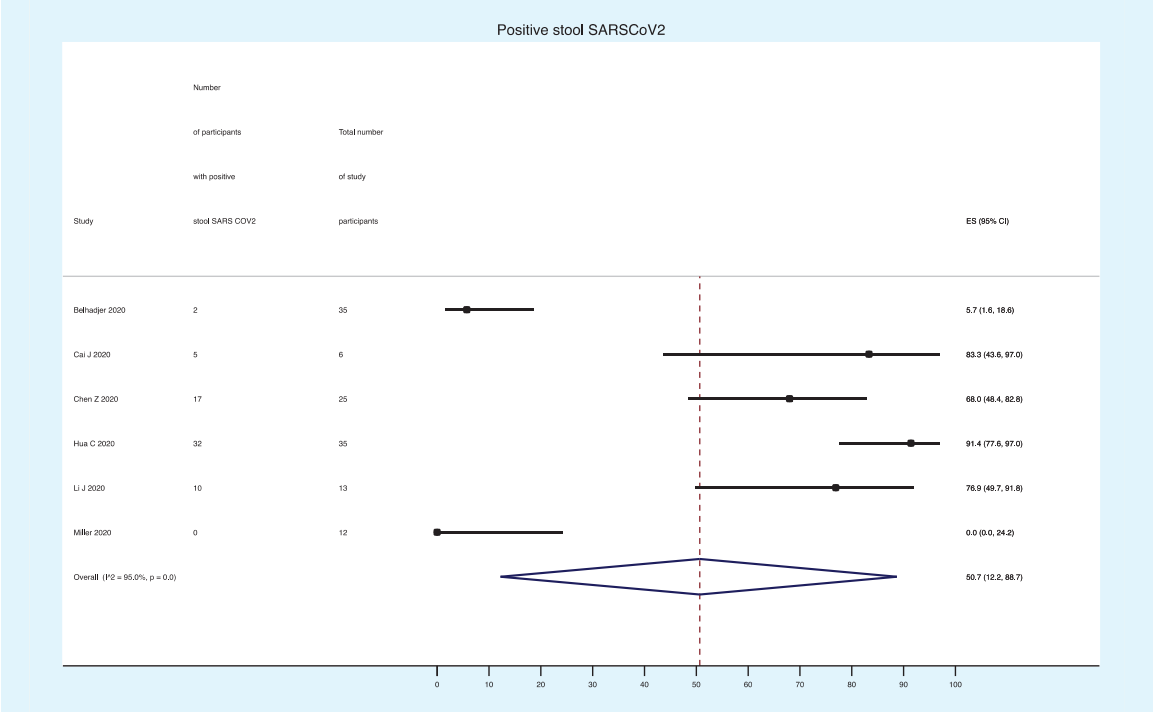

Figure 7. Pooled prevalence of positive fecal or anal swab PCR test for SARS-CoV-2.

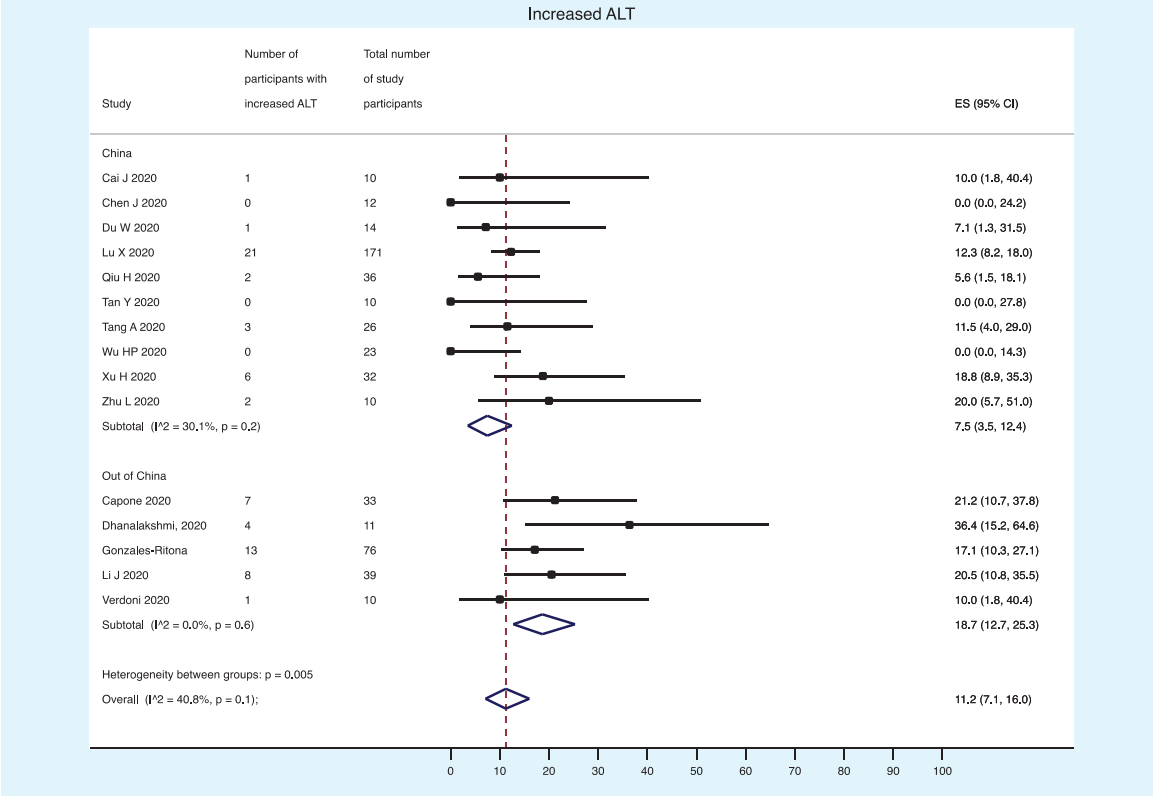

Figure 8. Pooled estimate of the prevalence of increased ALT levels in children with COVID-19.

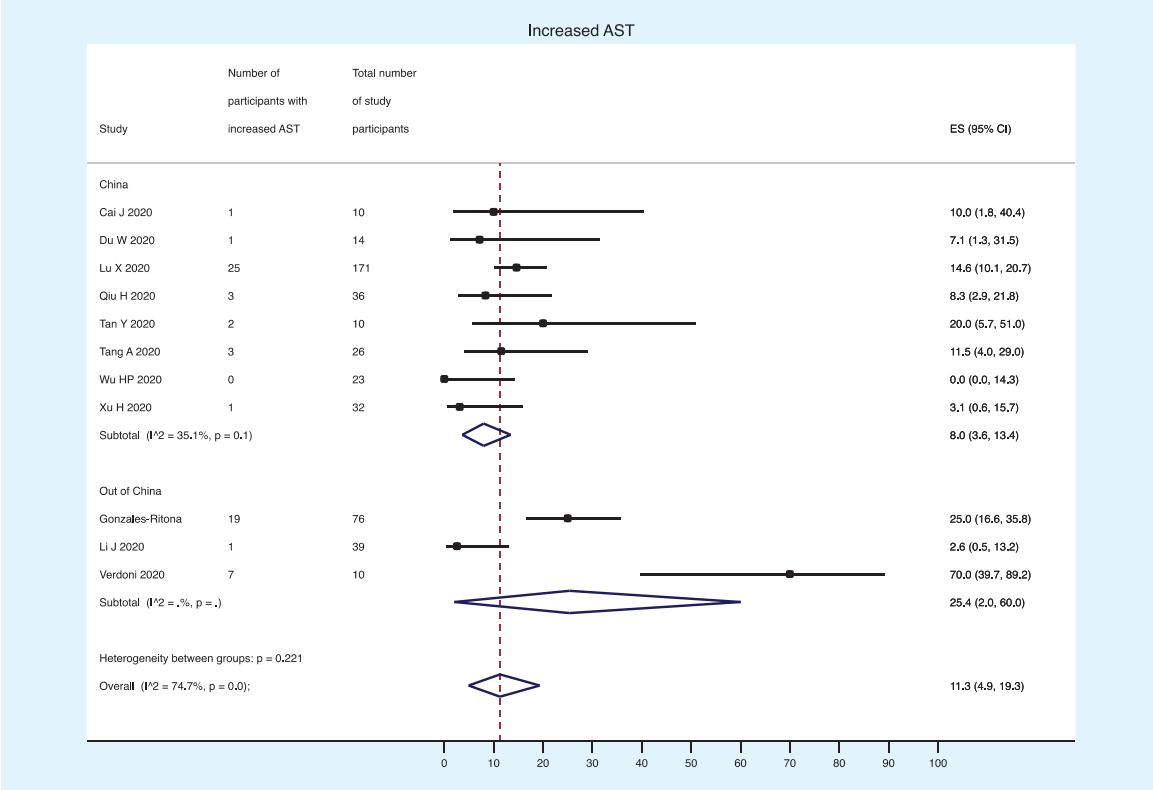

Figure 9. Pooled estimate of the prevalence of increased AST levels in children with COVID-19.

Table 1. Comparison of Pooled Estimates of Prevalence (95% CI) and Heterogeneity of Gastrointestinal Symptoms and Increased Transaminase in Children with and without MIS-C

Symptom	All studies	General COVID-19	MIS-C	*p* value between groups
Any GI symptom	42 studies[1]; n = 3327 33.8 (23.0, 45.4) I^2 = 97.5%	30 studies; n = 2313 16.3 (11.1, 22.3) 90.0%	14 studies; n = 1014 79.9 (68.7, 89.4) 90.0%	0.000
Diarrhea	40 studies[2]; n = 3392 17.2 (12.1, 22.8) 92.9%	33 studies; n = 2408 11.1 (8.9, 13.6) 57.8%	11 studies; n = 984 51.5 (46.5, 56.6) 30.2%	0.000
Nausea / vomiting	32 studies[3]; n = 2823 19.5 (12.1, 28.0) 96.0%	25 studies; n = 1934 11.0 (7.44, 15.1) 82.7%	10 studies; n = 889 58.6 (52.8, 64.3) 34.6%	0.000
Abdominal pain	23 studies[4]; n = 2167 21.8 (11.4, 33.8) 97.1%	16 studies; n = 1333 8.8 (5.0, 13.3) 81.2%	8 studies; n = 834 62.1 (11.3, 33.5) 16.1%	0.000
Increased ALT	15 studies[5]; n = 513 11.2% (7.1, 16.0) 40.8%	12 studies; n = 454 9.8 (5.7, 14.5) 37.6%	4 studies; n = 59 20.7 (10.2, 33.1) 0.0%	0.032
Increased AST	11 studies[6]; n = 447 11.3% (4.9, 19.3) 74.7%	10 studies; n = 432 8.9 (4.0, 15.0) 62.5%	2 studies; n = 15 53.5 (26.4, 79.8) Cannot be computed[7]	0.000

MIS-C: Multisystem inflammatory syndrome in children; GI: gastrointestinal

[1] *Participants of 2 studies were divided according to presence of MIS-C*
[2] *Participants of 4 studies were divided according to presence of MIS-C*
[3] *Participants of 3 studies were divided according to presence of MIS-C*
[4] *Participants of 1 study was divided according to presence of MIS-C*
[5] *Participants of 2 studies were divided according to presence of MIS-C*
[6] *Participants of 1 study was divided according to presence of MIS-C*
[7] *I^2 cannot be computed for <4 studies*

early months of the pandemic and they reported lower prevalence of GI symptoms. Our findings are consistent with a more recently published study by Bolia et al.[11] including 55 studies with 4369 patients. Similar to our study, 20% of their participants were diagnosed with MIS-C, which might explain the higher prevalence of GI symptoms as compared to earlier published studies.

MIS-C is a severe phenotypic manifestation of COVID-19 in children presenting with persistent fever and a constellation of symptoms including hypotension, multiorgan (e.g., cardiac, gastrointestinal, renal, hematologic, dermatologic and neurologic) involvement, and elevated inflammatory markers. Characteristically, respiratory symptoms were not present in all cases. Based on the World Health Organization (WHO) case definition,[16] MIS-C may be considered in the presence of acute gastrointestinal problems (diarrhea, vomiting or abdominal pain) when associated with other symptoms such as muco-cutaneous inflammation, shock, cardiac dysfunction or coagulopathy, and elevated markers of inflammation without other obvious microbial cause of inflammation in a child with laboratory evidence of COVID-19 or likely contact with confirmed COVID-19 case. Thus, children with COVID-19 who present with GI symptom(s) may warrant closer monitoring for earlier recognition and management of MIS-C.

In terms of hepatic manifestations, symptoms like jaundice and behavioral disturbance indicative of hepatic encephalopathy are rare in children with COVID-19. Elevated ALT was the most commonly reported hepatic biochemical derangement (11%) and its prevalence in children is slightly lower compared to adults (15-18%).[6,7] In a meta-analysis of 35 studies including 36 children (out of 6686 total participants), subgroup analysis showed that children with COVID-19 were less likely to present with increased ALT and AST (7%) compared with adult patients (24%) (p 0.0089).[7] The higher prevalence of liver injury observed in adults may be due to presence of more risk factors among adults such as co-morbid conditions of fatty liver and alcohol consumption.

Our review has a number of strengths. We performed a comprehensive literature search, including gray literature from prepublication repositories and a local unpublished study. This enabled us to include more studies in our analysis including children with MISC which was not included in the earlier report. A two-step hierarchical model of data extraction was performed, thus minimizing the inclusion of same patients who were enrolled in multiple studies with overlapping study period. We also described the studies that detailed the onset, type and duration of diarrhea, abdominal symptoms, hepatic manifestations, and gastrointestinal and hepatic imaging findings.

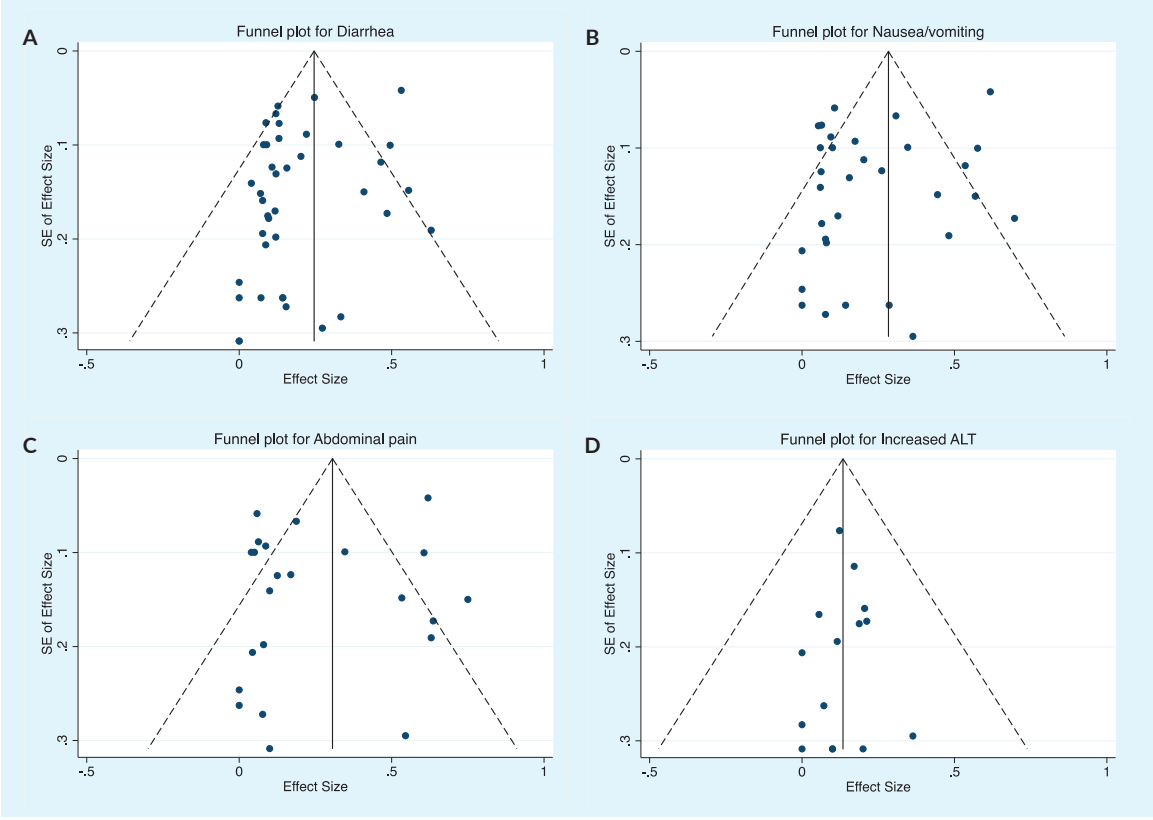

Figure 10. Funnel plots for pooled prevalence of **(A)** diarrhea, **(B)** nausea or vomiting, **(C)** abdominal pain, and **(D)** increased ALT in children with COVID-19.

However, majority of the studies came from the US and Europe, with less reports from Latin America, China, and other Asian countries. Hence the result of our review may not be applicable to other geographical regions. We may have missed studies with more detailed information as we did not include case reports and small case series with less than 10 participants which may have more detailed information on the character, onset or duration of diarrhea, abdominal pain, and vomiting. Furthermore, majority of included studies were review of surveillance databases and retrospective observational studies, thus are prone to incomplete data reporting and methodological differences. The definition of GI symptoms were not specified and there were differences in the cut-offs used to define elevated transaminases across studies. Subjective symptoms such as abdominal pain and nausea may be underreported particularly in young children who are not able to verbalize their symptoms yet. Most of the studies also did not account for the confounding variables in the estimation of association effect. Lastly, most studies did not specify if the GI symptoms occurred at presentation or developed during admission. Since some drugs used for COVID-19 may cause gastrointestinal adverse effects (e.g., chloroquine, hydroxychloroquine, steroids, lopinavir/ritonavir, favipiravir), the prevalence of GI symptoms due to COVID-19 may be overestimated, particularly in patients who had a more severe course.

CONCLUSION

Our review showed that a third of children with COVID-19 exhibit at least one GI symptom, but significantly increases up to 80% in patients diagnosed with MIS-C. Children with severe COVID-19 are 2.5 times more likely to present with GI symptom(s). The prevalence of elevated transaminase level is 10% and is likewise significantly higher in children with MIS-C (20-50%).

Statement of Authorship

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APPENDICES

Supplementary Table 1. Search Strategy

Database	Search strategy / Search terms	Date and time of search	Yield
PubMed.gov	("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date – Publication])) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) AND ("gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields] OR "gastrointestine"[All Fields] OR ("diarrhea"[MeSH Terms] OR "diarrhea"[All Fields] OR "diarrheas"[All Fields] OR "omiting"[All Fields] OR "diarrhoeas"[All Fields]) OR ("vomiter"[All Fields] OR "vomiters"[All Fields] OR "vomiting"[MeSH Terms] OR "vomiting"[All Fields] OR "vomit"[All Fields] OR "vomited"[All Fields] OR "vomits"[All Fields] OR "vomitings"[All Fields] OR "vomition"[All Fields] OR "omiting"[All Fields]) OR ("abdominal pain"[MeSH Terms] OR ("abdominal"[All Fields] AND "pain"[All Fields]) OR "abdominal pain"[All Fields]))	Jan 4, 2021; 9:00 AM	405
Cochrane Library	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2 AND Gastrointestinal OR Diarrhea OR Abdominal pain OR vomiting AND Child	Jan 4, 2021; 11:00 AM	26
Google Scholar	COVID-19AND gastrointestinal AND children	Jan 4, 2021; 1:00 PM	209
Medrxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2	Sep 1, 2021; 8:30 PM	133
Biorxiv.org	Casirivimab OR REGEN-COV OR REGN-COV2 AND COVID-19	Sep 1, 2021; 9:00 PM	161
Others	Hand-search, communication with study authors		24

Supplementary Table 2. Characteristics of Included Studies

Study ID (Author Year)	Study type	Country	Participants with demographic data	Participants with data on GI/hepatic manifestations	Median age years (IQR) or Mean age (SD)	Male (%)	Type of participants: General COVID-19/ MIS-C	At least 1 GI symptom	Diarrhea	Nausea Vomiting	Abdominal pain	Increased ALT	Increased AST
Alboorote 2021	Retrospective cohort study	Philippines	25	14	6.5 (SD 6.2)	68	General	4	2	4			
Antunez-Montes 2021	Ambispective multicenter cohort study	Latin America	409	409	3.0 (IQR 0.6-9.0)	54	Both	101	101				
Belhadjer 2020	Retrospective cohort study (multicenter)	France, Switzerland	35	35	10	51	MIS-C	29					
Cai J 2020	Case series	China	10	10	6.2 (range: 0.3-10.9)	40	General	0	0			1 (2x ULN)	1 (3.55x ULN)
Capone 2020	Retrospective cohort study	USA	33	33	8.6 (IQR 5.5-12.6)	61	MIS-C	32				7 (>80 U/L)	
Ceano 2020	Retrospective cohort study	Spain	58	58	2.9 (IQR 0.3-12)	64	General		7	9			
Chen J 2020	Retrospective cohort study (multicenter)	China	12	12	14.5 (IQR 9.25-15.75)	50	General	4	4			0 (>40 U/L)	
Chen Z 2020	Retrospective cohort study (multicenter)	China	32	32	9.5y (range 3m - 18y)	66	General	3	3				
CDCMMWR	Surveillance database	USA	2572	291	11 (range 0-17)	57	General		37	31	17		
Dhanalakshmi, 2020	Ambispective cohort center	India	19	11	6 (IQR 13m-16y)	27	MIS-C	6	3	4	6	4 (>40 U/L)	
Dodi 2020	Retrospective cohort study	Spain	14	14	1.8 (IQR?)	64	General		2	2			
Du W 2020	Retrospective cohort study (multicenter)	China	14	14	6.2 (0-16)	43	General	0	0	0	0	1 (>40 U/L)	1 (>40 U/L)

Supplementary Table 2. Characteristics of Included Studies *(continued)*

Study ID (Author Year)	Study type	Country	Participants with demographic data	Participants with data on GI/hepatic manifestations	Median age years (IQR) or Mean age (SD)	Male (%)	Type of participants: General COVID-19/ MIS-C	At least 1 GI symptom	Diarrhea	Nausea Vomiting	Abdominal pain	Increased ALT	Increased AST
Dufort 2020	Surveillance database	USA	99	99	NR	54	MIS-C	79	49	57	60		
Garazzino 2020	Retrospective cohort study (multicenter)	Italy	168	168	2.3 (IQR 0.3-9.6)	56	General	31	22	9			
Garcia-Salido 2020	Ambispective cohort study	Spain	74	74	8.1 (IQR 3-11.5)	61	Both		33	38			
Giacomet 2020	Retrospective cohort study (multicenter)	Italy	127	127	4.8 (IQR 0.3-8.5)	65	General	36	28	12	8		
Godfred-Cato 2020	Surveillance database	USA	570	570	8 (IQR 4-12)	55	MIS-C	518	303	352	353		
Gonzales-Dambrauskas 2020	Surveillance database (Critical Coronavirus and Kids Epidemiology Study)	20 countries from America and Europe	17	17	4 (range: 0.08-18)	65	General (Critical COVID)	6					
Gonzales-Jimenez 2020	Retrospective cohort study (multicenter)	Spain	101	101	9.4 (IQR 3-12.2)	57	General (Critical COVID)	58	33	35	35		
Gonzales-Ritona (unpublished)	Retrospective cohort study	Philippines	100	100	NR	54	Both		8	6	5	13/76 (>3x ULN)	19/76 (>3x ULN)
Gotzinger 2020	Surveillance database (ptbnet)	Europe	582	582	5 (IQR 0.5-12; range 3d-18y)	53	General	128					
Hua C 2020	Surveillance database	China	43	43	8.16 (SD 4.07, range 3m-14y)	60	General	3	3	2	2		
Kainth 2020	Retrospective cohort study	USA	65	65	10.3 (IQR 1.4m-16.3y)	51	General	40	7	17	11		
Kaushik 2020	Retrospective cohort study	USA	33	33	10 (IQR 6-13)	61	MIS-C		16	23	21		
Kim 2020	Surveillance database (COVID-NET)	USA	576	576	8 (IQR 9m-15y)	51	General	94	27	69	42		
Lee P 2020	Retrospective cohort study	USA	28	28	9 (range 0.1-17)	57	MIS-C	15					
Li J 2020	Retrospective cohort study	Singapore	39	39	NR	59	General	3	3			8 (cutoff not specified)	1 (cutoff not specified)
Li X 2020	Retrospective cohort study	China	14	14	6.33	43	General	1	1				
Lu X 2020	Retrospective cohort study	China	171	171	6.7y (IQR 2-9.8)	61	General		15	11		21 (>45 U/L)	25 (>50 U/L)
Mannheim 2020	Surveillance database (I-NEDSS)	USA	64	64	11 (IQR 7-16)	56	General		10	4	8		
Miller 2020	Retrospective cohort study	USA	44	44	7.3 (SD 4.98, range 7m-20y)	45	MIS-C	37	18	25	33		
Moraleda 2020	Retrospective cohort study (multicenter)	Spain	31	31	7.6 (IQR 4.5-11.5)	58	MIS-C	27					
Parri 2020	Retrospective cohort study (multicenter)	Italy	100	100	3.3	57	General		9	10	4		
Pereira 2020	Retrospective cohort study	Brazil	66	66	NR	50	Both	17					

Supplementary Table 2. Characteristics of Included Studies *(continued)*

Study ID (Author Year)	Study type	Country	Participants with demographic data	Participants with data on GI/hepatic manifestations	Median age years (IQR) or Mean age (SD)	Male (%)	Type of participants: General COVID-19/ MIS-C	At least 1 GI symptom	Diarrhea	Nausea Vomiting	Abdominal pain	Increased ALT	Increased AST
Pouletty 2020	Retrospective cohort study (multicenter)	France	16	16	10 (IQR 4.7-12.5)	50	MIS-C	13					
Prata-Barbosa 2020	Prospective cohort study (multicenter)	Brazil	79	79	4 (1-10.3)	54	Both		16	16			
Qiu H 2020	Retrospective cohort study (multicenter)	China	36	36	8.3 (SD 3.5)	64	General	2				2 (>40 U/L)	3 (>40 U/L)
Rabha 2020	Retrospective cohort study	Brazil	115	115	2 (IQR 11-8)	50	General	39	15	20	10		
Ramcharan 2020	Retrospective cohort study	England	15	15	8.8 (IQR 6.4-11.2)	73	MIS-C	13					
Shekerdamian 2020	Retrospective cohort study (multicenter)	USA, Canada	48	48	NR	52	General (Critical COVID)	1					
Song W 2020	Prospective cohort study	China	16	16	8.5 (range 11.5m-14)	63	General	0	0	0	0		
Tan X 2020	Retrospective cohort study	China	13	13	NR	31	General	4	2	1	1		
Tan Y 2020	Retrospective cohort study	China	10	10	7 (range 1-12)	30	General	2	NR	1	1	0 (>42 U/L))	2 (>37 U/L)
Tang A 2020	Retrospective cohort study	China	26	26	6.9 (0.7), range 1-13	35	General		2	2		3 (>45 U/L)	3 (>45 U/L)
Torres 2020	Ambispective cohort study	Chile	27	27	6	52	MIS-C		17	13	17		
Toubiana 2020	Retrospective cohort study	France	21	21	7.9 (range 3.7-16.6)	43	MIS-C	21					
Valente 2020	Prospective cohort study	Italy	27	27	84m (range 8d-210m)	74	General	8					
Verdoni 2020	Retrospective cohort study	Italy	10	10	7.5 (SD 3.5)	70	MIS-C	6	6			1 (≥100 U/L)	7 (>48 U/L)
Wang 2020	Retrospective cohort study (multicenter)	China	31	31	7y 1m (range 6m - 17y)	48	General	5	3	2			
Whittaker 2020	Retrospective cohort study (multicenter)	England	58	45	10 (IQR 6-14)	67	MIS-C		25	20	24		
Wu HP 2020	Retrospective cohort study	China	23	23	5y7m (range: 3m-17y8m)	39	General	2	2	0	1	0 (cut-off not specified)	0 (cut-off not specified)
Xu H 2020	Retrospective cohort study	China	32	32	9 (SD 4.7)	53	General					6 (>45 U/L)	1 (>45 U/L)
Zachariah 2020	Retrospective cohort study	USA	50	50	NR	54	General	7	2	3	5		
Zhang B 2020	Retrospective cohort study (multicenter)	China	46	46	105m (SD 64)	63	General	0					
Zhang C 2020	Retrospective cohort study (multicenter)	China	34	34	8 (IQR 4-14; range 1m-12y)	41	General		4	4			
Zheng F 2020	Retrospective cohort study (multicenter)	China	25	25	3 (IQR 3m-14y)	56	General		3	2	2		
Zheng G 2020	Retrospective cohort study (multicenter)	China	52	52	9y (IQR 4-12)	54	General	1					
Zhu L 2020	Case series	China	10	10	9.5 (IQR 6-12)	50	General	0	0	0		2 (>40 IU/L)	

Supplementary Table 3. Quality Assessment of Cohort/ Cross-sectional Studies

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
Alborote 2021	Y	Y	Y	Y	N	N	Y	NA	Y	U	N	N	Y	N	Fair
Antunez-Montes 2021	Y	Y	U	Y	N	N	Y	NA	Y	U	Y	N	Y	Y	Fair
Belhadjer 2020	Y	Y	U	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Ceano 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	N	N	Y	N	Fair
Chen J 2020	Y	Y	U	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Chen Z 2020	Y	Y	U	Y	U	N	Y	NA	Y	Y	Y	N	Y	N	Fair
CDCMMWR	Y	Y	U	Y	N	N	N	NA	Y	U	N	N	Y	N	Poor
Dhanalakshmi 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Dodi 2020	N	Y	Y	Y	N	N	N	NA	N	N	N	N	Y	N	Poor
Du W 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	N	N	Y	N	Fair
Dufort 2020	Y	Y	Y	Y	N	N	N	NA	Y	N	Y	N	Y	N	Fair
Garazzino 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	N	N	Y	N	Fair
Garcia-Salido 2020	Y	Y	Y	Y	N	N	Y	NA	N	N	Y	N	Y	N	Fair
Giacomet 2020	Y	Y	Y	Y	N	N	N	NA	Y	N	N	N	U	Y	Fair
Godfred-Cato 2020	N	Y	Y	Y	N	N	N	NA	Y	N	N	N	Y	N	Poor
Gonzales-Dambrauskas 2020	Y	Y	Y	Y	N	N	N	NA	N	U	Y	N	Y	N	Fair
Gonzalez-Jimenez	Y	Y	Y	Y	N	N	N	NA	Y	N	N	N	N	Y	Fair
Gonzales-Ritona	Y	Y	Y	Y	N	N	Y	NA	Y	U	Y	N	Y	N	Fair
Gotzinger 2020	Y	Y	U	Y	N	N	N	NA	Y	Y	N	N	Y	N	Fair
Hua C 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	N	N	Y	N	Fair
Kainth 2020	Y	Y	Y	Y	N	N	N	NA	Y	Y	Y	N	Y	Y	Good
Kaushik 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Kim 2020	N	Y	Y	Y	N	N	N	NA	Y	N	N	N	N	N	Poor
Lee P 2020	Y	N	Y	Y	N	N	Y	NA	Y	N	N	N	Y	N	Fair
Li J 2020 (SG)	Y	Y	Y	Y	N	N	Y	NA	Y	N	N	N	Y	N	Fair
Li X 020 (Shenzhen)	Y	Y	Y	Y	N	N	Y	NA	Y	Y	N	N	Y	N	Fair
Lu X 2020	Y	Y	Y	Y	N	N	N	NA	Y	Y	N	N	Y	N	Fair
Mannheim 2020	Y	Y	Y	Y	N	N	N	NA	Y	Y	N	N	Y	N	Fair
Mller 2020	Y	Y	Y	Y	N	N	N	NA	N	N	N	N	Y	N	Poor
Moraleda 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	N	N	Y	N	Fair
Parri 2020	Y	Y	U	Y	N	N	Y	NA	Y	U	Y	N	Y	N	Fair
Pereira 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Pouletty 2020	N	Y	N	Y	N	N	Y	NA	Y	N	Y	N	Y	N	Fair
Prata-Barbosa	Y	Y	Y	Y	N	N	N	NA	Y	N	N	N	Y	Y	Fair
Qiu H 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Good
Rabha 2020	Y	Y	Y	Y	N	N	Y	NA	Y	N	Y	N	Y	Y	Good
Ramcharan 2020	Y	Y	Y	Y	N	N	Y	NA	N	N	Y	N	Y	N	Fair
Shekerdamian 2020	Y	Y	Y	Y	N	N	N	NA	Y	N	Y	N	Y	N	Fair
Song W 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Good
Tan X 2020	N	Y	U	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Tan Y 2020	N	Y	U	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Tang A 2020	N	Y	U	Y	N	N	N	NA	Y	Y	Y	N	Y	N	Fair
Torres 2020	Y	Y	Y	Y	N	N	N	NA	Y	U	Y	N	Y	N	Fair
Toubiana 2020	Y	Y	U	Y	N	N	N	NA	N	Y	Y	N	Y	N	Fair
Valente 2020	Y	Y	U	Y	U	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Verdoni 2020	Y	Y	U	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Fair

Supplementary Table 3. Quality Assessment of Cohort/ Cross-sectional Studies *(continued)*

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Quality Rating
Wang 2020	Y	Y	U	Y	N	N	N	NA	Y	Y	N	N	Y	N	Fair
Whittaker 2020	Y	Y	U	Y	U	N	U	NA	Y	U	Y	N	Y	N	Fair
Wu HP 2020	Y	Y	U	Y	U	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Xu H 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Good
Zechariah 2020	Y	Y	Y	Y	N	N	N	NA	Y	Y	Y	N	Y	N	Fair
Zhang B 2020	Y	Y	U	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Zhang C 2020	Y	Y	Y	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Good
Zheng F 2020	Y	Y	U	Y	N	N	N	NA	Y	Y	Y	N	Y	N	Fair
Zheng G 2020	Y	Y	U	Y	N	N	Y	NA	Y	Y	Y	N	Y	N	Fair
Zhu L 2020	Y	Y	U	Y	N	N	N	NA	Y	Y	Y	N	Y	N	Fair

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Supplementary Table 4. Quality Assessment of Case Series Studies

Study	1	2	3	4	5	6	7	8	9	Quality Rating
Cai 2020	N	Y	U	Y	NA	N	Y	N	Y	Fair
Capone 2020	Y	Y	Y	Y	NA	Y	Y	Y	Y	Good

1. Was the study question or objective clearly stated?
2. Was the study population clearly and fully described, including a case definition?
3. Were the cases consecutive?
4. Were the subjects comparable?
5. Was the intervention clearly described?
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?
7. Was the length of follow-up adequate?
8. Were the statistical methods well-described?
9. Were the results well-described?