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Epidemiological features of coronavirus disease 2019 in children: a meta-analysis

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Abstract. – OBJECTIVE: Many studies have been published recently on the characteristics of the clinical manifestations of COVID-19 in children. The quality scores of literature are different, and the incidence of clinical manifestations and laboratory tests results vary greatly. Therefore, a systematic retrospective meta-analysis is needed to determine the incidence of the clinical manifestations of COVID-19 in children.

MATERIALS AND METHODS: Data from databases, such as PubMed, Web of science, EMBASE, Johns Hopkins University, and Chinese databases were analysed from January 31, 2020 to October 20, 2020. High-quality articles were selected for analysis based on a quality standard score. A meta-analysis of random effects was used to determine the prevalence of comorbidities and subgroup meta-analysis to examine the changes in the estimated prevalence in different subgroups.

RESULTS: Seventy-one articles involving 11,671 children were included in the study. The incidence of fever, respiratory symptoms, gastrointestinal symptoms, asymptomatic patients, nervous system symptoms, and chest tightness was 55.8%, 56.8%, 14.4%, 21.1%, 6.7%, and 6.1%, respectively. The incidence of multisystem inflammatory syndrome was 6.2%. Laboratory examination results showed that lymphocyte decreased in 12% and leukocytes decreased in 8.8% of patients, whereas white blood cells increased in 7.8% of patients. Imaging showed abnormalities in 66.5%, and ground-glass opacities were observed in 36.9% patients. Epidemiological history was present in 85.2% cases; severe disease rate was 3.33%. The mortality rate was 0.28%.

CONCLUSIONS: The clinical symptoms of COVID-19 in children are mild, and laboratory indicators and imaging manifestations are atypical. While screening children for COVID-19, in addition to assessing patients for symptoms as the first step of screening, the epidemiological history of patients should be obtained.

Key Words:
2019-nCoV, COVID-19, SARS-CoV-2, Coronavirus disease 2019, Children.

Introduction

The emergence of coronavirus disease 2019 (COVID-19) was first reported at the end of 2019. The disease rapidly spread worldwide in a few months and was declared a global pandemic by WHO in March 2020[1]. In the early stage of the epidemic, the reported number of children who were infected was relatively small, and children were considered not to be easily infected[2]. However, as time progressed, people began to pay attention to the rising number of cases in children[3,4] with a few reports of severe cases[5]. In most adult patients, the clinical manifestations included fever, cough, and fatigue, while most of the patients who died were middle-aged and elderly patients with more than one chronic underlying disease, such as cardiovascular or cerebrovascular disease or diabetes. It was reported that the longer it took to diagnose COVID-19 (more than 5 days from onset to diagnosis time), the higher the risk of death[6]. In adult patients with COVID-19, laboratory tests showed leukopenia, especially lymphopenia, and imaging tests showed ground-glass opacities[7]. Most children had relatively mild clinical symptoms. Common clinical manifestations in children included fever, dry cough, and fatigue and only a few children had upper respiratory symptoms, such as nasal congestion, runny nose, and sore throat. Some infected newborns and children had atypical symptoms, such as gastrointestinal problems including vomiting, diarrhoea, or only poor appetite and shortness of

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breath[8]. Laboratory and imaging tests in children were less sensitive and less specific than that in adults[9]. Our study, therefore, aimed to identify the clinical features of children with COVID-19 in order to help clinicians diagnose children suspected of having COVID-19 more easily and treat them.

Materials and Methods

Guidelines and Registry

This study is reported in accordance with the 2009 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (**Supplementary Table I** PRISMA Checklist). This systematic review and meta-analysis was registered in PROSPERO-The International Prospective Register of Systemic Reviews (CRD42020202211).

Data Collection

Computer retrieval of data from PubMed, EMBASE, Web of Science, Johns Hopkins University published data, as well as data from Chinese database CNKI, Wanfang, Chongqing Weipu data was conducted to collect literature reporting the characteristics of COVID-19 positive children. The retrieval time for data was from January 31, 2020, to October 20, 2020. Simultaneously, online database retrieval and manual retrieval were conducted, and the references included in the literature were also traced. Subject words and free words were used in the retrieval, and adjustments were made according to the characteristics of different databases. Data retrieval was not limited to any language or country. For the PubMed search strategy, three search categories were used in combination as follows:

#1 AND #2 AND #3, where #1 = (children) OR (child) OR (kid) OR (paediatric), #2 = (clinical feature) OR (epidemiology) OR (characteristics), and #3 = (2019-nCoV) OR (COVID-19) OR (SARS-CoV-2) OR (Corona Virus Disease 2019).

Literature Screening and Data Extraction

Two researchers independently searched and screened the literature, collected and cross-checked the data. If there was any dispute, it was discussed and clarified with consultation from the third researcher.

The inclusion criteria were as follows: (1) study type: cohort study, case-control study, and case analysis; (2) participants: children diagnosed with COVID-19; (3) observation index: the clinical manifestations of the patients included fever, cough, asymptomatic patients, imaging laboratory examination, severe cases, and deaths.

The exclusion criteria were as follows: (1) research without child description; (2) short case reports; (3) incomplete or missing analysis data and where no data could be obtained by contacting authors.

Quality Evaluation of the Included Studies

This retrospective study adhered to the National Institute for Clinical excellence guidelines for quality evaluation. The evaluation items were as follows: (1) in the case series, cases from medical institutions of different levels and various research centres were included; (2) the research hypothesis or purpose was clearly stated; (3) clear reports were included in the exclusion criteria; (4) measurements were clearly defined; (5) the collected data achieved the expected purpose; (6) patient recruitment period was clearly defined; (7) the main findings were clearly described, and (8) results were analysed and reported in layers. One point was awarded for each item (maximum 8 points), and a total score ≥ 4 indicating high-quality research[10]. Two researchers independently evaluated the quality and cross-checked the results.

Statistical Analysis

Statistical analyses were conducted using the Meta 4.11-0 Package in R Software Version 3.6.3. Before meta-analysis, the conversion of the original rate that conforms to a normal distribution was carried out first. The meta-analysis was carried out on the normal distribution or mode closest to the state distribution. A random- or fixed-effects model was selected according to heterogeneity: if $p>0.1$ and $I^2 \leq 50\%$, a fixed model was used, and if $p<0.1$ and $I^2>50\%$, the study was considered to have heterogeneity, and a random-effects model was used. According to the sample size of each independent study, different weightage was given, and the effective rate of each independent sample was combined to calculate the incidence rate and 95% confidence interval (CI). To explore heterogeneity, we performed subgroup analyses based on the location (region) and sample size (<50, ≥50).

Finally, a funnel graph was made, and the publication offset was statistically tested using the Egger method.

Ethics

As this is a systematic review, ethical approval was not required.

Results

Literature Screening Process and Results

A total of 2,742 relevant studies were initially selected. Subsequently 1,359 duplicates were deleted from these, and out of the remaining, 1,162 were deleted after reading titles and abstracts. A total of 71 studies[11-81] were selected after careful screening. The included studies involved 11,671 paediatric patients. The male to female ratio was 1.14:1. The literature screening process and results are shown in Figure 1. The characteristics of the included studies are shown in **Supplementary Table II**.

Basic Characteristics and Quality Evaluation Results of the Included Studies

The quality characteristics of included studies were 4-8 points, indicating they were high-quality studies (≥4 points; **Supplementary Table III**).

Meta-Analysis Results

The meta-analysis results have been reported in detail in Table I.

Clinical Manifestations

The incidence of fever, respiratory symptoms, gastrointestinal symptoms, asymptomatic patients, nervous system symptoms, and chest tightness was 55.8% (50.3%-61.3%), 56.8% (95%CI: 0.9%-62.5%), 14.4% (11.8%-17.2%), 21.1% (16.9%-25.8%), 6.7% (4.6%-9.2%), and 6.1% (3.9%-8.6%), respectively. The incidence of multisystem inflammatory syndrome (MIS-C) was 6.2% (2.8%-10.7%).

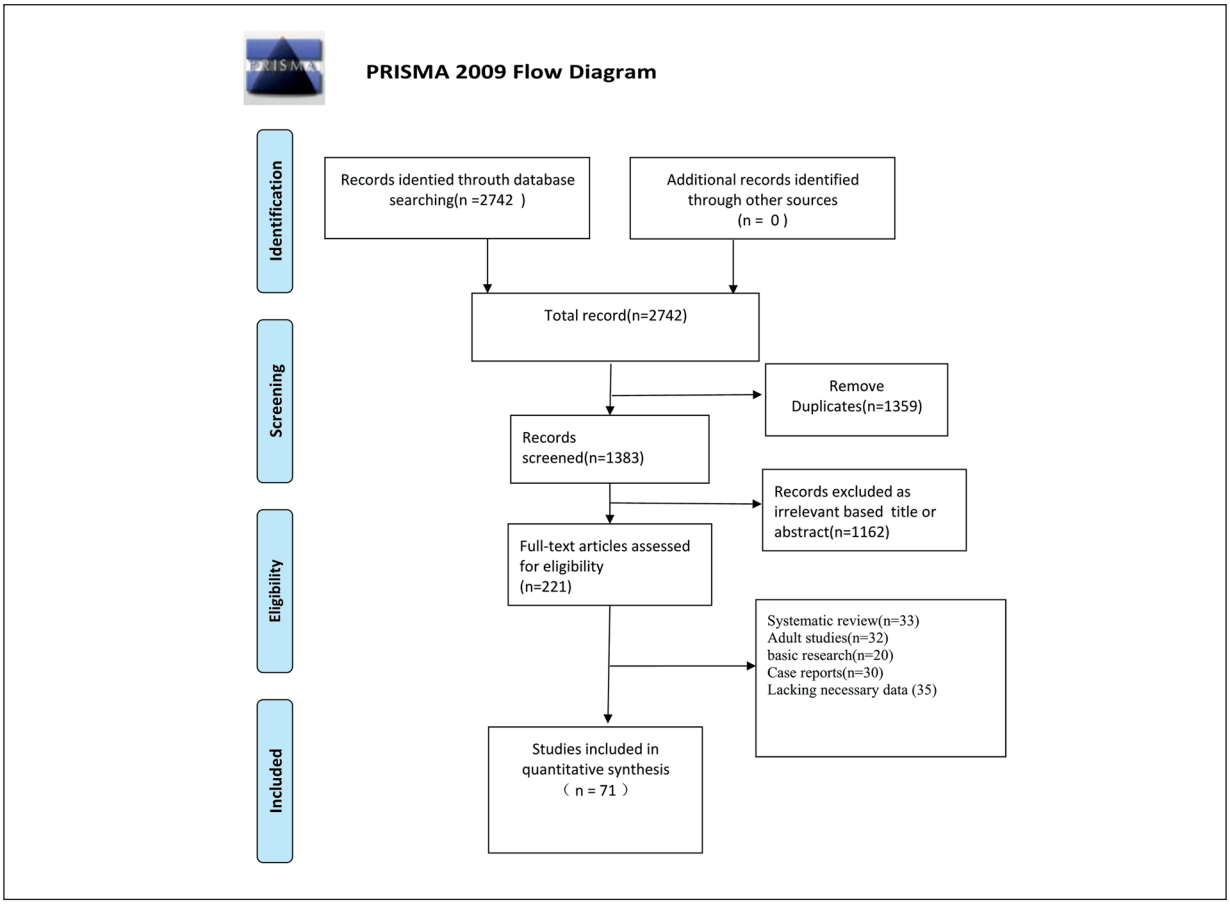

Figure 1. The flowchart of study selection.

Table I. Meta-analysis results.

Outcome indicators	Number of included studies	Sample size	Heterogeneity			Effect of model	Meta-analysis results
			p-values	I^2	t^2		R% (95% CI)
Clinical feature							
Asymptomatic	49	7664	< 0.01	0.027	92.7%	Random	21.1% (16.9%-25.8%)
Fever	68	7153	< 0.01	0.046	94.8%	Random	55.8% (50.3-61.3%)
Respiratory symptoms	66	6758	< 0.01	0.050	95.0%	Random	56.8% (50.9%-62.5%)
Gastrointestinal symptoms	60	6817	< 0.01	0.016	87.3%	Random	14.4% (11.8%-17.2%)
Neurological symptoms	45	5792	< 0.01	0.018	89.7%	Random	6.7% (4.6%-9.2%)
Chest pain, chest tightness and Fatigue	47	4999	< 0.01	0.022	89.4%	Random	6.1% (3.9%-8.6%)
Laboratory results							
Leukocytosis	28	1099	< 0.01	0.022	76.3%	Random	7.8% (4.6%-11.8%)
Leukopenia	32	1606	< 0.01	0.027	83.9%	Random	8.8% (5.4%-13.0%)
Lymphocytosis	35	2473	< 0.01	0.045	92.2%	Random	12.0% (7.4%-17.5%)
CRP	27	1033	< 0.01	0.049	87.7%	Random	22.2% (15.0%-30.5%)
ESR	8	254	< 0.01	0.132	94.1%	Random	20.5% (4.3%-44.6%)
D - dimer	15	769	< 0.01	0.013	70.5%	Random	11.4% (7.1%-16.7%)
PCT	18	902	< 0.01	0.092	94.4%	Random	17.5% (7.8%-30%)
LDH	16	646	< 0.01	0.048	87.4%	Random	32.3% (21.7%-44.0%)
IL-6	6	320	< 0.01	0.019	75.4%	Random	11.0% (4.1%-20.6%)
TNF-α	4	255	0.04	0.190	39.0%	Fixed	4.4% (2.2%-7.5%)
IFN-γ	v3	231	0.04	0.013	68.3%	Random	5.0% (2.6-8.2%)
ALT	22	1080	< 0.01	0.026	83.2%	Random	6.9% (3.5%-11.5%)
CK-MB	22	1197	< 0.01	0.067	93.3%	Random	13.5% (6.6%-22.4%)
Ferritin	5	158	< 0.01	0.035	78.8%	Random	5.6% (0.2%-17.6%)
BUN,	12	2114	0.03	0.020	49.7%	Fixed	1.2% (0.8%-1.7%)
Cr	12	2136	< 0.01	0.040	63.0%	Random	1.6% (0.6%-3.2%)
MIS-C	10	2246	< 0.01	0.014	92.0%	Random	6.2% (2.8-10.7%)
Imaging examination							
Imaging abnormality	41	1678	< 0.01	0.029	82.4%	Random	66.5% (60.5%-72.2%)
GGO	35	1407	< 0.01	0.028	81.7%	Random	36.9% (30.6%-43.4%)
Other results							
Epidemiological exposure	50	3147	< 0.01	0.056	93.1%	Random	85.2% (79.8%-89.9%)
Severe case	63	10340	< 0.01	0.019	91.6%	Random	3.33% (2.03%-4.94%)
Mortality	67	11309	0.05	0	22.7%	Fixed	0.28% (0.19%-0.39%)

Abbreviations: ALT, alanine aminotransferase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; LDH, lactate dehydrogenase; MIS-C multisystem inflammatory syndrome in children; IL-6, interleukin-6; PCT, Procalcitonin; ESR, Erythrocyte sedimentation rate; TNF-α,tumor necrosis factor α; IFN-γ, Interferon γ; Blood urea nitrogen; Cr, creatinine; GGO, Ground-glass opacities.

Laboratory Examinations

Lymphocyte count decreased in 12% (7.4%-17.5%) and leukocyte count decreased in 8.8% (5.4%-13.0%) patients. The white blood cell count increased in 7.8% (4.6%-11.8%) patients. Other markers such as alanine aminotransfease (ALT) 6.9% (3.5%-11.5%), creatine kinase-MB (CK-MB) 13.5% (6.6%-22.4%), blood urea nitrogen (BUN)1.2% (0.8%-1.7%), and creatinine (Cr) 1.6% (0.6%-3.2%) were also elevated. Elevated inflammatory markers C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), interleukin-6, Procalcitonin (PCT), D-dimer, Interferon-**γ** (IFN-γ), and tumor necrosis factor-**α** (TNF-α), Erythrocyte sedimentation rate (ESR), were 22.2% (15.0%-30.5%), 5.6% (0.2%-17.6%), 32.3% (21.7%-44.0%), 11.0% (7.1%-16.7%), 17.5% (7.8%-30%), 11.4% (7.1%-16.7%), 5.0% (2.6-8.2%), 4.4% (2.2%-7.5%), and 20.5% (4.3%-44.6%), respectively.

Imaging

Imaging abnormality rate was 66.5% (60.5%-72.2%), and ground-glass appearance was present in 36.9% (30.6%-43.4%) of cases.

Severe Cases and Mortality Rates

Of the included patients, 3.33% (2.03%-4.94%) were severe cases. The mortality rate was 0.28% (0.19%-0.39%).

Subgroup Analysis

In this study, except for mortality rates, other factors had apparent heterogeneity (I^2, 49.7%-95.0%). To explore the source of heterogeneity, the subjects were classified according to country (China, United States, Europe, and other countries) and sample size (<50, or ≥50), and further grouped by individual symptoms, such as fever, gastrointestinal symptoms, respiratory symptoms, and asymptomatic cases. The subgroup analysis results were consistent with the overall results, and there was no significant difference between the heterogeneity of each subgroup and overall heterogeneity, indicating that the region and sample size of the study were not the primary sources of heterogeneity (Table II).

Sensitivity Analysis

We performed a sensitivity analysis to investigate the influence of each individual study on the overall summary odds ratio by omitting each study turn by turn and re-estimating the summary odds ratio. The results did not change significantly, indicating that the observations were relatively stable (Figure 2).

Publication Bias

The meta-analysis of the observed indicators of the number of patients with fever produced funnel plots, and the results showed that the distribution of the left and right distribution symmetry was not good (Figure 3). The *p*-values checked by Egger's regression test were 0.013, indicating that publication bias may exist.

Discussion

Clinical Manifestations

Based on the clinical characteristics of the existing paediatric cases, children with COVID-19 can be divided into five clinical types: asymptomatic, mild, common, severe, and critically severe infections[8]. Most COVID-19 positive

Table II. Results of subgroup analysis.

Outcome indicators	Number of included studies	Sample size	Heterogeneity			Effect of model	Meta-analysis results
			p-values	I^2	t^2		R% (95% CI)
Fever							
China	33	1349	< 0.01	69.1%	0.015	Random	48.6% (43.2%-54.2%)
US	10	2535	< 0.01	97.8%	0.059	Random	59.5% (43.9%-74.1%)
Europe	15	1851	< 0.01	95.7%	0.05	Random	60.4% (48.7%-71.5%)
other countries	8	1023	< 0.01	95.9%	0.07	Random	70.1% (51.4%- 85.9%)
N < 50	39	867	< 0.01	78.1%	0.04	Random	59.7% (52.4%-66.7%)
N ≥ 50	29	6282	< 0.01	97.40%	0.045	Random	51.7% (43.8%- 59.6%)
Gastrointestinal symptoms							
China	30	1308	< 0.01	70.4%	0.014	Random	7.8% (5.1%-11.2%)
US	8	2470	< 0.01	95.7%	0.025	Random	20.5% (12.2%-30.4%)
Europe	14	1807	< 0.01	83.0%	0.01	Random	17.9% (13.4%-22.9%)
other countries	8	1232	< 0.01	88.6%	0.017	Random	24.1% (16.1%- 33.3%)
N < 50	32	702	< 0.01	77.8%	0.04	Random	12.6% (7.8%-18.5%)
N ≥ 50	28	6115	< 0.01	91.7%	0.013	Random	15.2% (12.0%- 18.6%)
Respiratory symptoms							
China	33	1349	< 0.01	83.4%	0.032	Random	51.5% (44.3%-58.7%)
US	10	2535	< 0.01	98.0%	0.066	Random	65.8% (49.6%-80.2%)
Europe	15	1851	< 0.01	96.8%	0.066	Random	60.4% (46.9%-73.1%)
other countries	8	1023	< 0.01	95.1%	0.059	Random	57.5% (39.8%-74.4%)
N < 50	39	867	< 0.01	82.1%	0.052	Random	56.9% (48.8%- 64.7%)
N ≥ 50	27	5891	< 0.01	97.6%	0.050	Random	56.6% (47.9%-65.0%)
Asymptomatic							
China	28	1228	< 0.01	84.7%	0.034	Random	21.7% (15.5%-28.6%)
US	3	507	0.08	60.6%	0.005	Random	10.1% (4.6%-17.5%)
Europe	12	5533	< 0.01	94.6%	0.017	Random	19.9% (13.9%-26.8%)
other countries	6	396	< 0.01	96.4%	0.116	Random	27.3% (6.9%-54.6%)
N < 50	29	575	< 0.01	73.6%	0.035	Random	17.7% (11.9%-24.4%)
N ≥ 50	20	7664	< 0.01	96.5%	0.027	Random	24.8% (18.6%-31.5%)

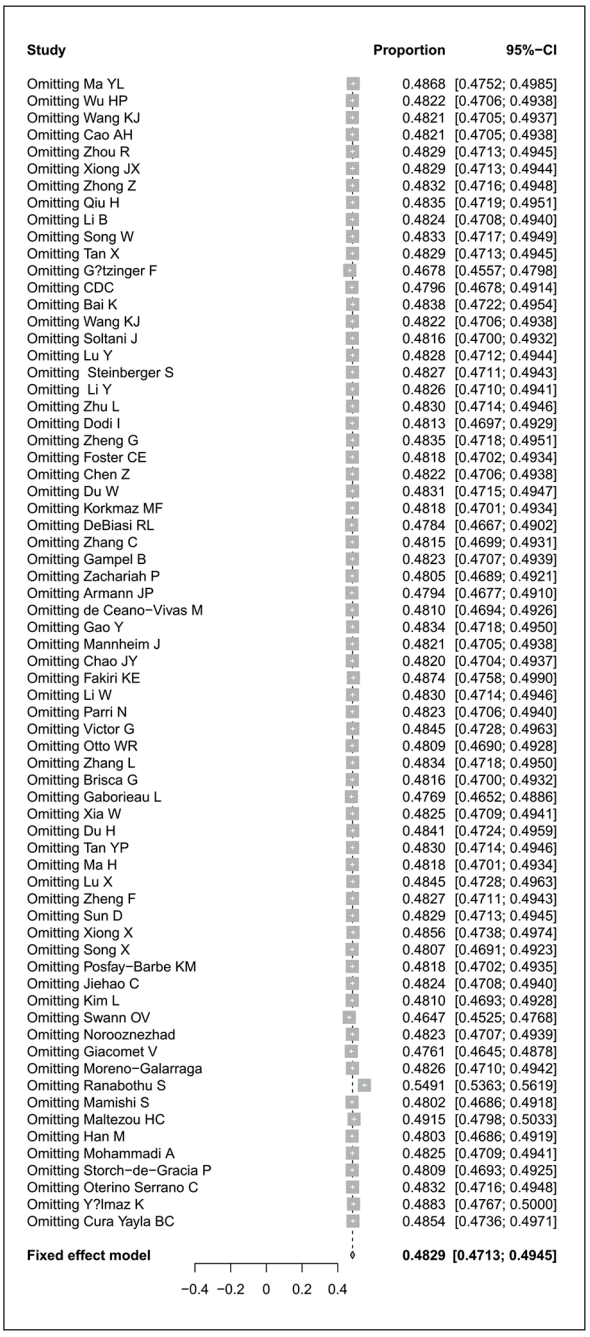

Figure 2. Sensitivity analysis of fever factors.

children were in the mild category. Fever and cough were the most common clinical symptoms in adults. A meta-analysis of adults from 43 studies involving 3,600 patients were included. Among these patients, fever (83.3% [95% CI, 78.4%-87.7%]), cough (60.3% [95% CI, 54.2%-66.3%]), and fatigue (38.0% [95% CI, 29.8%-46.5%]) were the most common clinical

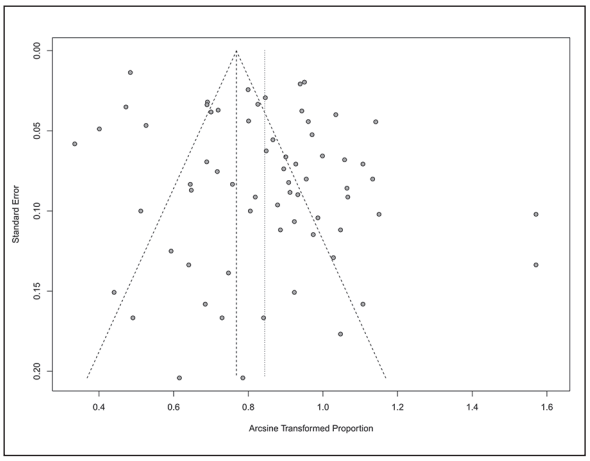

Figure 3. Funnel plot of publication bias of fever factors.

symptoms[82]. Compared with adults, this study found that the incidence of fever among children was 55.8% (50.3%-61.3%), the incidence of respiratory symptoms was 56.8% (50.9%-62.5%), and the incidence of chest tightness was 6.1% (3.9%-8.6%). In general, the clinical manifestations in children, especially the symptoms of fatigue, were not typical, which may be due to children's inability to express symptoms in words. As for the incidence of gastrointestinal symptoms[83], a study of 204 adults from Wuhan, China, found that 103 patients (50.5%) reported a digestive symptom, including lack of appetite in 81 (78.6%) cases and diarrhoea in 35 (34%) cases. However, the incidence of gastrointestinal symptoms in children in this study was 14.4%, which was much lower than that in adults. Han et al[84] reported that 19.4% of adults had diarrhea as the first symptom, while Wang et al[26] reported that among 31 children in six provinces in Northern China, 4 (12.9%) had vomiting and diarrhea as the first clinical manifestation. It is worth noting that the proportion of children with fever in this study is only 54.1%, which is very low. In China temperature detection checkpoints are found in public places, such as airports and subways. However, it appears that temperature measurements are of only a little value in children.

Since the clinical symptoms in children were relatively mild and atypical, the proportion of asymptomatic patients may be higher in children than in adults. The incidence of asymptomatic patients in this study is 21.1% (16.9%-25.8%)[85]. A meta-analysis of adult cases found a prevalence of asymptomatic infection in 9.0% (95% CI, 5.5%-

14.6%) of patients. Nishiura et al[86] investigated 565 Japanese citizens evacuated from Wuhan at the end of January and revealed that the incidence of asymptomatic infections was 30.8%. Another example is the "Diamond Princess" cruise ship, which was isolated in Japanese waters in early February due to SARS-CoV-2 infection where it was found that the incidence of asymptomatic infections was 51.7%[87]. However, a recent study from New York[88] reported that 29 (87.9%) of 33 pregnant women who tested positive for SARS-CoV-2 on admission did not have symptoms of COVID-19 at the time of treatment. From the above data, we can conclude that the number of asymptomatic patients was underestimated earlier since such patients are often not diagnosed due to their asymptomatic presentation. These patients are still contagious[89], and not diagnosing them may lead to great difficulties in preventing and controlling the pandemic. Asymptomatic infected patients must be taken into account in planning for epidemic prevention and control, and there should be an increased emphasis on obtaining epidemiological history. As stated in this study, 85.2% of the COVID-19 children had an epidemiological history.

Laboratory Examinations and Imaging Examination

In a systematic evaluation of adults[82], lymphatic cell reduction was found in 57.4% of patients, and a few studies showed that those with lymphopenia had a 3-fold higher risk of developing severe COVID-19[90]. This study found that the lymphocytes decreased in 12% of children, which could also explain the lower rate of severe disease (3.33%) and lower mortality rate (0.28%) in children, against the severe rate of 25.6% and mortality rate 3.6%, respectively, in adults[82,91]. SARS-COV-2 may directly attack lymphocytes or destroy lymphoid organs, which are important components of the collective immune response. Because the symptoms of children are mild, all inflammatory markers are rarely increased, and the inflammatory markers which were most commonly increased were CRP (22.2%), PCT (17.5%), LDH (32.3%), and ESR (20.5%). Others, such as ferritin, TNF-α, IFN-γ, ALT, CK-MB, and Cr were not usually found to be elevated.

In terms of imaging, a meta-analysis of adults[92] found that the chest imaging abnormality rate in patients with confirmed COVID-19 was 91.6%, and ground-glass opacities were seen in 68.1% cases. Our study found that the imaging abnormality rate was 66.5%, and ground-glass opacities were seen in 36.9% of children. One reason is the airway expression of the SARS-COV-2 receptor (ACE2). Also, the expression of transmembrane serine protease 2 (TMPRSS2) is lower in children than in adults[93]. Therefore, screening in children, and in asymptomatic patients, should not rely on blood biochemical and imaging tests but should consider the gold standard of viral nucleic acid testing of respiratory specimens.

Multisystem Inflammatory Syndrome in Children (MIS-C)

Since April 2020, eight cases of children with severe inflammatory shock due to COVID-19 were reported in London, UK[94], and more attention was drawn to this phenomenon due to its critical nature, disproving the previous notion that children with COVID-19 always presented with mild disease. The disease was clinically similar to Kawasaki Disease, involving multiple organ systems, often accompanied by increased inflammatory markers, which can readily lead to a shock[95]. It has been reported that 68% of MIS-C require admission to intensive care units and these patients had a mortality rate of 1.7%[96]. However, the incidence of such cases is low (6.2%).

Limitations

Our study has a few key limitations. First, we found considerable heterogeneity between studies and significant publication bias between several subgroups. Subgroup analysis failed to identify the source of heterogeneity, which would affect the accuracy of meta-analysis. Second, the study was analysed during the outbreak. Many areas affected by COVID-19 have not yet released clinical data sets, which could skew the results of this analysis. While the literature included different regions and hospitals to exclude data duplication, a possibility of data duplication cannot be eliminated completely.

Conclusions

This review provides a comprehensive description of the clinical characteristics of children with COVID-19 and provides clinical evidence which can be useful in the prevention and control of the epidemic. The overall symptoms of COVID-19 children were mild, and the prognosis was good.

The primary basis for diagnosing infections with human coronaviruses is Real-Time Polymerase Chain Reaction (RT-PCR) performed on upper or lower respiratory tract secretions. When screening children for COVID-19, suspected patients should not be immediately excluded based on normal peripheral white blood cells and lymphocyte counts or normal imaging findings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Data curation: Ji-Gan Wang, Zhi-Juan Zhong; Formal analysis: Yu-Fang Mo; Investigation: Li-Chuan Wang; Methodology: Rui-Chen; Project administration: Ji-Gan Wang, Rui-Chen; Software: Ji-Gan Wang. Supervision: Ji-gan Wang; Writing – original draft: Zhi-Juan Zhong, Yu-Fang Mo; Writing – review & editing: Ji-Gan Wang.

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