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Gastrointestinal manifestations of pediatric coronavirus disease and their relationship with a severe clinical course: A systematic review and meta-analysis

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Abstract

Background: Data on the gastrointestinal (GI) manifestations of Pediatric Corona Virus Disease (COVID-19) is conflicting and the relationship between GI involvement and the severity of COVID-19 disease has not been evaluated. The objectives of this systematic review was to determine the GI manifestations of pediatric COVID-19 and to evaluate their role as risk factors for a severe clinical course.

Methods: A systematic literature search was carried out in PubMed and Scopus for studies published before December 31, 2020 with information about the GI manifestations of pediatric COVID-19. Patients with a severe and non-severe clinical course were compared using the inverse variance heterogeneity model and odds ratio (OR) as the effect size. A sensitivity analysis was performed if the heterogeneity was high among studies.

Results: A total of 811 studies were identified through systematic search of which 55 studies (4369 patients) were included in this systematic review. The commonest GI symptoms were diarrhea – 19.08%(95%CI:10.6–28.2), nausea/vomiting 19.7%(95%CI:7.8–33.2) and abdominal pain 20.3%(95%CI:3.7–40.4). The presence of diarrhea was significantly associated with a severe clinical course with a pooled OR of 3.97 (95%CI: 1.80–8.73; $p < 0.01$). Abdominal pain and nausea/vomiting were not associated with disease severity.

Conclusions: Diarrhea, nausea/vomiting or abdominal pain are present in nearly one-fifth of all children with COVID-19. The presence of diarrhea portends a severe clinical course.

Introduction

Children account for 1-3% of the cases of coronavirus disease 2019 (COVID-19) reported around the world. (1) Pediatric symptoms are variable and a tetrad of cough, fever, dyspnea, and malaise are the most commonly reported symptoms. However, apart from the respiratory system, COVID-19 impacts other systems, of which gastrointestinal manifestations are the commonest. (2)

Recognizing the GI symptoms of COVID-19 in children is important as they have GI manifestations more often than adults do. (3) GI symptoms may be the sole presenting symptoms of COVID-19 in a child. They may precede respiratory symptoms or may manifest later during the disease course. Pooled analyses which included patients reported till April 2020 showed that gastrointestinal manifestations are quite common in pediatric COVID-19, with nearly 25% exhibiting at least one GI symptom. The commonly reported symptoms being diarrhoea, nausea/vomiting and abdominal pain. (4)

With the recognition of multisystem inflammatory syndrome (MIS-C), a manifestation of pediatric COVID-19 characterised by intense systemic inflammation and multi-organ failure, GI symptoms have been further highlighted in the pediatric age-group. Radia et al. in a meta-analysis of 735 individual cases of MIS-C found that 71% had GI symptoms. (5) MIS-C was first reported in early May and there is a need for updated data on the GI manifestations of COVID-19 that accounts for these children as well.

Available data suggests that an asymptomatic or mild disease course is more common in the pediatric age-group as compared to adults . However, severe cases and deaths do occur in children too and have been reported worldwide. In a pooled analysis of 27 studies (4857 patients), 4% children had severe disease. (2) A young age and the presence of underlying co-morbidities have been documented as risk factors for a severe disease course in children. (1) In adults, the presence of GI symptoms has also been correlated with increased odds of critical

disease. (6) However, in the pediatric age group it is unclear whether the presence of gastrointestinal symptoms also portends a severe disease course.

Hence, this meta-analysis was conducted to evaluate the frequency of GI symptoms in pediatric COVID-19 and to figure out whether they were a risk factor for severe clinical course of the disease.

Methods

This systematic review and meta-analysis has been performed using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Criteria for Considering the studies for review

Inclusion and exclusion of studies was planned using the PECO format – Participants, Exposure group, Control group and Outcomes. Participants included all children (< 19 years) with COVID -19. A COVID-19 diagnosis was considered in children who either had a positive real time polymerase chain reaction (RTPCR) for SARS-CoV-2 in the nasopharyngeal swab or had compatible clinical symptoms with the presence of a positive ELISA IgG or IgM for SARS-CoV-2. Exposure group was cases of pediatric COVID-19 with gastrointestinal manifestations. Controls were children with COVID-19 without gastrointestinal manifestations. Outcome studied was children with a severe clinical course that was determined using any one of the following criteria:

- patients requiring pediatric intensive care unit (PICU) care
- patients developing organ dysfunction
- patients who have been categorized to have severe/critical disease according to standard criteria (7)
- Patients who did not survive

Search Strategy

A literature search was carried out systematically with no time or language restrictions using the electronic databases - PubMed and Scopus for keywords related to the inclusion criteria to identify relevant cohort or cross-sectional studies. The references of the included studies were also reviewed manually to ensure the inclusion of all pertinent articles. The detailed search strategy has been described in Supplementary Table 1.

Last search for articles was performed on 31st December 2020.

Data extraction

Three reviewers independently extracted data using a predetermined criterion. The following data was extracted from each study: number of patients, study setting, demographic data, gastrointestinal manifestations and number of patients having a severe and non-severe clinical course. Any discrepancy in data extraction was resolved by mutual discussion.

Quality Assessment

The studies reporting the prevalence data were evaluated by the Appraisal tool for Cross-Sectional Studies (AXIS). This tool comprises of a total of 20 items evaluating the various aspects of the methodological quality of the studies pertaining to aims/ objectives, study design, sample size, reference population, representativeness, non-response, appropriateness and validity of risk and outcome variables, approach to statistical significance, completeness of methodology, description and internal consistency of data, synchrony between the methods, results, discussion and conclusion, description of limitation of the study, potential conflicts of interest and adherence to ethical principles. Each item is rated by three options: 'Yes" (Y) – when it meets the description of the evaluation criterion, 'no' (N) – when the particular criterion is not met or 'Unclear' (U) – when there is insufficient information to evaluate a particular criterion. (8)

The quality of the studies included in the comparative data analysis was evaluated by the Joanna Briggs Institute (JBI) critical appraisal checklist. The risk of bias was assessed

through ten questions that evaluated the comparability of groups, matching, criteria for identifying the groups, validity of measurement tools, uniformity in exposure assessment, approach to confounder identification, appropriateness of length of exposure and appropriateness of statistical analysis used. (9) Individual questions were assessed as Yes, No or Unclear.

Statistical analysis

The inverse variance heterogeneity model has been utilised for ascertaining the summary effect in this meta-analysis. The pooled prevalence of the individual gastrointestinal symptoms – diarrhea, nausea/vomiting, abdominal pain, dysgeusia and anorexia were expressed as proportion and 95%CI. The data was presented in a forest plot. The risk of occurrence of gastrointestinal symptoms in patients with severe as compared to non-severe disease course were described using odds ratios (OR). Heterogeneity between studies was assessed using I^2 values. I^2 values of more than 75% would indicate high heterogeneity. A p value of less than 0.05 was considered statistically significant. Further, sensitivity analysis was performed by excluding each study to investigate the effect on the overall pooled prevalence and heterogeneity. Poor quality and outlier studies were considered for exclusion in sensitivity analysis. Small study effects, which may be due to a publication bias, was investigated by the Luis Furuya Kanamori (LFK) index and DOI plot. A value of LFK index <1 is indicative of no symmetry, between 1 and 2 indicates minor symmetry and more than 2 is indicative of major asymmetry. Meta-analysis was performed using MetaXL softwarev5.3 software (*EpiGear International, Sunrise Beach, Australia*).

Results

A total of 811 records were found using the systematic search strategy. After removing 143 duplicate studies, 668 articles were screened by title and abstract and were excluded if they

were not about the COVID-19 (n = 6), did not involve patients in the pediatric age-group (n = 131), did not contain information about the gastrointestinal manifestations of COVID-19 (n = 215), were case reports (n=126), were review articles (n = 129), was a study protocol only (n = 4), was an erratum (n =1) or did not involve human subjects (n = 1). The selection strategy followed is summarised in **Figure 1**.

Finally, 55 studies were selected for inclusion in this systematic review. (10-64) Seven studies had data comparing severe with non-severe disease course and were included in the meta-analysis evaluating the association of GI symptoms with the severity of the disease course.

Study Characteristics

The characteristics of the 55 studies that were included in the final analysis are summarised in **Table 1**. Twenty-three of the studies were multi-centric while the rest (n=32) of the studies were from single centres. Most were from China (20/55, 36.3%) followed by those from USA (10/55,18%), Italy (5/55,9%) and Iran (5/55,9%). This review included 4369 patients (median 41 (6-570) patients per study) and 1829 were males. MIS-C was the diagnosis in 886 (20.2%).

Risk of bias assessment

The risk of bias assessment of the included studies have been summarised in Supplementary Tables 2 and 3.

Gastrointestinal symptoms

The pooled prevalence of diarrhea was 19.08% (95%CI: 10.6% to 28.2%) (**Figure 2**). This data was obtained from 49 studies comprising 4008 children. A high degree of heterogeneity (I2 =95%) was found which could not be eliminated on sensitivity analysis

The pooled prevalence of nausea/vomiting (40 studies, 3480 patients, **Figure 3)** and abdominal pain (31 studies, 2518 patients, **Figure 4**) was1 9.7% (95% CI 7.8% to 33.2%)

and 20.3% (95% CI 3.7% to 40.4%) respectively. The I^2 statistic for these respective symptoms was 97% and 98%.

Other GI symptoms were recorded only in a handful of the studies. Data regarding anorexia/feeding difficulties was available in 7 studies with a pooled prevalence of 10% (95% CI 0% to 26%), $I^2 = 95\%$, while dysgeusia was reported in only 4 studies and had a prevalence of 3% (95% CI 0% to 7%), $I^2 = 66\%$.

Gastrointestinal symptoms and their association with a severe clinical course

Information regarding the clinical course (severe vs non-severe) was given in 37 studies which included 2670 (848 severe, 1822 non-severe) patients. Seven studies assessed the association of diarrhea with a severe disease course. It was found that it was significantly associated with the severity of the clinical course of the disease with an OR of 3.97 (95% CI, 1.80–8.73; $p < 0.01$) (**Figure 5a**). There was nonsignificant heterogeneity among studies with an I^2 of 48%. There was no asymmetry for small study effects (LFK index = -0.28, supplementary figure 1a)

Nausea and vomiting as a risk factor for a severe disease was assessed in 6 studies. No association was found between its presence and the severity of the disease (OR 2.59 [95% CI, 0.79–8.44). (**Figure 5b**) There was significant heterogeneity amongst studies (I^2=78%) which persisted even after a sensitivity analysis. There was no asymmetry for small study effects (LFK index = 0.68, supplementary figure 1b) Similarly, abdominal pain which was assessed in 4 studies was not found to be a risk factor for severe disease (OR 0.34 [95% CI, 0.076-1.55]). (**Figure 5c**). There was no asymmetry for small study effects (LFK index = 0.78, supplementary figure 1c).

Discussion

This is the first meta-analyses in children studying the gastrointestinal manifestations of COVID-19 and their association with the severity of the clinical course of the disease. To sum up the results, abdominal pain was the commonest gastrointestinal symptom seen in 20% children, followed by nausea and/or vomiting in 19.7%, and diarrhoea in 19%. The presence of diarrhea was a risk factor for a severe clinical course (OR 3.97) but not nausea/vomiting or abdominal pain.

The entry of SARS-CoV-2 into the host cells is facilitated by the angiotensin converting enzyme-2 (ACE2) which is considered as a receptor for the virus. Apart from the respiratory tract, these receptors are also present in the GI tract and in individuals affected by SARS-CoV-2 the presence of the viral RNA has been demonstrated in almost the entirety of the GI tract. The viral RNA has also been demonstrated in the stools of patients of COVID-19 and it has been shown that the fecal RT-PCR may continue to be positive even after respiratory viral shedding ceases. (65) The passage of SARS-CoV-2 in stool and its ability to survive in sewage water is a public health concern.(66) While feco-oral virus transmission has been suggested, (67) its persistence in polluted water bodies may result in further mutations within the SARS-CoV-2 genome, though not as frequently as the antigenic shifts and drifts seen in influenza.

The GI symptoms of SARS-CoV-2 may be caused either by a direct invasion of the virus or by immune-mediated tissue injury. When the ACE2-expressing enterocytes are infected by the virus, it may lead to mucosal inflammation, malabsorption, and unbalanced intestinal secretion causing diarrhea. This was demonstrated by Effenberger et al when they showed that SARS-CoV-2 infection prompted an inflammatory response in the gut, as evidenced by elevated levels of serum IL-6 and fecal calprotectin. (68)

In the first few published series of COVID-19 patients, the proportion of patients with GI symptoms was low. However, with the spread of the pandemic , this prevalence has increased, probably owing to increasing awareness about the non-respiratory symptoms of the disease among clinicians. The first meta-analysis of the GI manifestations of COVID-19 in children was performed by Akobeng et al. They analysed nine studies (published till 1 April 2020), comprising 280 patients and found that the pooled prevalence of diarrhoea, vomiting and abdominal pain was12.4%, 10.3% and 5.4% respectively. (4) Subsequently, Wang et al. carried out a meta-analysis of GI symptoms in children in which studies published till 10 August, 2020 were included. Their analysis included 38 studies (3028 patients) and they found that the total incidence of GI symptoms was 17.7%. (69) The pooled prevalence of the individual symptoms was not assessed in this study. We included 55 studies published till 31st December, 2020 and found that the gastrointestinal symptoms of abdominal pain, nausea/vomiting and diarrhea were found in nearly one-fifth of all children with COVID-19, suggesting a steady rise in the incidence of reported GI symptoms in children over time.

Xu et al. demonstrated that the GI tissues had a relatively higher ACE2 expression compared to the pulmonary tissues, with their expression in the lungs increasing with age. (70) This data may explain the differences in the symptoms of COVID-19 between children and adults, with gastrointestinal symptoms being more common in children and its respiratory manifestations being more common in adults. In various meta-analyses containing mainly adult patients, the pooled estimates of the prevalence of diarrhea, nausea/ vomiting and abdominal pain have been reported to range from 7.4-9.1%, 4.6-7.8% and 2.7 – 3.5% respectively suggesting that these GI symptoms are less common in adults as compared to children. (6,71-73) This is in contradiction to the report by Mao et al. who had reported a

similar frequency of GI symptoms in children and adults in a meta-analysis of 35 studies (till 10 April, 2020). However, their analysis included only 266 children (vs 6402 adult patients). Moreover, it did not include children with MIS-C which was first reported only in early May.(5)

The current literature suggests that children with COVID-19 fare better than adults and are relatively spared form developing severe disease manifestations. The factors that potentially protect children from developing severe COVID-19 disease are – the absence of co-morbidities, a good regenerative capacity of the lung and lack of immune senescence (74) The presence of a strong innate immune response as a result of frequent viral infections during childhood has also been postulated as a protective factor. Though relatively uncommon, severe clinical manifestations do occur in a small proportion of children and it is important to try and identify the risk factors for the same. Studies in adults have suggested that GI symptoms play a role in the overall picture of the disease with those having GI symptoms having a more severe clinical course. Mao et al. in a meta-analysis of 6 studies (2014 patients) of whom 247 had gastrointestinal involvement found that those with GI symptoms had an increased risk of a severe clinical course with an OR of 3.97. They found that patients with severe manifestations of COVID-19 had a higher likelihood for abdominal pain as a symptom when compared to those without a severe clinical course. (6) The prognosis of children with COVID-19 with GI manifestations is unclear and conflicting. Giacomet et al. in an Italian cohort of 127 children reported that GI symptoms were more frequently associated with a severe disease phenotype. Amongst the individual GI symptoms, they found that the presence of vomiting and diarrhea but not abdominal pain to correlate with disease severity.(14) Gonzalez et al. in a cohort of 101 pediatric COVID-19 patients from 15 centres across Spain found that after adjusting for the confounding factors, those with the presence of either vomiting, abdominal pain or diarrhea had a higher risk of

admission to the pediatric intensive care unit.(10) On the other hand in a study of 45 children with MIS-C neither of the individual GI symptoms portended a more severe course. (18) On a pooled analysis we found that patients with diarrhea, but not abdominal pain and nausea/vomiting correlated with disease severity.

The strength of our meta-analysis is the fact that it includes a large number of patients (55 studies including a total of 4369 patients) who hail from a diverse regional background. Information from observational studies done in fifteen different countries have been included in our analysis and our results are likely a true depiction of the clinical picture of pediatric COVID-19. This is in contrast to the initial reports which consisted of data originating mainly from China. In our analysis, we have also included studies that were not in English. Google Translate®, a free, web-based program was used for the translation.

Our meta-analysis is not without limitations. Firstly, a large number of the included studies were retrospective in nature. Secondly, there was a lot of heterogeneity which could not be eliminated on sensitivity analysis. Thirdly, the aim of most of the included studies was primarily to describe the clinical profile of children with COVID-19. It is well known that respiratory symptoms are the most common symptoms of COVID-19 and hence it is possible that the GI manifestations were under-reported in them. Fourthly, As most of the studies included hospital-based data it is conceivable that our estimates represent the prevalence of gastrointestinal manifestations only in children who require hospital admission. We excluded all studies (n=215) that did not contain information about gastrointestinal symptoms, and the absence of information was not assumed to equate that these symptoms were absent. Lastly, the different studies included in this meta-analysis used different definitions to define severe COVID-19 which probably contributed to the heterogeneity that was observed.

To conclude, our systematic review and meta-analysis has re-affirmed the fact that GI manifestations are common in pediatric COVID-19. Our analysis suggests that the presence of diarrhea probably portends a severe clinical course and there is a need for focussed attention to the care of children who have diarrhea as a symptom of COVID-19. Prospective studies are needed to confirm our findings.

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Legends to Figures

Figure 1. PRISMA flow diagram depicting the flow of information through different phases of the systematic review.

Figure 2. Prevalence of diarrhea in children with COVID-19.

Figure 3. Prevalence of Nausea/Vomiting in children with COVID-19.

Figure 4. Prevalence of Abdominal Pain in children with COVID-19.

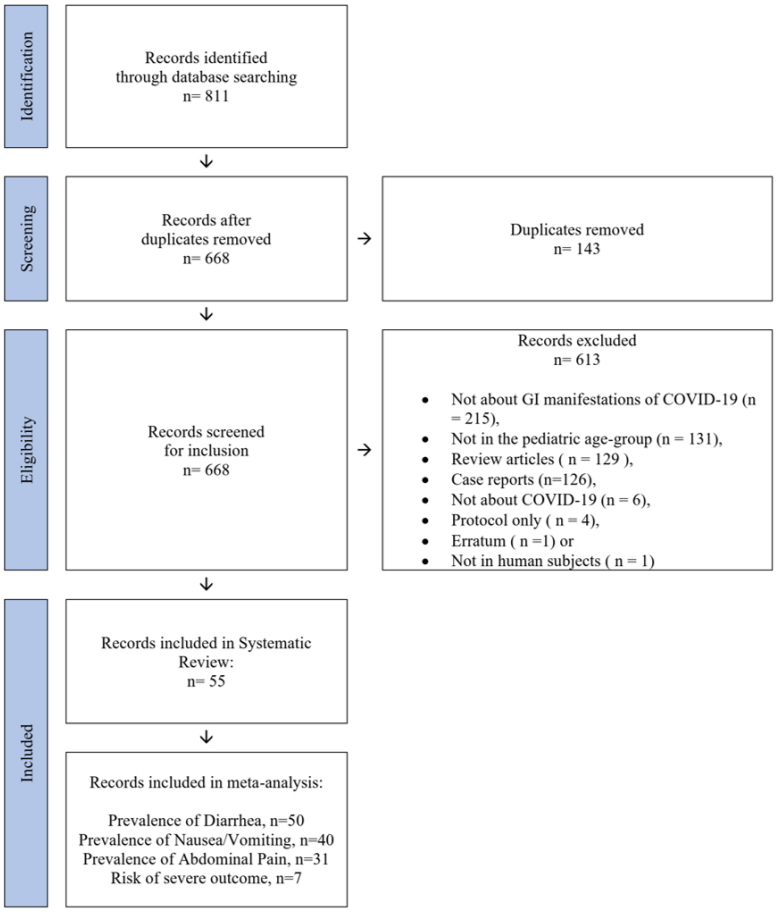
Figure 5 Forest plot showing pooled odds ratio of **a.** Diarrhea being associated with severe clinical course. **b.** Nausea/vomiting being associated with severe clinical course**. c.** Abdominal being associated with severe clinical course.

Supplementary Figure 1. DOI Plot to ascertain publication bias in association of (a) diarrhea (b) nausea/vomiting (c) abdominal pain with severe clinical outcomes

Table 1. Demographic data and clinical presentation of patients

First Author	Country	Study Design	n	Mean Age (Months)	Gender (Male)	Fever	Respiratory Symptoms	Diarrhea	Nausea/ Vomiting	Abdominal Pain	Severe	Non-severe
Gonzalez Jimenez D	Spain	Retrospective	101	112.8	58	82	60	33	35	35	30	71
GarcÃa-Salido A	Spain	Prospective	71	97.2	45	61	23	33	38	40/45	74	0
Esmaeili Dooki M	Iran	Retrospective	18	82.44	12	16	6	6	7	6	-	-
Zhang Y	China	Retrospective	41	71.16	23	24	8	2	0	0	0	41
Giacomet V	Italy	Retrospective	127	57.6	83	105	82	28	12	8	20	107
Al-Omari A	Saudi Arabia	Prospective	16	126	15	5	6	4	2	0	0	16
Song X	USA	Retrospective	54	99.6	25	41	24	-	-	-	18	36
Storch-de-Gracia P	Spain	Retrospective	39	108	23	32	17	14	15	12	15	24
Mamishi S	Iran	Retrospective	45	84	23	41	16	16	23	26	14	31
Godfred-Cato S	USA	Retrospective	570	96			359	303	352	353	364	206
Adedeji IA	Nigeria	Prospective	53	12.63	28	9	11	5	3	4	0	51
Li J	Singapore	Retrospective	39	96	23	13	4	3	0	0	0	39
Blumfield E	USA	Retrospective	19	96	10	17	13	9	-	2	14	5
Davies P	UK	Retrospective	78	132	52	78	-	50	49	48	78	0
Xiong X	China	Retrospective	244	82	150	99	120	15	23	4	3	241
Zhang C	China	Retrospective	34	33	14	26	21	4	4	-	0	34
Kaushik S	USA		33	120	20	31	11	16	23	21	33	0
Miller J	USA	Retrospective	44	87.6	20	44	11	18	25	33	44	0
Tullie L	UK	Retrospective	8	138	5	8	0	8	8	8	-	-
Garazzino S	Italy	Retrospective	168	27.6	94	138	82	22	9	0	2	166
Tan YP	China	Retrospective	10	84	3	4	2	0	1	1	0	10
Shen Q	China	Retrospective	9	96	3	4	1	2	-	-	0	9
Wang D	China	Retrospective	31	85	-	20	14	3	-	-	0	
Tan X	China	Retrospective	13	96	4	6	7	2	1	1	1	12
Pereira MFB	Brazil	Retrospective	66	117.5	33	53	30	-	-	-	26	40
Qiu, H.	China	Retrospective	36	99.6	23	13	7	-	-	-	0	36
Xia, W.	China	Retrospective	20	25.5	13	12	13	3	2	-	0	20
Whittaker, E.	UK	Retrospective	58	108	25		12	30	26	31	29	29
Liu, W.	China	Retrospective	6	36	2	6	6	-	4	-	1	5
Sun, D.	China	Retrospective	8	80	6	6	6	3	4	0	8	0
Zachariah, P	USA	Retrospective	50	138	27	40	23	-	-	-	9	41
Du, W	China	Retrospective	14	74	6	5	3	0	0	0	0	-
Song, W	China	Retrospective	16	102	10	5	6	0	0	0	0	-
Chen, J	China	Retrospective	12	174	6	7	7	4	-	-	0	12
Du, H	China	Retrospective	182	72	120	79	81	9	7	7	4	178
Parri, N	Italy	Retrospective	130	72	73	67	54	10	15	-	9	121
Mithal, L.B	USA	Retrospective	10	2	7	9	8	4	3	-	-	-
Xiong, X.-L	China	Retrospective	244	14	19	99	14	15	23	4	-	-
Derespina, K.R	USA	Retrospective	70	180	43	85	84	30	44	-	21	49
Zhang, B	China	Retrospective	46	96	29	10	15	0	0	0	-	-
Chen, Z	China	Retrospective	32	114	21	20	10	6	-	-	0	32
Mahmoudi, S	Iran	Retrospective	35	90	22	27	28	9	10	4	14	-
Brisca, G	Italy	Retrospective	24	82.8	-	20	18	3	2	-	-	-
Mamishi, S	Iran	Retrospective	24	82.8	11	24	15	3	5	5	17	6
Parri, N	Italy	Retrospective	170	45	95	82	73	19	24	13	-	-
Shahbaznejad, L	Iran	Retrospective	10	64	6	8	8	7	6	0	-	-
El Fakiri, K	Morocco	Retrospective	74	84	34	8	5	4	-	-	0	74
Guo, Y	China	Retrospective	80	72	52	38	39	6	-	-	-	80
Krasnova, E.I.	Russia	Prospective	218			218	43	39	14	-	-	-
Sarangi, B	India	Retrospective	50	72	28	17	15	2	-	-	0	-
Chua, G.T.	China, Hong Kong, South Korea	Prospective	423	100.4	254	145	239	34	7	12	0	-
Cairoli, H.	Argentina	Retrospective	191	92.4	103	55	54	6	-	-	0	-
Leibowitz, J.	USA	Retrospective	20	1	19	-	4	4	4	-	-	-
Hosseninasab, A.	Iran	Retrospective	13	60	9	11	13	-	-	-	0	-
Popova, R.V.	Russia	Retrospective	36	-	-	-	-	23	-	21	-	-

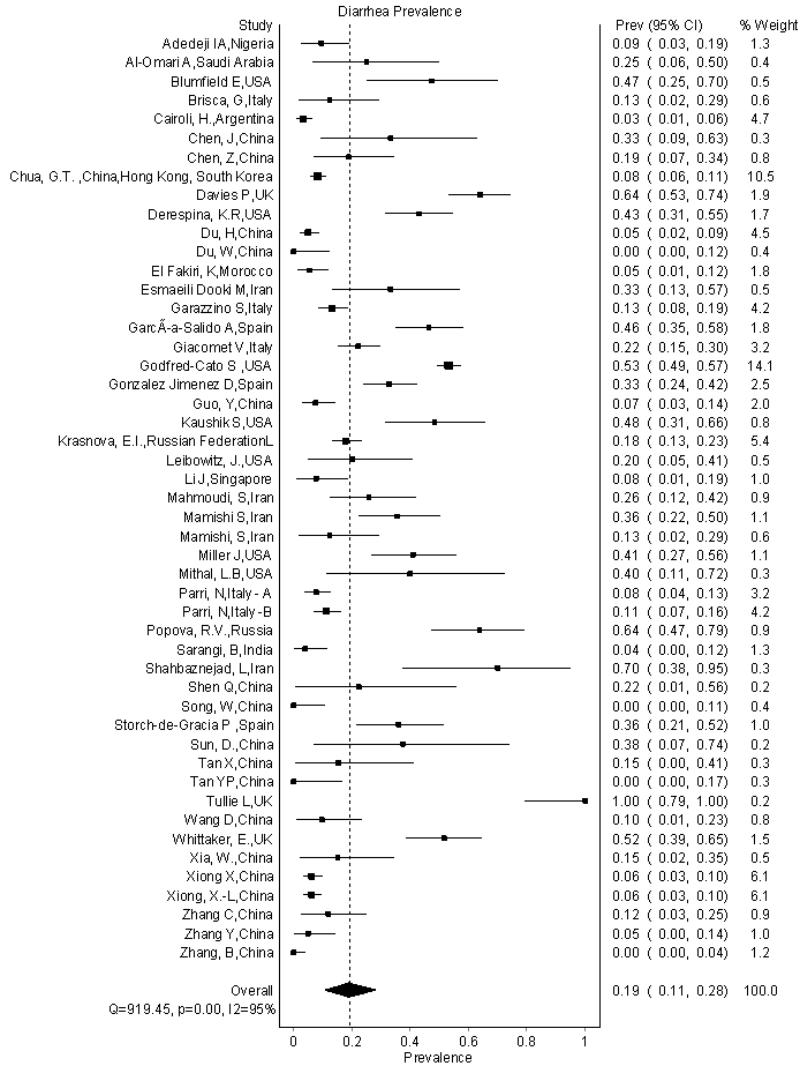
Figure 1. PRISMA flow diagram depicting the flow of information through different phases of the systematic review.



PRISMA flow diagram depicting the flow of information through different phases of the systematic review.

266x355mm (96 x 96 DPI)

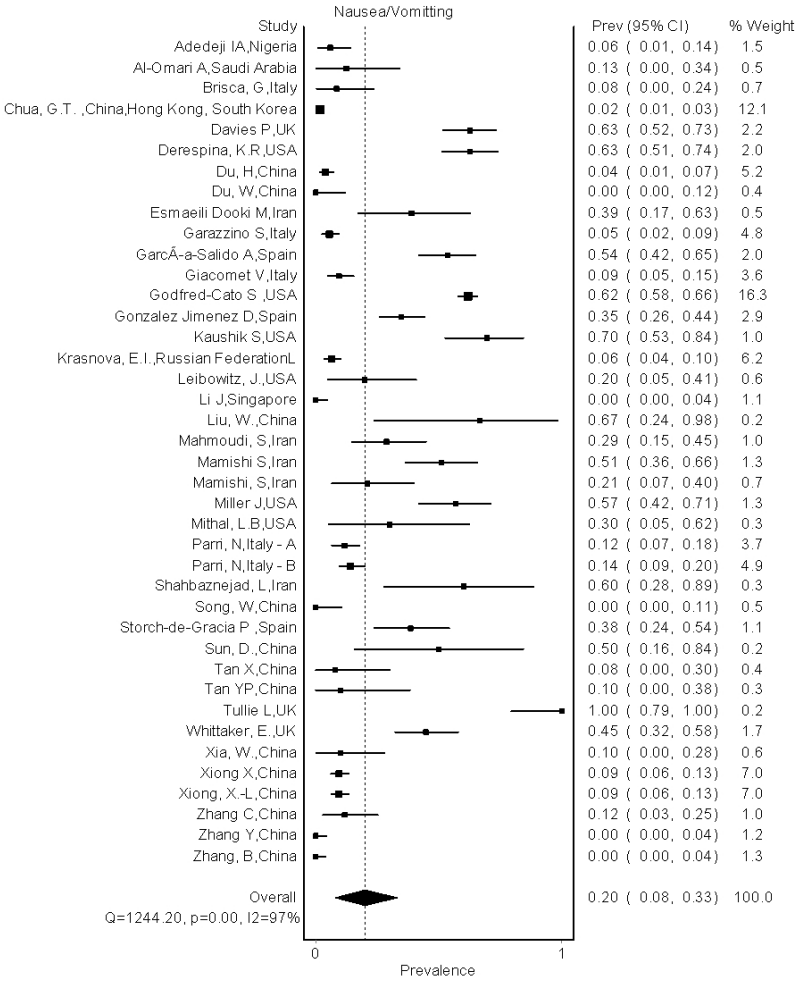
Figure 2. Prevalence of diarrhea in children with COVID-19.



Prevalence of diarrhea in children with COVID-19

190x275mm (96 x 96 DPI)

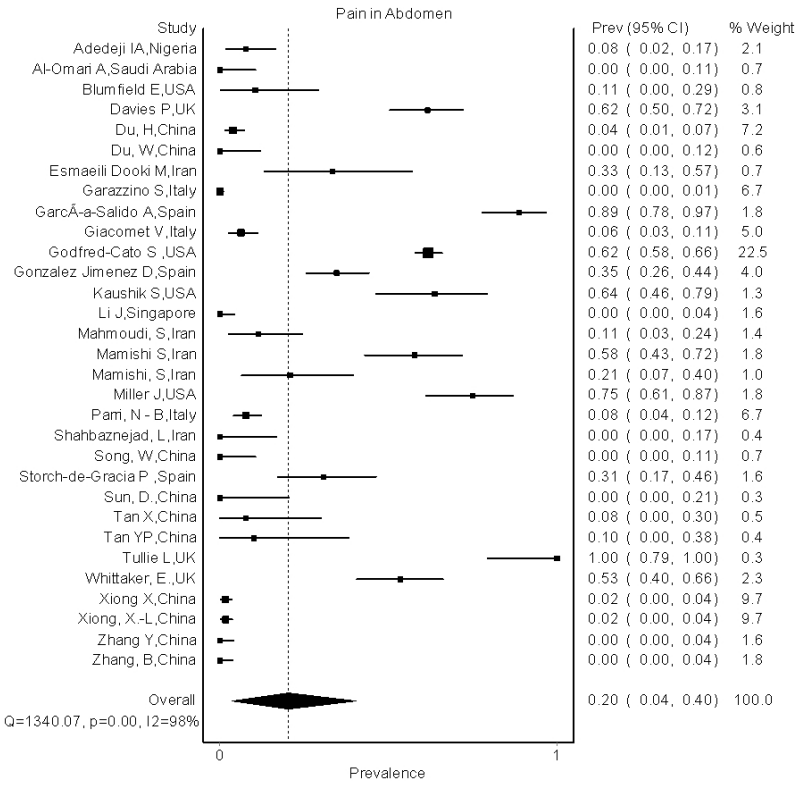
Figure 3. Prevalence of Nausea/Vomiting in children with COVID-19.



Prevalence of Nausea/ Vomiting in children with COVID-19

266x355mm (96 x 96 DPI)

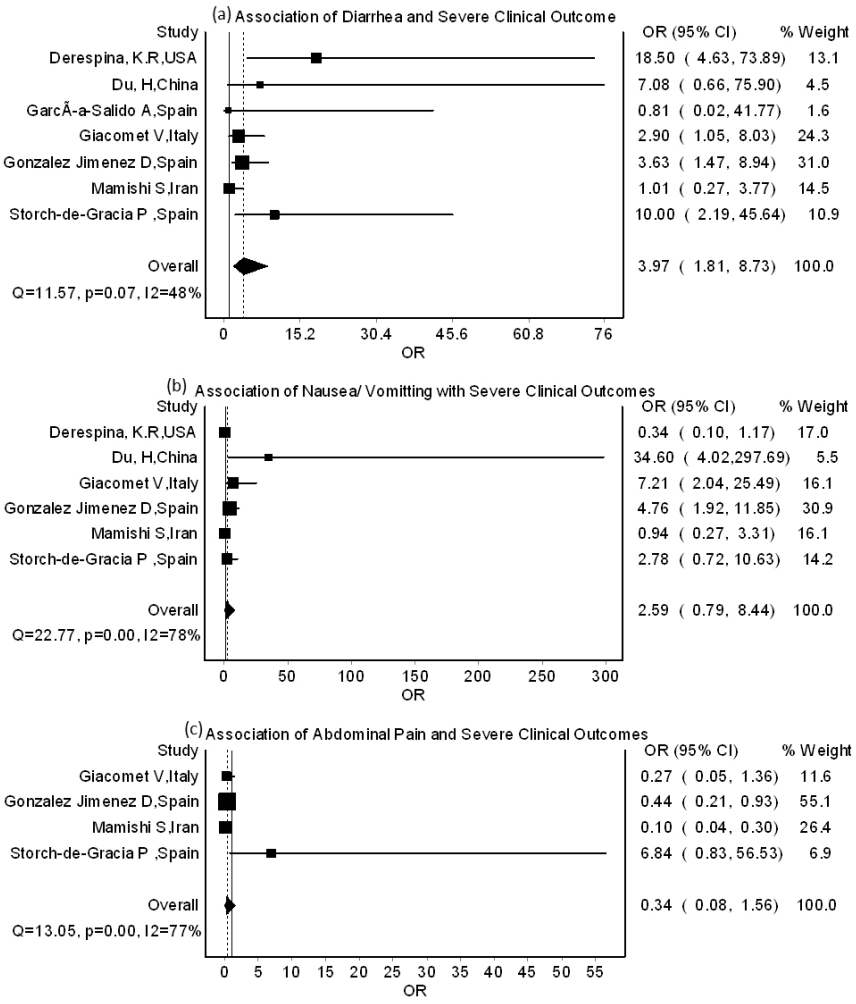
Figure 4. Prevalence of Abdominal Pain in children with COVID-19.



Prevalence of abdominal pain in children with COVID-19

266x355mm (96 x 96 DPI)

Forest plot showing pooled odds ratio of (a) Diarrhea, (b) Nausea/ Vomitting and © Abdominal Pain being associated with severe clinical course



Forest plot showing pooled odds ratio of (a) Diarrhea, (b) Nausea/ Vomiting and © Abdominal Pain being associated with severe clinical course

266x355mm (96 x 96 DPI)