



COVID-19 소아 환자의 임상 양상 및 실험실적 특징: 체계적문헌고찰 및 메타분석

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(2020년 10월 4일 접수 · 2020년 12월 14일 수정 · 2020년 12월 15일 승인)

Clinical and Laboratory Features of Pediatric Patients with COVID-19: Systematic Review and Meta-analysis

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(Received October 4, 2020 · Revised December 14, 2020 · Accepted December 15, 2020)

ABSTRACT

Background: Although the identification of clinical and laboratory features in pediatric COVID-19 patients is essential in establishing an appropriate treatment plan, a systematic review and meta-analysis on the topic has yet to be reported. **Methods:** We searched MEDLINE, Embase, and Web of Science to access clinical and laboratory characteristics as well as clinical outcomes of children with COVID-19 infection. A meta-analysis using random-effect model was performed to estimate pooled prevalence and 95% confidence intervals. **Results:** Among the 532 studies initially collected, 12 articles were finally included in the meta-analysis. Among the investigated 320 pediatric patients with COVID-19, fever (48.2%) and cough (39.3%) were the most common symptoms. Almost one third of patients (30.4%) were asymptomatic. In laboratory findings, only 11.4% of pediatric patients experienced lymphocytopenia. Increased inflammatory markers including c-reactive protein (18.6%) and procalcitonin (32.4%) were observed. Only a few patients needed mechanical ventilation and intensive care support, and only one death was reported. **Conclusion:** Pediatric patients with COVID-19 infection exhibited milder symptoms and more favorable outcomes compared to adults. However, considering the high rate of asymptomatic pediatric patients, close monitoring is required to prevent community infection in asymptomatic conditions and hidden disease progression.

KEYWORDS: Children, COVID-19, Clinical and laboratory features, Systematic review, Meta-analysis

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has now been declared a pandemic, raising concern from scientific communities worldwide.¹⁾ According to the World Health Organization report published in December

2020, the COVID-19 pandemic has yielded an alarming 66,243,918 infection cases and 1,528,984 deaths, prompting an urgent response from governments, medical organizations, and laboratories alike.²⁾

In a recent review on 72,314 COVID-19 infection cases

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conducted by the Chinese Center for Disease Control and Prevention, the proportion of cases in children younger than 10 years of age was relatively low at approximately 1%.³⁾ However, given that the progression of COVID-19 has been frequently observed in the form of community-based infections including familial infections, the probability of pediatric COVID-19 cases may increase. In addition, children are considered to be at high risk for viral infection in the respiratory tract and subsequent progression to pneumonia; also, the immune response to viral infections in children can cause serious damage to essential organs.⁴⁻⁵⁾ Additionally, COVID-19 has been reported to result in pneumonia via severe inflammation of the lungs, which can be fatal in children.⁶⁾ Therefore, it is important to establish an appropriate treatment guideline for COVID-19 in children. To establish a treatment guideline, it is necessary to first accumulate and analyze the characteristics of pediatric patients with COVID-19.

In previous literature, common clinical features in adult patients with COVID-19 include lower respiratory tract symptoms such as fever, cough, and dyspnea, which are similar to those of other major coronavirus infections of the past, namely Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).⁷⁻⁸⁾

Several studies have also reported the clinical profile of COVID-19 infection in children; however, since the sample size of most studies was not big, there is a need to pool data from such studies and to deduce meaningful results. To that end, the current study contains an analysis of the current literature on pediatric COVID-19 infection and reports relevant clinical and laboratory features.

Methods

Search Strategy

We performed a systematic review on previous literatures in MEDLINE, Embase, Web of Science with the following keywords: (coronavirus OR COVID-19 OR SARS-CoV-2) AND (pediatric* OR neonate* OR infant* OR child* OR adolescent*). Literature published between 1 January and 3 April 2020 were searched, and no restriction on publication language was applied. Results from the initial search strategy were first screened by title and abstract. After independent screening of the titles and abstracts of every article by two authors, the remaining articles were reviewed (by reading full

text) to assess their eligibility for meta-analysis. Among articles that reported duplicate information from identical patients, we selected the study with the most recent and comprehensive data.

Inclusion and Exclusion Criteria

Eligible studies met the following criteria: (1) demonstrates clinical feature and laboratory data of patients with COVID-19 ≤ 18 years; and (2) provides sufficient information for data extraction. Exclusion criteria were: (1) reviews and expert opinions; (2) *in vitro* or animal studies; or (3) case report or case series with less than 2 cases.

Data extraction and Quality assessment

Two investigators independently extracted data from each included study, and discrepancies were resolved by consensus. The extracted information included the first author's name, country, study duration, diagnostic method, number of reported cases, cases in the intensive care unit (ICU), age, sex, clinical characteristics including sign and symptoms, laboratory findings, severity, and clinical outcomes. The clinical characteristics included fever, cough, fatigue/myalgia, dyspnea/tachypnea, and no symptoms (asymptomatic). The laboratory findings included lymphocytes, c-reactive protein (CRP) and procalcitonin (PCT). If the lymphocyte level was lower than $1.2 \times 10^9/L$, it was defined as lymphocytopenia. A CRP level < 10 mg/L and a PCT level < 0.46 ng/mL were defined as high CRP and high PCT, respectively. The disease severity was defined as the need for mechanical ventilation. The clinical outcomes included were as follows: (a) the need for intensive care unit (ICU) care, (b) discharge, (c) death, and (d) duration of hospitalization.

For quality assessment, we used the Joanna Briggs Institute critical appraisal checklist for case-series.⁹⁾ This checklist consists of 10 questions to assess the risk of bias and to confirm adequate reporting and statistical analysis. The highest score for each publication was 10 points.

Statistical analysis

Percentages, median values, and mean values were reported to describe the clinical characteristics of children with COVID-19. For studies reporting only medians and interquartile ranges, mean and variance values were calculated by using appropriate formulas.¹⁰⁾ For meta-analyses, pooled prevalence and 95% confidence intervals (CIs) were estimated to summarize the weighted effect size for clinical, laboratory

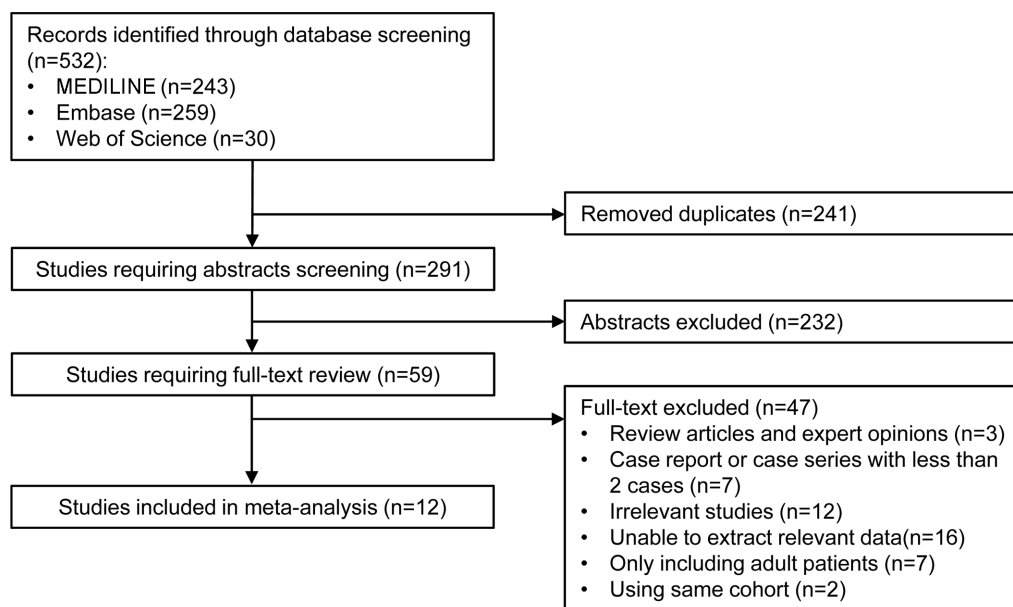


Fig. 1. Flow diagram of study selection

characteristics and clinical outcomes of children with COVID-19, and mean value and 95% CI were estimated for duration of hospitalization using a random-effect model. Publication bias was assessed using Egger's regression test of the funnel plots. For measures of heterogeneity, I^2 statistics and τ^2 were calculated. All statistical analyses were performed using R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria) meta packages. This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Results

Identification and characteristics of the included studies

A detailed flow chart of the study selection process is presented in Fig. 1. A total of 532 studies were retrieved through electronic databases. After the removal of duplicates, 291 records were initially identified, and the titles and abstracts were screened under the inclusion criteria. From this initial review, full texts of 59 studies were assessed for eligibility. In the end, data on a total of 320 patients from 12 articles were investigated for this meta-analysis.^{3,11-21)} Characteristics of the included studies are presented in Table 1. All included studies in meta-analysis were conducted in China. Diagnosis of COVID-19 was confirmed according to either the World Health Organization interim guidance or Chinese National Health Commissions guideline (Table 1).²²⁻²³⁾

For the quality assessment, all studies met nine of the ten critical appraisal criteria defined by the Joanna Briggs Institute except those related to the consecutive and complete inclusion of patients.

Quantitative data synthesis

As shown in Table 2 and Supplementary Fig. S1, fever (48.2%) and cough (39.3%) were the most common symptoms. In addition, pediatric COVID-19 patients were found to frequently experience fatigue/myalgia (8.4%) and dyspnea or tachypnea (6.9%). Almost one-third of the patients (30.4%) were asymptomatic.

The meta-analyses results of laboratory findings in children with COVID-19 are displayed in Table 3 and Supplementary Fig. S2. Only 11.4% of pediatric patients with COVID-19 experienced lymphocytopenia. Increased inflammatory markers including CRP and PCT were observed in 18.6% and 32.4% of patients, respectively.

Severity and clinical outcomes in children with COVID-19 are shown in Table 4 and Supplementary Fig. S3. Regarding the severity of COVID-19 infection, 3.2% of pediatric patients required mechanical ventilation, and 4% of patients were treated at the ICU. In the case of clinical outcomes, 1.9% of patient death was reported. Most patients were discharged after recovery within 14 days (13.1 days, 95% CI; 10.4-15.8).

The Egger's tests and funnel plots for detecting publication bias showed no significant results except death (Supplementary

Table 1. Characteristics of studies included in the systematic review

Study	Sample size		Age Median (range)	Country	Setting	Study duration ^a	Samples	RNA detection
	(male, %)							
Lu X, et al. ³	171 (60.8)		6.7yr (1d-15yr)	China	Wuhan Children's Hospital	Jan 28-Feb 26	Nasopharyngeal or throat swabs	RT-PCR
Su L, et al. ¹¹	9 (66.7)		3.6yr (11m-9yr)	China	Jinan Infectious Disease Hospital	Jan 24-Feb 24	Sputum and nasopharyngeal swabs	RT-PCR
Zhou Y, et al. ¹²	9 (44.4)		1yr (7m-3yr)	China	Sehzhzen Third People's Hospital	Jan 20 -Feb 10	N/R	RT-PCR
Wei M, et al. ¹³	9 (22.2)		7m (2m-11m)	China	N/R	Dec 8-Feb 6	Nasopharyngeal swabs	RT-PCR
Li W, et al. ¹⁴	5 (80.0)		3yr (10m-6yr)	China	Fifth Affiliated Hospital of Sun Yat-sen University	Jan 28-Feb 8	N/R	RT-PCR
Zheng F, et al. ¹⁵	25 (56.0)		3yr (3m-14yr)	China	10 hospitals across Hubei province	Feb 1-Feb 10	Throat swabs and/or nasopharyngeal swabs	Nucleic acid test
Cai J, et al. ¹⁶	10 (40.0)		6.2yr (3m-10.9yr)	China	Children's Hospital in Shanghai, Hainan, Hefei in Anhui province, and Qingdao in Shandong province	Jan 19-Feb 3	Nasopharyngeal or throat swabs	RT-PCR
Liu H, et al. ¹⁷	4 (50.0)		3yr (2m-9yr)	China	Xinhua Hospital and Maternal and Child Health Hospital of Hubei Province	Jan 27-Feb 14	Throat swabs	RT-PCR
Liu W, et al. ¹⁸	6 (66.7)		3yr (1-7yr)	China	Tongji Hospital	Jan 7-Jan 15	Throat swabs	RT-PCR
Qiu H, et al. ¹⁹	36 (63.9)		8.3yr (mean), (1-6yr)	China	Ningbo Women and Children's Hospital, Third Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital of Wenzhou	Jan 17-Mar 1	Upper nasopharyngeal swabs	RT-PCR
Wang D, et al. ²⁰	31(48.3)		7.1yr (6m-17yr)	China	21 hospitals in 6 provinces of Sshaanxi, Gansu, Ningxia, Hebei, Henan and Shandong	Jan 25-Feb 21	Nasopharyngeal swabs	RT-PCR
Liu M, et al. ²¹	5 (80.0)		5yr(7m-13yr)	China	The First Affiliated Hospital of Chongqing Medical University and Chongqing Three Gorges Central Hospital	Feb 17 -N/R	Throat swabs	RT-PCR

d, days; m, months; N/R, not reported; RT-PCR, reverse transcription polymerase chain reaction, yr, Years.

^aAll studies were conducted in 2020.

Table 2. Meta analyses of clinical characteristics

Study	Sample size (N)	N (%)				
		Fever	Cough	Fatigue /myalgia	Dyspnea /tachypnea	Asymptomatic
Lu X, et al. ³	171	71 (41.5)	83 (48.5)	13 (7.6)	N/R	27 (15.8)
Su L, et al. ¹¹	9	2 (22.2)	1 (11.1)	N/R	N/R	6 (66.7)
Zhou Y, et al. ¹²	9	4 (44.4)	2 (22.2)	N/R	N/R	5 (55.6)
Wei M, et al. ¹³	9	4 (44.4)	2 (22.2)	N/R	N/R	1 (11.1)
Li W, et al. ¹⁴	5	1 (20.0)	1 (20.0)	N/R	N/R	4 (80.0)
Zheng F, et al. ¹⁵	25	13 (52.0)	11 (44.0)	N/R	2 (8.0)	N/R
Cai J, et al. ¹⁶	10	8 (80.0)	6 (60.0)	N/R	0	N/R
Liu H, et al. ¹⁷	4	3 (75.0)	3 (75.0)	1 (25.0)	N/R	0
Liu W, et al. ¹⁸	6	6 (100.0)	6 (100.0)	N/R	1 (16.7)	0
Qiu H, et al. ¹⁹	36	13 (36.1)	7 (19.4)	N/R	1 (2.8)	10 (27.8)
Wang D, et al. ²⁰	31	20 (64.5)	14 (45.2)	3 (9.7)	N/R	4 (12.9)
Liu M, et al. ²¹	5	2 (40.0)	2 (40.0)	N/R	N/R	3 (60.0)
Meta-analyses outcomes (random-effects model)						
Patients with positive outcome/included patients (n)		147/320	138/320	17/206	4/77	60/285
Proportion (%)		48.2	39.3	8.4	6.9	30.4
95% CI		38.4-58.1	28.9-50.7	5.3-13.2	2.7-16.2	17.5-47.4
I ² statistics		41	51	0	0	69
τ ²		0.16	0.26	0	0	0.75
P-value		0.07	0.02	0.48	0.61	<0.01
P-value of Egger's test		0.2847	0.4173	0.1758	0.8337	0.1957

CI, confidence interval; N/R, not reported

Fig. S4, Supplementary Fig. S5, Supplementary Fig. S6).

Discussion

The COVID-19 pandemic requires great attention, particularly due to the high transmission and prevalence of pneumonia that may accompany COVID-19 infection.¹⁸⁾ Particular consideration of more vulnerable patient groups is important, as different symptoms and risk factors may exist depending on patient attributes. Children are one such group; yet although data on COVID-19 cases are accumulating at an extremely rapid pace, information on pediatric cases are scarce. However, the exceptional vulnerability of children to viral infections calls for the identification of clinical and laboratory features in pediatric COVID-19 patients for the improvement of children-specific diagnosis and treatment. This systematic review and meta-analysis was conducted to investigate the early pediatric characteristics of the COVID-19 outbreak before the mutation of the new strains.

In this systematic review and meta-analysis, the clinical data of pediatric COVID-19 infection cases were summarized and

analyzed. We included 320 patients for major clinical manifestations, among whom 280 patients exhibited meaningful laboratory findings.

Common symptoms observed in the pediatric COVID-19 patients were similar to those in adults with COVID-19, but showed a difference in frequency.²⁴⁾ While previous meta-analyses on adults with COVID-19 demonstrated that approximately 90% of adult patients experienced fever, the proportion was about half in children.²⁵⁻²⁶⁾ Cough, the second most commonly reported symptom in adults, was also frequently observed in pediatric patients, but its frequency was about two thirds of that in adults. These findings indicated that children with COVID-19 infection displayed milder symptoms compared to adults in terms of clinical manifestations.

SARS-CoV infection has also been reported to cause lymphocytopenia. It was also shown in our study of children with COVID-19, but the incidence rate was only about 10%, which was significantly lower than 40% of that in adults with COVID-19.²⁵⁾ Additionally, in our study, only 4% of pediatric patients were severe enough to require ICU care. The significantly low proportion of pediatric patients that experienced lympho-

Table 3. Meta-analyses of laboratory characteristics

Study	N (%)		
	Lymphocytopenia ^a	High CRP ^b	High PCT ^c
Lu X, et al. ³	6 (3.5)	33 (19.3)	105 (61.4)
Su L, et al. ¹¹	0	0	3 (33.3)
Zhou Y, et al. ¹²	0	2 (22.2)	N/R
Wei M, et al. ¹³	N/R	N/R	N/R
Li W, et al. ¹⁴	N/R	1 (20.0)	N/R
Zheng F, et al. ¹⁵	N/R	N/R	N/R
Cai J, et al. ¹⁶	0	3 (30.0)	7 (70.0)
Liu H, et al. ¹⁷	N/R	N/R	N/R
Liu W, et al. ¹⁸	4 (66.7)	5 (83.3)	N/R
Qiu H, et al. ¹⁹	11 (30.6)	1 (2.8)	6 (16.7)
Wang D, et al. ²⁰	2 (6.5)	3 (9.7)	1 (3.2)
Liu M, et al. ²¹	0	N/R	N/R
Meta-analyses outcomes (random-effects model)			
Patients with positive outcome/included patients (n)	23/277	48/277	122/257
Proportion (%)	11.4	18.6	32.4
95% CI	3.8-29.5	9.7-32.6	11.8-63.2
I ² statistics (%)	78	55	88
τ ²	1.9154	0.5433	1.7262
P-value	<0.01	0.03	<0.01
P-value of Egger's test	0.7273	0.9333	0.1896

CRP, c-reactive protein; N/R, not reported; PCT, procalcitonin

^aLymphocytopenia was defined as lower than 1.2×10^9 /L.

^bHigh CRP was defined as higher than 10 mg/L.

^cHigh PCT was defined as higher than 0.46 ng/mL.

cytopenia or ICU care suggests that severe symptoms and outcomes due to COVID-19 are less frequently manifested in children. Also, it is noteworthy that pediatric COVID-19 patients showed more favorable clinical outcomes than adults, with only one reported death among the 288 cases investigated in the current study. A previous COVID-19 study reported 51 deaths among 191 adult inpatients, a much higher proportion compared to the results of this study.²⁷⁾ This may be due to the fact that much less pediatric COVID-19 patients required intensive or critical care compared to adults, as reported in previous meta-analyses.²⁵⁻²⁶⁾ In another cohort study performed on 2143 pediatric patients, the incidence of severe and critical cases in children (5.9%) was lower than that in adults (18.5%), which was in line with our findings.²⁸⁾ In general, children are considered much more vulnerable to infection and ensuing diseases; yet the counterintuitive results found here may be explained by the difference in immune system response and function between adults and children.²⁸⁾ For instance, immature immune functions, such as lack of binding

ability to cell receptors for COVID-19, may lead to an attenuated response to COVID-19.

High PCT and CRP in pediatric COVID-19 patients were found in this study. Increased inflammatory markers including CRP and PCT were commonly reported laboratory values in children and adolescents with COVID-19.²⁹⁾ In a previous study comparing the clinical manifestations in adults and children with COVID-19, the incidence rate of high PCT in pediatric COVID-19 patients was 35.7%, similar to the value in our study, and higher than that in adult COVID-19 patients (24.5%).³⁰⁾ A high incidence of high PCT values may be helpful to detect COVID-19 infection in children who usually have milder symptoms than adults.

Furthermore, while the rate of asymptomatic COVID-19 infections is not well known, a study conducted on the passengers of the cruise ship "Diamond Princess," which recently experienced an outbreak of COVID-19, reported an asymptomatic rate of 17.9%.³¹⁾ In the current study, the proportion of asymptomatic COVID-19 infections in pediatric

Table 4. Meta-analyses of severity and clinical outcomes

Study	N (%)				
	Severity		Outcomes		
	Mechanical ventilation	ICU care	Discharge	Death	Duration of hospitalization (mean, range) ^a
Lu X, et al. ³	3 (1.8)	3 (1.8)	149 (87.1)	1 (0.6)	N/R
Su L, et al. ¹¹	0	0	9 (100.0)	N/R	2-3 week
Zhou Y, et al. ¹²	N/R	0	0	0	N/R
Wei M, et al. ¹³	0	0	N/R	N/R	N/R
Li W, et al. ¹⁴	N/R	N/R	3 (60.0)	N/R	13.0 (12-14)
Zheng F, et al. ¹⁵	2 (8.0)	2 (8.0)	N/R	0	N/R
Cai J, et al. ¹⁶	N/R	N/R	10 (100.0)	0	N/R
Liu H, et al. ¹⁷	N/R	N/R	N/R	N/R	N/R
Liu W, et al. ¹⁸	N/R	1 (16.7)	6 (100.0)	0	10.0 (5-13)
Qiu H, et al. ¹⁹	N/R	N/R	36 (100.0)	0	14 (10-20)
Wang D, et al. ²⁰	0	0	24 (77.4)	0	N/R
Liu M, et al. ²¹	N/R	N/R	N/R	N/R	N/R
Meta-analyses outcome (random-effects model)					
Patients with positive outcome/included patients (n)	5/245	6/260	237/277	1/288	45/54
Proportion (%) or mean	3.2	4	83	1.9	12.4
95% CI	1.5-6.8	2-7.9	65.4-92.7	0.7-5.1	8.2-16.5
I ² statistics (%)	0	0	64	0	89
τ ²	0	0	0.90	0	11.6
P-value	0.51	0.46	<0.01	0.78	<0.01
P-value of Egger's test	0.7221	0.4724	0.8066	0.0226	0.7027

CI, confidence interval; ICU, intensive care unit, N/R, not reported

^aSu L, et al. study was excluded from meta-analysis of hospitalization duration.

patients were found to be 30.4%, which was approximately 2-fold higher than results from previous studies and 3-fold higher than those from MERS-CoV (12.5%).³²⁾ Such results must be taken into close consideration, since it has been revealed that an asymptomatic COVID-19 patient can transmit the virus to another individual.³³⁾ In general, the major route of transmission for children was familial, because children mainly need extensive support from adult caregivers and therefore have many opportunities for close contact.¹⁶⁾ This situation, on the contrary, means that children can easily spread the virus to their families. Care for asymptomatic COVID-19 infected children may increase the risk of transmission by not being aware of the infection. Also, previous results have demonstrated the progression of pneumonia induced by COVID-19 through computed tomography imaging in asymptomatic pediatric patients, suggesting that severe diseases may develop without awareness of the infection.³⁴⁾ Thus, careful monitoring of asymptomatic cases in pediatric

COVID-19 patients is needed in order to prevent familial transmission and severe harm in the children themselves.

Despite the value of the current study, which focuses on a particularly vulnerable patient population in the midst of a chaotic pandemic, there exist a few limitations. Regarding some of the studies included in this paper, the small number of cases, retrospective non-randomized design, and case-series design are some examples. Also, every included study was conducted in China; however, considering that China was the area of initial infection, this may be inevitable. Furthermore, despite a previous report of higher incidence of infection in infants under 3 years of age, a correlation between incidence of COVID-19 infection and age could not be investigated in this study as most of the data in included the studies were not organized based on age. However, to the best of our knowledge, this study is the first systematic review and meta-analysis evaluating pediatric clinical features of COVID-19 infection and will serve as an ideal basis for further research

on not only pediatric patients but also other vulnerable patient groups in the COVID-19 pandemic.

Conclusion

This systematic review and meta-analysis analyzed clinical and laboratory data in pediatric patients with COVID-19 infection. Children with COVID-19 exhibited milder symptoms and more favorable outcomes compared to adults. However, considering the high rate of asymptomatic pediatric patients, close monitoring is required to prevent community infections in asymptomatic conditions and hidden disease progression.

Conflict of Interest

We declare no conflict of interests.

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