Digestive system symptoms and function in children with COVID-19
A meta-analysis
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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; I² = 84%), that of nausea or vomiting was 7% (95% CI: 5–11; I² = 77%), and that of abdominal pain was 4% (95% CI: 2–9; I² = 79%). In addition, the pooled incidence of increased alanine aminotransferase was 8% (95% CI: 5–15; I² = 46%), and the pooled incidence of increased aspartate aminotransferase was 6% (95% CI: 1–4; I² = 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
sensitivities of COVID-19 in children are not uncommon. Gastrointestinal symptoms have significant in the early diagnosis of children and the guidance of treatment. 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; review, animal experiments and case reports; and studies without full text, studies with incomplete information, and studies from which data extraction was impossible.

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. 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 $P \leq 0.1$ and $I^2 \leq 50\%$, this indicated that the study had homogeneity, and the fixed effect model was used for combined analysis. If $P < 0.1$ 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.

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
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
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 1
Baseline characteristics of the included studies.

| Author   | Year | Research type | Study area | Number of patients | Gender (M/F) | Age (Mean ± SD) | Age < 5 yr, n (%) |
|----------|------|---------------|------------|--------------------|--------------|-----------------|------------------|
| Sun[9]   | 2020 | Retrospective | China      | 8                  | 6/2          | 8.0 (1.7–15.0)  | 5 (40.0%)        |
| Cai[10]  | 2020 | Retrospective | China      | 10                 | 4/6          | 6.2 (3.3–10.9)  | 3 (30.0%)        |
| Garazzino[11] | 2020 | Retrospective | Italy      | 168                | 94/74        | 2.3 (0.3–9.6)   | 104 (61.9%)      |
| Qiu[12]  | 2020 | Retrospective | China      | 36                 | 23/13        | 8.3 (1.0–16.0)  | 10 (28.0%)       |
| Su[13]   | 2020 | Retrospective | China      | 9                  | 3/9          | 3.5 (0.9–9.8)   | 5 (55.6%)        |
| Xia[14]  | 2020 | Retrospective | China      | 20                 | 13/7         | 2.1 (1.0–14.6)  | 14 (70.0%)       |
| Xu[15]   | 2020 | Retrospective | China      | 10                 | 6/4          | 6.0 (1.7–15.0)  | 4 (40.0%)        |
| Lu[16]   | 2020 | Retrospective | China      | 171                | 104/67       | 6.7 (1.0–15.0)  | 71 (41.5%)       |
| Wang[17] | 2020 | Retrospective | China      | 31                 | 15/16        | 7.1 (0.5–17.0)  | <50%             |
| Bai[18]  | 2020 | Retrospective | China      | 25                 | 14/11        | 11.0 (6.5–14.5) | <50%             |
| Catherine[19] | 2020 | Retrospective | USA        | 57                 | 32/25        | 10.7 (0.1–20.2) | <50%             |
| Du[20]   | 2020 | Retrospective | USA        | 182                | 120/62       | 6.0 (0.0–15.0)  | 88 (58.4%)       |
| Lin[21]  | 2020 | Retrospective | USA        | 1295               | 716/479      | 7.35±5.99       | <50%             |
| Zhang[22] | 2020 | Retrospective | China      | 46                 | 29/17        | 8.0 (4.0–14.0)  | 16 (35.0%)       |
| Mannheim[23] | 2020 | Retrospective | USA        | 64                 | 28/36        | 11.0 (7.0–16.0) | 15 (23.0%)       |
| Parri[24] | 2020 | Retrospective | Italy      | 130                | 73/57        | 6.0 (0.0–11.0)  | 41 (31.5%)       |
| Ranabothu[25] | 2020 | Retrospective | USA        | 1353               | 694/659      | /                | 439 (32.4%)      |
| Shekerdemian[26] | 2020 | Retrospective | USA        | 48                 | 25/23        | 13.0 (4.2–16.6) | 14 (30.0%)       |
| Xiong[27] | 2020 | Retrospective | China      | 244                | 150/94       | 1.2 (0.3–7.8)   | 109 (44.7%)      |

### Table 2
Quality assessment of the included studies.

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

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

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?
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 “≥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.
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; I² = 74%) of patients experience significant gastrointestinal symptoms, and 3% (95% CI: 2–4; I² = 57%) of patients exhibit liver damage. As the severity of the disease increases, digestive symptoms and liver damage become more pronounced.[19] 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...
respiratory symptoms.\textsuperscript{[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.\textsuperscript{[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 changes in liver function involving 3907 patients, thereby providing a comprehensive view of digestive system performance changes in liver function. Third, the severity of COVID-19 varied across different countries or regions.\textsuperscript{[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 gastrointestinal involvement.
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.

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