Meta-Analysis of Observational Studies in Epidemiology

Medicine®

OPEN

Digestive system symptoms and function in children with COVID-19

A meta-analysis

Jiajia Wang, PhD[a], Xiaofeng Yuan, PhD[b,*]

Abstract

The prevalence of children exhibiting coronavirus disease 2019 (COVID-19) with digestive system involvement remains unknown. Therefore, we aimed to quantify the impact of COVID-19 on the digestive system of children.

In this meta-analysis, we searched PubMed, Embase, and Web of Science from January 1, 2020, to June 31, 2020. We also searched for COVID-19 publications in specific journals for more comprehensive results. We included studies that reported the epidemiological and clinical characteristics of COVID-19, and we excluded duplicate publications, reviews, animal studies, case reports, publications without the full text, studies with incomplete information, and studies from which data extraction was impossible.

We conducted a meta-analysis of the incidence of gastrointestinal symptoms and changes in liver function involving 19 studies. The pooled prevalence of diarrhea was 10% (95% CI: 7–14; $I^2 = 84\%$), that of nausea or vomiting was 7% (95% CI: 5–11; $I^2 = 77\%$), and that of abdominal pain was 4% (95% CI: 2–9; $I^2 = 79\%$). In addition, the pooled incidence of increased alanine aminotransferase was 8% (95% CI: 5–15; $I^2 = 46\%$), and the pooled incidence of increased AST was 15% (95% CI: 9–26; $I^2 = 66\%$). The pooled rate of recovery was 97% (95% CI: 94–100; $I^2 = 86\%$), and the pooled rate of death, which was 1% (95% CI: 1–4; $I^2 = 48\%$), was much smaller than the recovery rate.

Our research shows that digestive system symptoms and function in children with COVID-19 are not uncommon. More attention should be paid to this unique group of patients.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, COVID-19 = coronavirus disease 2019, NIH = National Institutes of Health, PRISMA statement = Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.

Keywords: children, COVID-19, gastrointestinal symptoms, liver injury, meta-analysis

1. Introduction

In December 2019, a cluster of an unidentified form of acute respiratory pneumonia cases, named coronavirus disease 2019 (COVID-19) by the World Health Organization, brought great challenges to global public health.[1] By June 19, 2020, more than 8,385,440 confirmed cases, including 450,686 deaths, had been reported from more than 150 countries or regions globally.

SARS-CoV-2 is considered to be the causal agent of this viral pneumonia. Patients generally have typical acute respiratory disease manifestations, and even fatal respiratory failure can occur.[2,3] Studies have shown that the entry of SARS-CoV-2 into human cells requires the ACE2 receptor, and ACE2 is widely distributed in various tissues throughout the body. Other studies combined with the latest autopsy reports have confirmed that COVID-19 is not only a respiratory disease but also may affect other human systems. The digestive system, gastrointestinal tract, and liver all abundantly express ACE2,[4] and fecal-oral transmission has been confirmed to be possible. Studies have shown that children with COVID-19 generally have mild symptoms, and their prognosis is relatively good.[5] However, reports have increasingly shown that potential comorbidities and coinfections in infants and young children in particular have a critical presentation, with infants below 6 months having a significantly increased risk of critical disease severity.[6] Moreover, the period of SARS-CoV-2 positivity in children's stool is significantly increased compared with that in adults within their families.[5] According to reports, COVID-19 patients' gastrointestinal symptoms mainly include anorexia, nausea, vomiting, abdominal pain, and diarrhea. Additionally, abnormal liver enzyme indicators and liver damage are observed, which is consistent with the expression and distribution of ACE2 in the digestive tract.[5] The latest reports show that gastrointestinal

Editor: Khaled Saad.

The research does not involve patients, so ethical approval was not necessary.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Changchun University of Chinese Medicine, Changchun, [b] Department of Pediatrics, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun, China.

[*] Correspondence: Xiaofeng Yuan, Department of Pediatrics, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun 130021, China (e-mail: yuanxiaofeng0812@163.com).

How to cite this article: Wang J, Yuan X. Digestive system symptoms and function in children with COVID-19: a meta-analysis. Medicine 2021;100:11 (e24897).

Received: 13 August 2020 / Received in final form: 2 February 2021 / Accepted: 4 February 2021

http://dx.doi.org/10.1097/MD.0000000000024897

symptoms of COVID-19 in children are not uncommon. Gastrointestinal symptoms have significance in the early diagnosis of children and the guidance of treatment.[7] Therefore, it is necessary to clarify the common gastrointestinal symptoms and the characteristics of liver function in pediatric patients with COVID-19 to provide clinical guidance for their treatment. We thus conducted a systematic review and meta-analysis of studies that have reported gastrointestinal symptoms, liver injury, and prognosis in children with COVID-19.

2. Methods

2.1. Literature inclusion and exclusion criteria

The inclusion criteria were as follows: retrospective study; definite diagnosis of COVID-19; and language limited to Chinese and English.

The exclusion criteria were the following: duplicate publication; review, animal experiments and case reports; and studies without full text, studies with incomplete information, and studies from which data extraction was impossible.

2.2. Search strategy

In this systematic review and meta-analysis, we searched the PubMed, Embase, and Web of Science databases from January 1, 2020 to June 17, 2020. In addition, we also searched for COVID-19 publications in the WHO publication database, "The Lancet" COVID-19 Resource Center, "New England Medical Journal," "Journal of the American Medical Association," "Medical Journal," "Gastrointestinal Diseases," "American Journal of Gastroenterology," and the US Centers for Disease Control and Prevention for more comprehensive results. The search terms were "SARS-CoV-2 infection," "2019 novel coronavirus infection," "2019-nCoV infection," "coronavirus disease 2019," "child," "children," and "pediatric."

2.3. Literature screening and data extraction

The literature search, screening, and information extraction were all independently completed by 2 researchers. When there were doubts or disagreements, the decision was made after discussion or consultation with a third party. The data extraction included the author; year; study area; research type; number of cases; and prevalence of clinical gastrointestinal symptoms, such as vomiting, nausea, diarrhea, and abdominal pain. According to the liver injury defined in the article, we extracted 2 serological indicators: alanine aminotransferase (ALT) and aspartate aminotransferase (AST). COVID-19 was diagnosed on the basis of the study criteria, with reference to WHO guidance.

2.4. Literature quality assessment

Two researchers independently conducted literature quality evaluations using the National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies.[8] When the opinions were inconsistent, it was decided through discussion or consultation with the third person. The meta-analysis was performed based on the related items of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (PRISMA statement).

2.5. Data synthesis and statistical analysis

The present meta-analysis was performed with the metaprop command of the meta package in R (version 4.0.1) for pooling single-armed rates. Stata (version 15.1) with the command metareg was used for meta-regression. If the heterogeneity test revealed $P \geq .1$ and $I^2 \leq 50\%$, this indicated that the study had homogeneity, and the fixed effect model was used for combined analysis. If $P < .1$ and $I^2 > 50\%$, this indicated that the study had heterogeneity, and a sensitivity analysis, meta-regression, and subgroup analysis were used to find the source of heterogeneity. If the heterogeneity was still large, we used the random-effects model, or we set aside the results and used a descriptive analysis. When the number of documents included in a single outcome index was more than 10, the publication bias of each outcome was analyzed using a funnel plot and Egger test.

3. Results

3.1. Results of the literature search

In total, 2232 articles were obtained by searching PubMed, Embase, and Web of Science. After excluding duplicate studies, 920 articles remained. By further browsing the abstracts of the articles, we narrowed the results to 367 articles. Finally, the full texts were read to obtain 19 articles that could be used for the meta-analysis (Fig. 1).

3.2. Baseline characteristics and quality assessment of the included studies

3.2.1. Baseline characteristics. Overall, 19 retrospective studies were included in this meta-analysis. The sample size ranged from 8 to 1353, and 3907 patients were included in the present meta-analysis. Patients in 12 studies were from China, patients in 5 studies were from the United States, and patients in 2 studies were from Italy. All patients were children. The baseline characteristics of the included studies are shown in Table 1.[5–7,9–24]

3.2.2. Quality assessment of the included studies. The quality assessment of these included studies is shown in Table 2.

3.3. Results of the meta-analysis

3.3.1. Prevalence of gastrointestinal symptoms. All 19 studies reporting gastrointestinal symptoms in patients with COVID-19 at diagnosis were combined. Sixteen studies, including 3210 patients, reported the prevalence of diarrhea. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 84\%$, $P < .01$). The pooled prevalence of diarrhea was 10% (95% CI: 7–14) (Fig. 2).

Twelve studies, including 2466 patients, reported the prevalence of nausea or vomiting. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 77\%$, $P < .01$). The pooled prevalence of nausea or vomiting was 7% (95% CI: 5–11) (Fig. 2).

Four studies, including 1843 patients, reported the prevalence of abdominal pain. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 79\%$, $P < .01$). The pooled prevalence of nausea or vomiting was 4% (95% CI: 2–9) (Fig. 2).

3.3.2. Incidence of abnormal liver function. There were 8 studies on abnormal liver function. Eight studies, including

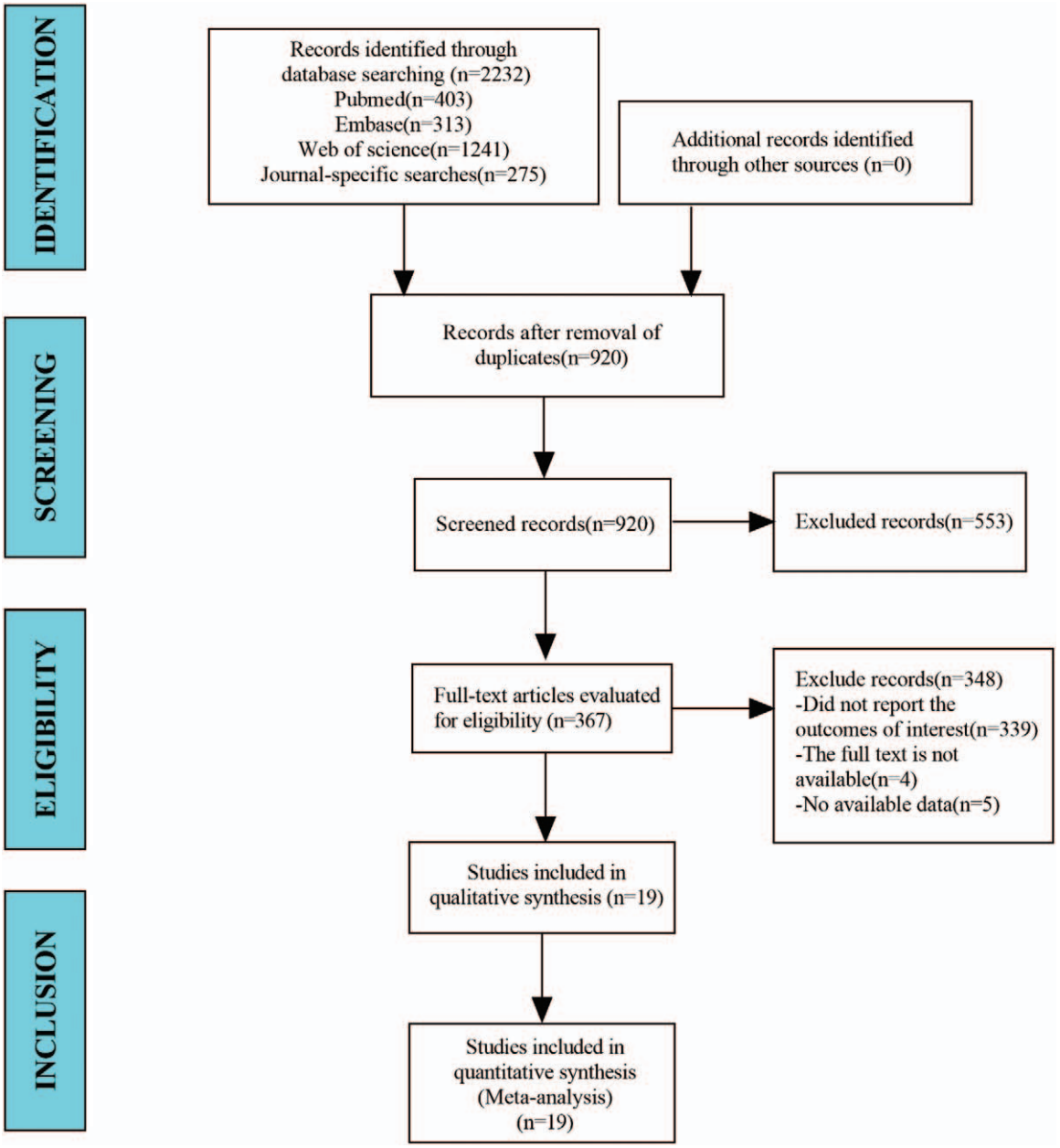

Figure 1. Flow diagram for selection of studies.

405 patients, reported the incidence of increased ALT. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 46\%$, $P = .07 < 0.1$). The pooled incidence of increased ALT was 8% (95% CI: 5–15) (Fig. 3).

Seven studies, including 385 patients, reported the incidence of increased AST. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 66\%$, $P < .01$). The pooled incidence of increased AST was 15% (95% CI: 9–26) (Fig. 3).

3.3.3. Prognosis of pediatric patients. Five studies, including 400 patients, reported the recovery rate. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 86\%$, $P < .01$). The pooled recovery rate was 97% (95% CI: 94–100) (Fig. 4).

Six studies, including 1753 patients, reported the death rate. Meta-analysis was performed through a random-effects model due to significant heterogeneity ($I^2 = 48\%$, $P = .09 < 0.1$). The pooled death rate was 1% (95% CI: 1–4) (Fig. 4).

3.3.4. Subgroup analysis. To further understand the differences in gastrointestinal complications and liver function of children in different regions and at different ages, we conducted a subgroup analysis. First, we analyzed the differences between more than 50% of the samples in the group over 5 years old (50%≥5 years) and 50% of the samples in the group under 5 years old (50%<5 years). We found a higher proportion of

Table 1

Baseline characteristics of the included studies.

Author	Year	Research type	Study area	Number of patients	Gender (M/F)	Age	Age < 5 yr, n (%)
Sun[9]	2020	Retrospective	China	8	6/2	8.0 (0.17–15.0)	5 (40.0%)
Cai[10]	2020	Retrospective	China	10	4/6	6.2 (0.3–10.9)	3 (30.0%)
Garazzino[11]	2020	Retrospective	Italy	168	94/74	2.3 (0.3–9.6)	104 (61.9%)
Qiu[7]	2020	Retrospective	China	36	23/13	8.3 (1.0–16.0)	10 (28.0%)
Su[5]	2020	Retrospective	China	9	3/9	3.5 (0.92–9.8)	5 (55.6%)
Xia[12]	2020	Retrospective	China	20	13/7	2.1 (1d-14.6)	14 (70.0%)
Xu[13]	2020	Retrospective	China	10	6/4	6.0 (0.17–15.0)	4 (40.0%)
Lu[14]	2020	Retrospective	China	171	104/67	6.7 (1d-15.0)	71 (41.5%)
Wang[15]	2020	Retrospective	China	31	15/16	7.1 (0.5–17.0)	< 50%
Bai[16]	2020	Retrospective	China	25	14/11	11.0 (6.3–14.5)	< 50%
Catherine[17]	2020	Retrospective	USA	57	32/25	10.7 (0.1–20.2)	< 50%
Du[18]	2020	Retrospective	China	182	120/62	6.0 (0.0–15.0)	88 (58.4%)
Lin[19]	2020	Retrospective	USA	1295	716/479	7.35±5.99	< 50%
Zhang[20]	2020	Retrospective	China	46	29/17	8.0 (4.0–14.0)	16 (35.0%)
Mannheim[21]	2020	Retrospective	USA	64	28/36	11.0 (7.0–16.0)	15 (23.0%)
Parri[6]	2020	Retrospective	Italy	130	73/57	6.0 (0.0–11.0)	41 (31.5%)
Ranabothu[22]	2020	Retrospective	USA	1353	694/659	/	439 (32.4%)
Shekerdemian[23]	2020	Retrospective	USA	48	25/23	13.0 (4.2–16.6)	14 (30.0%)
Xiong[24]	2020	Retrospective	China	244	150/94	1.2 (0.3–7.8)	109 (44.7%)

patients in the "50%≥5 years" group presenting with diarrhea than in the "50%<5 years" group (11% [95% CI: 6–19] vs 8% [95% CI: 5–13]; $P < .01$). However, the opposite result was also found for nausea or vomiting (7% [95% CI: 4–11] vs 9% [95% CI: 7–12]; $P < .01$). In the investigation of liver function, the incidence of increased AST was higher in the "50%≥5 years" group than in pediatric patients with COVID-19 in the "50%< 5 years" group (18% [95% CI: 9–36] vs 9% [95% CI: 5–15];

Table 2

Quality assessment of the included studies.

	Question*									Overall Rating	
Author	1	2	3	4	5	6	7	8	9	Reviewer 1	Reviewer 2
Sun	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Cai	Yes	Yes	NR	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Garazzino	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Qiu	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Su	Yes	Yes	NR	CD	NA	Yes	CD	NA	Yes	Fair	Fair
Xia	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Xu	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Lu	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Wang	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Bai	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Catherine	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Du	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Lin	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Zhang	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Mannheim	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Parri	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Ranabothu	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Shekerdemian	Yes	Yes	Yes	CD	NA	Yes	CD	Yes	Yes	Fair	Fair
Xiong	Yes	Yes	NR	CD	NA	Yes	CD	Yes	Yes	Fair	Fair

CD = cannot determine, NA = not applicable, NIH = National Institutes of Health, NR = not reported.

* The NIH Quality Assessment Tool for Case Series Studies poses 9 questions:

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?

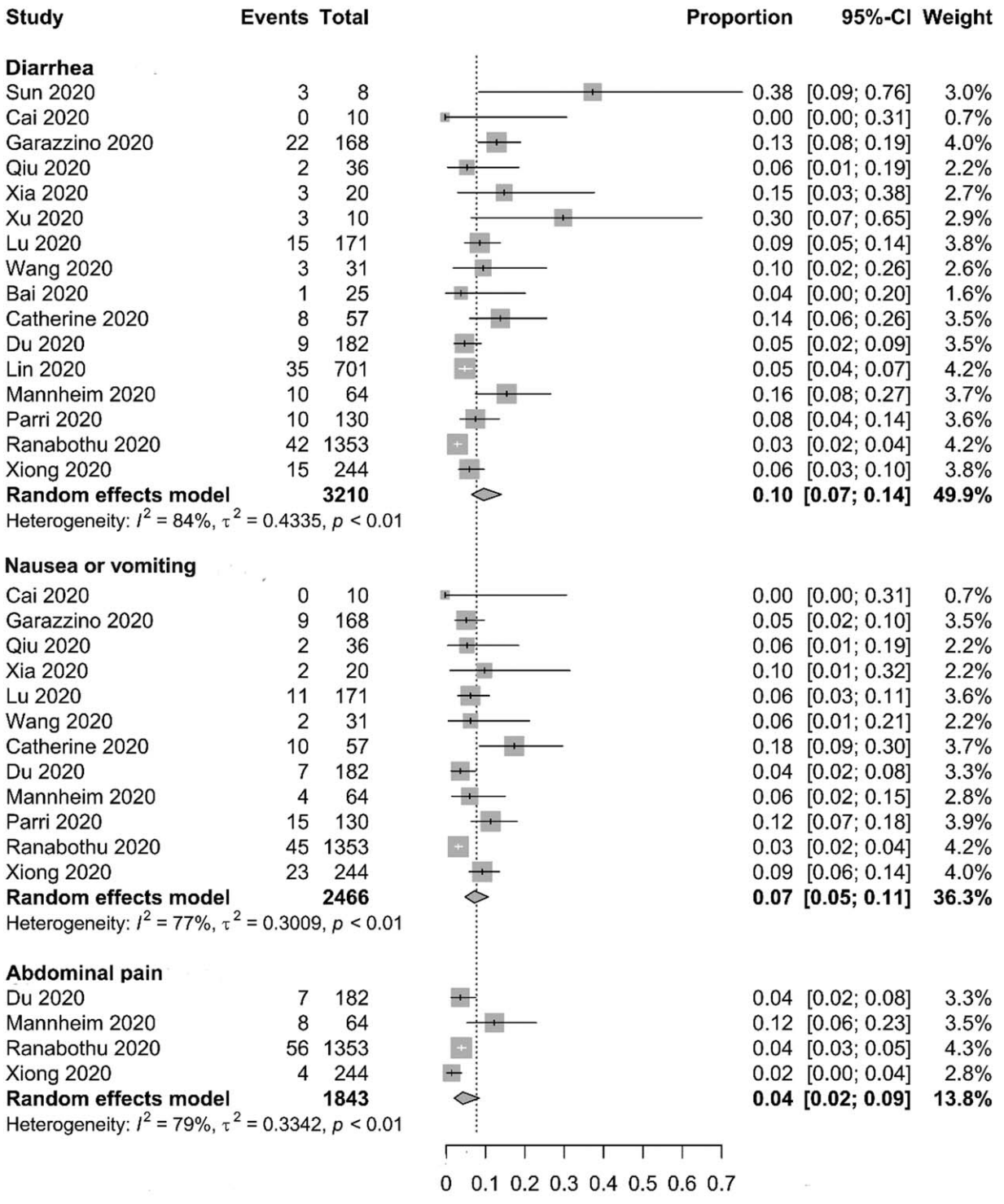

Figure 2. Pooled estimate of the prevalence of gastrointestinal symptoms in children with COVID-19.

P=.02), and the incidences of increased ALT (7%[95% CI: 4–11] vs 12%[95% CI: 4–38]; P=.08) and the rate of death (1%[95% CI: 0–10] vs 1%[95% CI: 1–4]; P=.05) were similar in the "0%≥5 years" group and the "50%<5 years" group (Table 3).

Additionally, we also studied the differences between Chinese children and European or American children. For GI symptoms, we found that the prevalence of diarrhea (11%[95% CI: 7–18] vs 8%[95% CI: 5–14]; P<.01) and nausea (or vomiting) (8%[95% CI: 6–10] vs 7%[95% CI: 4–16]; P<.01) was higher in China than in Europe and America. However, in the analysis of serological indicators of liver injury, we only found a higher proportion of patients with increased AST in China than in

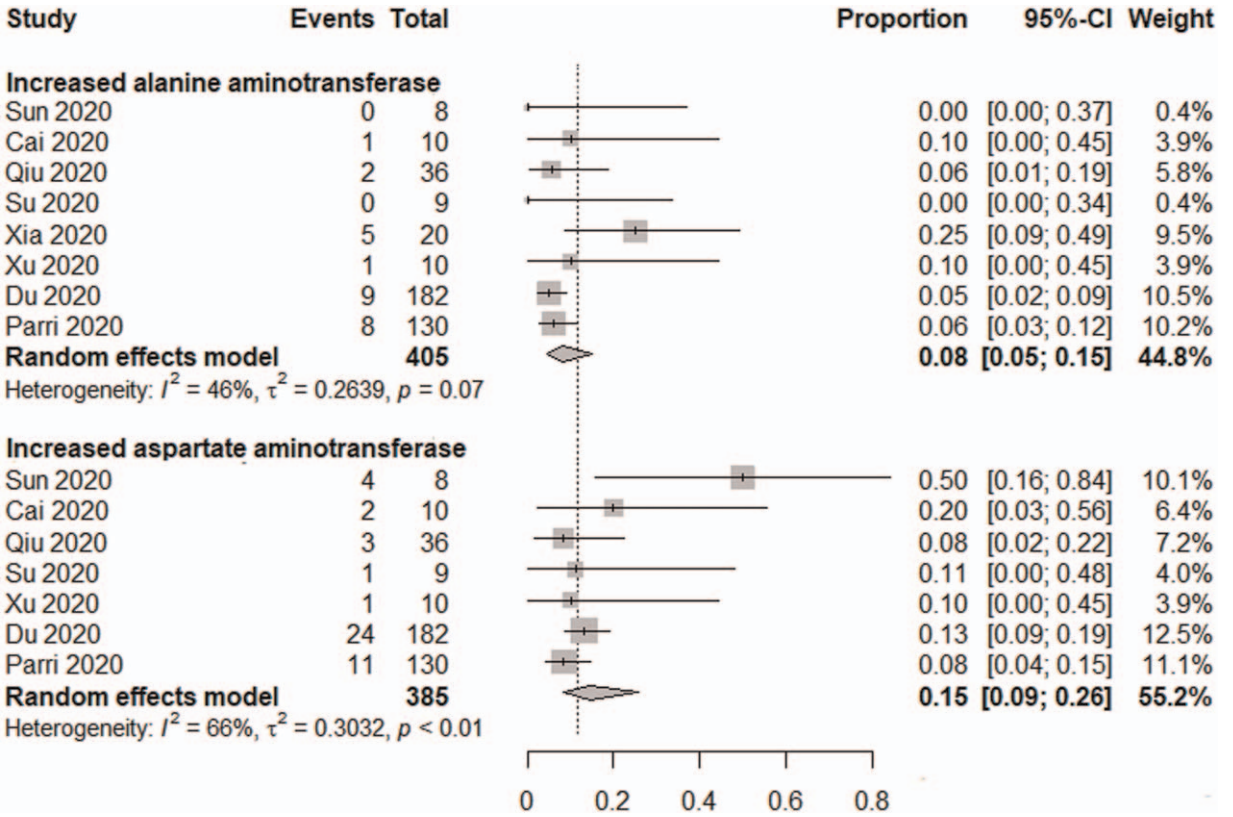

Figure 3. Pooled estimate of the incidence of liver injury in children with COVID-19.

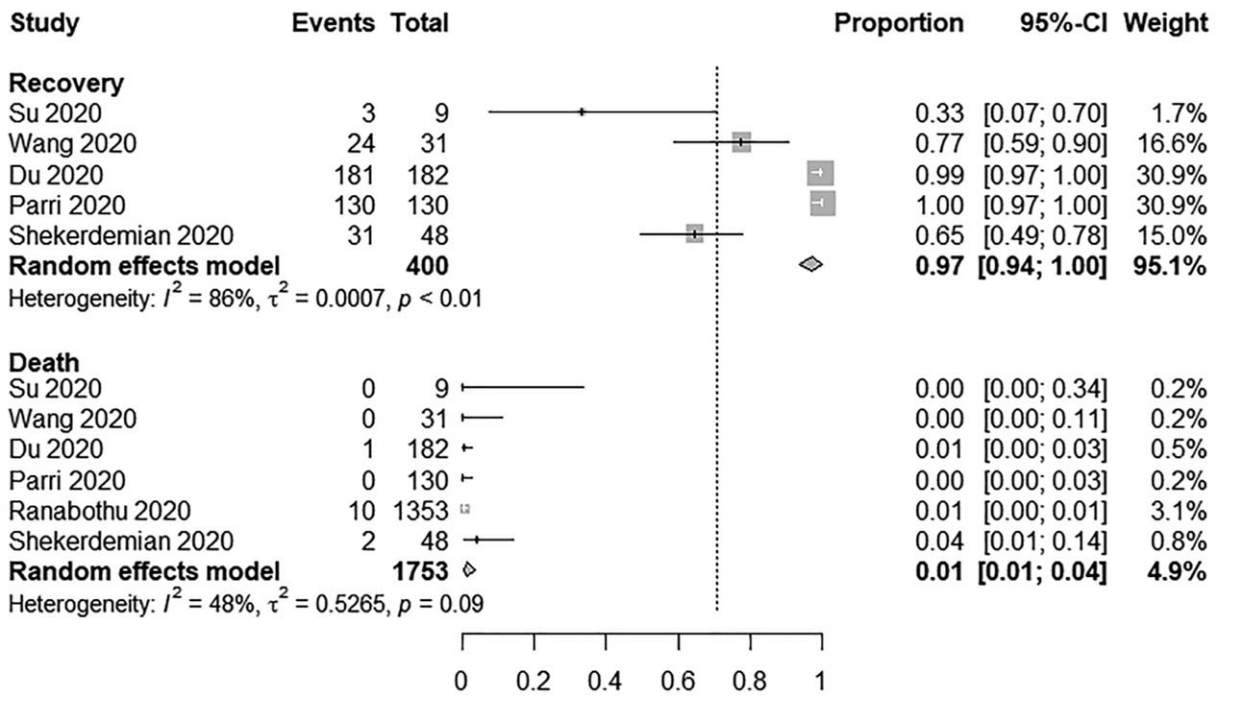

Figure 4. Pooled estimate of the prognosis of pediatric patients with COVID-19.

Table 3

Subgroup analysis of GI, liver function, and prognosis in children with COVID-19.

Factors	Subgroup	Study (n)	Rate (%)	95% CI		I^2	P
				LCI	UCI		
GI symptoms							
Diarrhea	Age=50%≥5 yr	11	11	6	19	87	<.01
	Age=50%<5 yr	5	8	5	13	75	
	China	10	11	7	18	70	<.01
	Europe and America	6	8	5	14	91	
Nausea or vomiting	Age=50%≥5 yr	8	7	4	11	78	<.01
	Age=50%<5 yr	4	9	7	12	18	
	China	7	8	6	10	0	<.01
	Europe and America	5	7	4	15	89	
Liver function							
ALT	Age=50%≥5 yr	5	7	4	11	0	.08
	Age=50%<5 yr	3	12	4	38	77	
	China	7	10	5	20	53	.05
	Europe and America	1	6	3	12	/	
AST	Age=50%≥5 yr	5	18	9	36	70	.02
	Age=50%<5 yr	2	9	5	15	0	
	China	6	17	9	32	62	.02
	Europe and America	1	8	5	15	/	
Prognosis							
Recovery	Age=50%≥5 yr	2	66	25	100	82	<.01
	Age=50%<5 yr	3	80	61	100	91	
	China	3	82	61	100	83	<.01
	Europe and America	2	82	54	100	94	
Death	Age=50%≥5 yr	2	1	0	10	43	.05
	Age=50%<5 yr	4	1	1	4	61	
	China	3	1	0	5	0	.05
	Europe and America	3	1	0	6	75	

Europe and America (17%[95% CI: 9–32] vs 8%[95% CI: 5–15]; $P=.02$), while the proportion of patients with increased ALT was similar in the 2 groups (10%[95% CI: 5–20] vs 6%[95% CI: 3–12]; $P=.05$). Moreover, we analyzed the prognosis of different age groups. Treatment measures for different age groups were mainly symptomatic and respiratory support, and there is no significant difference. Therefore, the prognosis, including recovery (82%[95% CI: 61–100] vs 82%[95% CI: 54–100]; $P<.01$) and death (1%[95% CI: 0–5] vs 1%[95% CI: 0–6]; $P=.05$), of pediatric patients was also similar in the 2 groups (Table 3).

3.4. Sensitivity analysis

Sensitivity analysis eliminates each included study one by one and performs a summary analysis on the remaining studies to assess whether a single included study has an excessive impact on the results of the entire meta-analysis. The results showed that none of the studies had an excessive impact on the results of the meta-analysis (see Figure S1–7, Supplemental Content, http://links.lww.com/MD/F868, http://links.lww.com/MD/F869, http://links.lww.com/MD/F870, http://links.lww.com/MD/F871, http://links.lww.com/MD/F872, http://links.lww.com/MD/F873, http://links.lww.com/MD/F874, which illustrates that none of the studies had an excessive impact on the results of the meta-analysis), indicating that the results of the remaining studies were stable and reliable.

3.5. Publication bias

The 2 funnel plots drawn in the study were basically symmetrical, and Egger test ($P=.055$; $P=.366$) based on the 2 funnel plots showed that there was no obvious publication bias in these studies (Fig. 5).

4. Discussion

Many studies have confirmed that the digestive system of patients with COVID-19 is significantly affected.[23,25] Our main focus was to analyze gastrointestinal symptoms and liver function changes in children with COVID-19. With the gradual deepening of research, it has become clear that COVID-19 can invade a variety of tissues in the human body, causing dysfunction of multiple organ systems and eventually even inducing fatal respiratory failure. ACE2 is an important target by which COVID-19 invades cells, and ACE2 is abundantly expressed in the gastrointestinal tract and liver; consequently, gastrointestinal involvement and liver injury in patients with COVID-19 are common. According to Ren Mao et al's meta-analysis, 4% (95% CI: 2–5; $I^2=74\%$) of patients experience significant gastrointestinal symptoms, and 3% (95% CI: 2–4; $I^2=57\%$) of patients exhibit liver damage. As the severity of the disease increases, digestive symptoms and liver damage become more pronounced.[4] It has been reported in the literature that, during the COVID-19 pandemic, some patients initially showed abdominal symptoms without fever or respiratory manifestations.[26] A multicenter study reported that there were 204 critically ill COVID-19 patients in 3 hospitals when the disease initially broke out in China. Among them, 103 (50%) patients had digestive symptoms as the main symptom, and 6 (3%) patients showed only digestive symptoms and no changes in

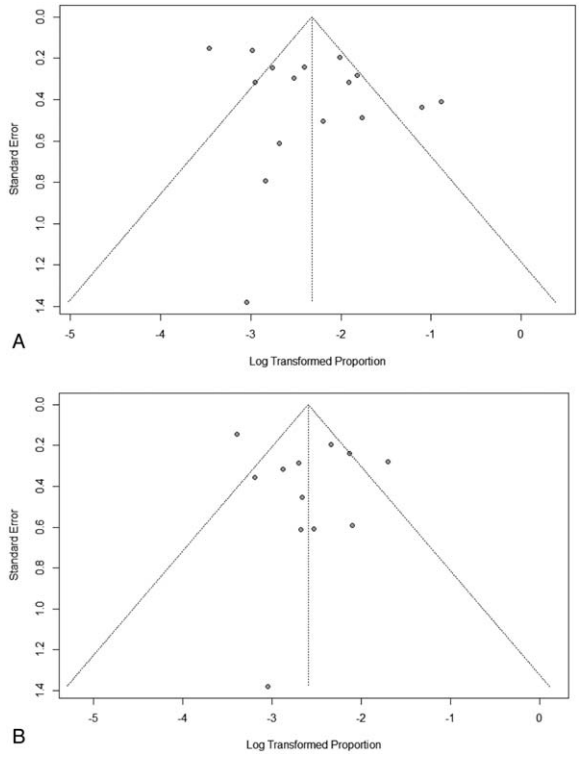

Figure 5. Funnel plot for publication bias for prevalence of diarrhea (A) and nausea or vomiting (B).

respiratory symptoms.[27] There are also reports showing that approximately 10% of patients have gastrointestinal symptoms without changes in respiratory function; thus, it is recommended that gastrointestinal symptoms be included earlier in the COVID-19 diagnostic standard.[4] In this article, we summarized 19 articles on children with COVID-19, and we conducted a meta-analysis of the incidence of gastrointestinal symptoms and changes in liver function involving 3907 patients, thereby providing a comprehensive view of digestive system performance in children with COVID-19.

The gastrointestinal symptoms of children with clinical digestive tract involvement generally involve vomiting or nausea, diarrhea, or abdominal pain.[21] Liver injury mainly includes increased ALT, AST, and total bilirubin levels.[21] According to our results, the incidences of vomiting or nausea, diarrhea, and abdominal pain were 7% (95% CI: 5–11; I2 = 77%), 10% (95% CI: 7–14; I2 = 84%), and 4% (95% CI: 2–9; $I^2 = 79\%$), respectively, and the incidences of increased ALT and AST levels were 8% (95% CI: 5–15; I2 = 46%) and 15% (95% CI: 9–26; I2 = 79%), respectively. These symptoms indicate that COVID-19 invades the gastrointestinal and liver tissues, causing gastrointestinal dysfunction and liver parenchymal cell damage. Although many studies suggest that the gastrointestinal symptoms in children with COVID-19 are mild or moderate, the period required for SARS-CoV-2 results to become negative in pediatric patients does not seem to be affected by the severity of the disease. Considering that the delayed removal of viral RNA in the feces of patients yields a potential risk of transmission, especially in rehabilitation patients, it is particularly important to pay attention to the diagnosis of COVID-19 in children and to standards for viral RNA negativity in asymptomatic patients.[7] It is worth noting that the gastrointestinal tract showed parenchymal organ changes during the pathological examination of adult cadavers. On the other hand, there have been reports of pediatric deaths, especially in infants and young children who are coinfected or have underlying congenital diseases.[21] However, whether children will show changes after gastrointestinal tract involvement needs to be explored via additional research. Most literature reports have shown that children infected with SARS-CoV-2 generally have mild symptoms or are not easily noticeable. Importantly, most of their infections come from intrafamily transmission because the existence of potentially asymptomatic or mild infections promotes further community transmission.[7]

Through a subgroup analysis of gastrointestinal involvement in children, we summarized the differences in age and regional factors in children's gastrointestinal involvement. We found that, compared with children younger than 5 years of age, children who were older than 5 years were more likely to show diarrhea symptoms (11% [95% CI: 6–19] versus 8% [95% CI: 5–13]]; $P < .01$). However, the opposite result was found for nausea or vomiting (7% 95% CI [95% CI: 4–11] vs 9% [95% CI: 7–12]; $P < .01$). In the investigation of liver function, the results showed that the incidence of increased AST was higher in the "50%≥5 years" group than in pediatric patients with COVID-19 in the "50%<5 years" group (18% [95% CI: 9–36] vs 9% [95% CI: 5–15]; $P = .02$). In the analysis of prognosis, no differences were found in age, country, or region. Additionally, we also studied the differences between Chinese and European children. We found that the gastrointestinal involvement of Chinese children is more serious than that of children in Europe and the United States. There may be many reasons for this phenomenon. First, the sequence and ease of SARS-CoV-2 transmission in different countries have shown significant differences, and there are differences in the abundance of ACE2 gene expression in different races.[5,28] Second, there are different treatment interventions in different countries or regions.[29] However, in general, all children with COVID-19 have a good prognosis, and they more often are asymptomatic or exhibit mild symptoms. Because many studies have reported that children with COVID-19 possibly have a longer period of viral positivity, we cannot ignore the potential risk of disease transmission from children with COVID-19.

This meta-analysis also has several limitations. First, evaluation of the methodological quality indicated that the quality of the evaluated research literature was relatively low. Second, due to insufficient data reported in the original publication, we were unable to assess the impact of other factors (such as sex and comorbidities) on the diagnosis of gastrointestinal symptoms and changes in liver function. Third, the severity of COVID-19 varied across studies, which may explain the heterogeneity of this meta-analysis. The heterogeneity of gastrointestinal symptoms was high, while the heterogeneity of liver function was moderate. Finally, due to the disease characteristics of COVID-19, the sample size in most of the studies included in this meta-analysis was not large, which may have also led to some bias in the results.

5. Conclusion

In conclusion, our review found that digestive system symptoms and liver damage in children are not uncommon but are often overlooked. Emerging studies have reported that gastrointestinal involvement in children includes vomiting or nausea, diarrhea, abdominal pain, and abnormalities of liver cell-related enzymes (ALT, AST), which are similar to the symptoms of gastrointesti-

nal involvement in adults. However, we also found that different ages, countries, and regions are associated with differences in pediatric digestive tract involvement and liver injury. Therefore, more clinical and experimental research is still needed to further reveal the role of digestive system involvement in COVID-19 progression and its underlying mechanisms.

Author contributions

JW wrote the manuscript, XY conceived the manuscript. All authors have read and approved the final manuscript.
Conceptualization: Jiajia Wang.
Writing – original draft: Jiajia Wang.
Writing – review & editing: Xiaofeng Yuan.

References

[1] Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109: 102433.
[2] Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.
[3] Gao X, Jin Z, Tan X, et al. Hyperbranched poly (beta-amino ester) based polyplex nanopaticles for delivery of CRISPR/Cas9 system and treatment of HPV infection associated cervical cancer. J Control Release 2020; 321:654–68.
[4] Mao R, Qiu Y, He J-S, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:667–78.
[5] Parri N, Magista AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. Eur J Pediatr 2020;179:1315–23.
[6] Su L, Ma X, Yu H, et al. The different clinical characteristics of corona virus disease cases between children and their families in China—the character of children with COVID-19. Emerg Microbes Infect 2020; 9:707–13.
[7] Qiu H, Wu J, Hong L, et al. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis 2020;20:689–96.
[8] Conti P, Stellin L, Caraffa A, et al. Advances in mast cell activation by IL-1 and IL-33 in Sjogren's Syndrome: promising inhibitory effect of IL-37. Int J Mol Sci 2020;21:4297.
[9] Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. World J Pediatr 2020;16:251–9.
[10] Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis 2020;71:1547–51.
[11] Garazzino S, Montagnani C, Dona D, et al. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill 2020;25:2000600.
[12] Xia W, Shao J, Guo Y, et al. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. Pediatr Pulmonol 2020;55:1169–74.
[13] Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nat Med 2020;26:502–5.
[14] Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663–5.
[15] Wang D, Ju XL, Xie F, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. Zhonghua Er Ke Za Zhi 2020;58:269–74.
[16] Bai K, Liu W, Liu C, et al. Clinical analysis of 25 COVID-19 infections in children. Pediatr Infect Dis J 2020;39:e100–3.
[17] Foster CE, Moulton EA, Munoz FM, et al. Coronavirus Disease 2019 in children cared for at Texas Children's Hospital: initial clinical characteristics and outcomes. J Pediatric Infect Dis Soc 2020;9: 373–7.
[18] Du H, Dong X, Zhang JJ, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. Allergy 2021;76:510–32.
[19] Lin EE, Blumberg TJ, Adler AC, et al. Incidence of COVID-19 in pediatric surgical patients among 3 US Children's Hospitals. JAMA Surg 2020;155:775–7.
[20] Zhang B, Liu S, Zhang J, et al. Children hospitalized for coronavirus disease 2019 (COVID-19): a multicenter retrospective descriptive study. J Infect 2020;81:e74–5.
[21] Mannheim J, Gretsch S, Layden JE, et al. Characteristics of hospitalized pediatric COVID-19 cases in Chicago, Illinois, March– April 2020. J Pediatric Infect Dis Soc 2020;9:519–22.
[22] Ranabothu S, Onteddu S, Nalleballe K, et al. Spectrum of COVID-19 in Children. Acta Paediatr 2020;109:1899–900.
[23] Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with Coronavirus Disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr 2020;174:868–73.
[24] Xiong XL, Wong KK, Chi SQ, et al. Comparative study of the clinical characteristics and epidemiological trend of 244 COVID-19 infected children with or without GI symptoms. Gut 2021;70:436–8.
[25] Zhou Z, Zhao N, Shu Y, et al. Effect of gastrointestinal symptoms in patients with COVID-19. Gastroenterology 2020;158:2294–7.
[26] Song Y, Liu P, Shi XL, et al. SARS-CoV-2 induced diarrhoea as onset symptom in patient with COVID-19. Gut 2020;69:1143–4.
[27] Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–73.
[28] Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: implications for risk, severity, and outcomes. FASEB J 2020;34:8787–95.
[29] Rubin EJ, Baden LR, Morrissey S. Audio interview: making decisions about Covid-19 testing and treatment for your patients. N Engl J Med 2020;382:e25.