Received: 18 June 2020 | Accepted: 30 July 2020

DOI: 10.1002/jmv.26398

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19)

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Funding information
The Key Project of Tianjin Health Care Professionals, Grant/Award Number: 16KG166; The Program of Tianjin Science and Technology Plan, Grant/Award Number: 18ZXDBSY00170; National Natural Science Foundation of China, Grant/Award Number: 81771589

Abstract

To provide a comprehensive and systematic analysis of demographic characteristics, clinical symptoms, laboratory findings, and imaging features of coronavirus disease 2019 (COVID-19) in pediatric patients. A meta-analysis was carried out to identify studies on COVID-19 from 25 December 2019 to 30 April 2020. A total of 48 studies with 5829 pediatric patients were included. Children of all ages were at risk for COVID-19. The main illness classification ranged as: 20% (95% confidence interval [CI]: 14%-26%; $I^2 = 91.4\%$) asymptomatic, 33% (95% CI: 23%-43%; $I^2 = 95.6\%$) mild and 51% (95% CI: 42%-61%; $I^2 = 93.4\%$) moderate. The typical clinical manifestations were fever 51% (95% CI: 45%-57%; $I^2 = 78.9\%$) and cough 41% (95% CI: 35%-47%, $I^2 = 81.0\%$). The common laboratory findings were normal white blood cell 69% (95% CI: 64%-75%; $I^2 = 58.5\%$), lymphopenia 16% (95% CI: 11%-21%; $I^2 = 76.9\%$) and elevated creatine-kinase MB 37% (95% CI: 25%-48%; $I^2 = 59.0\%$). The frequent imaging features were normal images 41% (95% CI: 30%-52%; $I^2 = 93.4\%$) and ground-glass opacity 36% (95% CI: 25%-47%; $I^2 = 92.9\%$). Among children under 1 year old, critical cases account for 14% (95% CI: 13%-34%; $I^2 = 37.3\%$) that should be of concern. In addition, vomiting occurred in 33% (95% CI: 18%-67%; $I^2 = 0.0\%$) cases that may also need attention. Pediatric patients with COVID-19 may experience milder illness with atypical clinical

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manifestations and rare lymphopenia. High incidence of critical illness and vomiting symptoms reward attention in children under 1 year old.

KEYWORDS
2019-nCoV, children, coronavirus, COVID-19, meta-analysis, SARS-CoV-2

1 | INTRODUCTION

An outbreak of the coronavirus disease 2019 (COVID-19) is spreading rapidly around the world, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. As of 26 July 2020, the COVID-19 pandemic has resulted in approximately 15 785 641 confirmed cases, including 640 016 deaths worldwide.[1] In the early stage, the majority of cases were concentrated in middle-aged and old people. Under the ongoing pandemic situation, children cases are showing an increasing trend in many countries of the world: In China, a large cohort study on the epidemiological characteristics of children with COVID-19 included 2135 cases[2]; In the United States, it was reported that 74 children were admitted to pediatric intensive care units in 19 states; On a global scale, it was estimated 176 190 children infected with SARS-CoV-2 by 6 April 2020.[3] One meta-analysis found that fever and cough occurred in adults up to 92.8% and 63.4%, respectively.[4] Another study showed lymphopenia occurred in 57.4% of an adult patient with COVID-19.[5] Although some previous studies have demonstrated that SARS-CoV-2 infection affects adults and children differently,[6-8] the data of a systematic meta-analysis on characteristics of children with COVID-19 are still lacking. Thus, in our research, we reviewed and analyzed the studies and reported cases from 25 December 2019 to 30 April 2020 to provide evidence-based data involving clinical manifestations of COVID-19 in pediatric patients. It will help to formulate policies on controlling SARS-CoV-2 transmission among children for pediatricians and public health specialists.

2 | METHODS

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered in PROSPERO as CRD42020191099.

2.1 | Search strategies

To identify studies pertaining clinical, laboratory, and imaging features in children with COVID-19, we systematically searched from PubMed, Web of Science, Chinese Wanfang and China National Knowledge Infrastructure databases for relevant articles published through 30 April 2020. Moreover, additional records identified from World Health Organization (WHO)/Center for Disease Control reports, medRxiv, bioRxiv, SSRN, and Google Scholar. We also reviewed the references of all identified articles to identify additional studies. Search terms were as follows: novel coronavirus, nCoV, SARS2 vaccine, Wuhan coronavirus vaccine, 2019 novel coronavirus, novel coronavirus 2019, 2019-nCoV, COVID-19, Wuhan coronavirus, Wuhan pneumonia and SARS-CoV-2. These terms were used in combination with "AND" or "OR." The literature review was performed independently by two investigators (XJC and TQZ), with a third reviewer (YMS) resolving any disputes as needed.

2.2 | Inclusion criteria

We included published papers (cohort studies, case series, and case reports) that given available data about the demographic information, clinical, laboratory, and image features in children with COVID-19. Pediatric population was defined as under 18 years old. SARS-CoV-2 nucleic acid was teased by RT-PCR in accordance with the WHO guideline.[9] The level of laboratory test items was determined according to the following standards: normal white blood cell: 5.5 to 12.0×10^9/L, leukocytosis: more than 12.0×10^9/L, leukopenia: less than 5.5×10^9/L, lymphopenia: less than 1.2×10^9/L, high PCT: more than 0.046 ng/mL, high CRP: more than 10 mg/L, high LDH: more than 300 U/L, high ALT: more than 45 U/L, high AST: more than 50 U/L, high Creatinine: more than 62 μmol/L, high blood urea nitrogen: more than 7.1 mmol/L, high CK: more than 170 U/L, high CK-MB: more than 25 U/L, high D-dimer: more than 0.55 mg/L. We excluded studies that did not report original data or clear diagnostic criteria, and no relevant outcome.

2.3 | Data collection

Two authors (XJC and TQZ) independently extracted relevant information, including first author, publication year, sex (male, %), country, number of COVID-19 patients, age distribution (ratio of <1, 1-5, 6-10, 11-15, and >15 years) and contact history. The severity of COVID-19 was defined according to the clinical characteristics, laboratory testing, and chest imaging, including asymptomatic infection, mild, moderate, severe and critical cases.[10] The diagnostic criteria were as follows: Asymptomatic infection: The child had no clinical symptoms or signs, chest imaging was normal, and only 2019-nCoV nucleic acid test was positive; mild: the acute upper respiratory tract infection was the main manifestations and some children may only have digestive symptoms. Some children may have no fever. Physical examination shows no auscultatory abnormalities;

Moderate: with pneumonia, most of children have fever and cough, which are dry cough at first and then phlegm cough. Some of them may have wheezing, but without obvious hypoxia such as shortness of breath, sputum or dry snoring and/or wet snoring can be heard in the lungs. Some children only found lung lesions on chest computed tomography (CT) without any clinical symptoms and signs, which is called subclinical type; Severe: Early onset of respiratory symptoms such as fever and cough, some can be accompanied by gastrointestinal symptoms, disease progression often occurs in about 1 week, with hypoxia performance, and dyspnea occurs, oxygen saturation is less than 0.92; critical: children may rapidly progress to acute respiratory distress syndrome or respiratory failure. They may also develop shock, coagulation dysfunction or other multiple organ dysfunction, which may endanger their lives. Moreover, we extracted clinical performance data including fever, cough, sore throat, tachycardia, rhinorrhea, nasal congestion, tachypnea, diarrhea, vomiting, myalgia or fatigue, hypoxemia, and chest pain. Clinical laboratory results were extracted based on blood routine tests, liver function tests, renal function measurement, cardiac function, inflammatory factors and D-dimer. Distributions for all imaging: normal, ground-glass opacity (GGO), local patchy shadowing, bilateral patchy shadowing, white lung change and pleural effusion.

2.4 | Quality assessment

We used the quality assessment tool for case series studies published by the National Institutes of Health to assess the methodological quality of included studies.[11] We scored 0 or 1 point for each item according to the criteria and added scores for all items to generate an overall quality score that ranged from 0 to 8. Based on the overall score, we classified studies as low (≥7), moderate (5-6), or high risk of bias (≤4). Any disagreement was resolved through discussion by all investigators.

2.5 | Statistical analysis

We performed data analysis using metan packages in STATA (version 12.0; Stata Corp, College Station, TX). Statistical heterogeneity between studies was evaluated with Cochran's Q test and the I^2 statistic. The I^2-value of less than 50% was equivalent to no heterogeneity, whereas values greater than 50% was equivalent to large heterogeneity among studies. Freeman-Tukey double arcsine transformation was used to stabilize the variance of specific prevalence rates between the included studies.[12] To account for the potential heterogeneity of studied population in each study reflected by different geographic locations, ethnicity, age group, and so forth, a random-effect model using the DerSimonian and Laird method was used to aggregate effect sizes to estimate the overall pooled prevalence and corresponding 95% confidence intervals (CIs). To explore the reasons for heterogeneity, subgroup analyses were applied based on the study type (noncase reports vs case reports). The Begg's funnel plot was performed to evaluate the publication bias. P value of less than .05 was identified as statistically significant.

3 | RESULTS

3.1 | Study selection, general characteristics, and quality assessment

A total of 2048 relevant studies were collected from databases and other sources based on the search strategies. We used Endnote Software (Version X7; Thompson Reuters, CA) to remove 992 duplicate studies. According to the title and abstract, 1003 relevant studies were excluded, and then, five studies were removed by reading the full text. Finally, a total of 48 studies[2,13-59] were included in this meta-analysis in according with the inclusion criteria. The PRISMA flow diagram of the included studies is listed in Figure 1. The general characteristics of the included studies are shown in Table 1. One study was from Singapore, one from Korea, one from Spain, one from America, and one from Iranian. The rest of the studies were all from China. The number of patients ranged from 1 to 2490, and male patients ranged from 0 to 1408. Twenty-nine studies were case reports, sixteen studies were case series, and the rest three studies were cohort studies. Total scores of the included studies ranged from 3 to 8 and mean scores were 5.69. The percentage scores were used for ordinal categorization of the studies as low quality (≤4, 25%), medium quality (5-6, 43.8%), and high quality (≥7, 31.2%). The detailed results on quality assessment are listed in the Supporting Information material 1 (Table S1).

3.2 | Characteristics of COVID-19 in children

3.2.1 | Demographical characteristics

Figure 2 presents a summary of the age distribution of all participants. Among all the children cases, 17% (95% CI: 15%-18%; I^2 = 48.6%) was under 1 year old at diagnosis, 24% (95% CI: 19%-29%; I^2 = 80.6%) 1 to 5 years old, 25% (95% CI: 19%-31%; I^2 = 88.7%) 6 to 10 years old, 20% (95% CI: 16%-24%; I^2 = 82.7%) 11 to 15 years old and 18% (95% CI: 8%-28%; I^2 = 96.7%) were 15 years old or more.

Gender was shown as the proportion of males (M). Male gender of the children with COVID-19 was 55% (95%CI: 53%-58%; I^2 = 33.4%; P = .030). The proportion of cases with known contact history was estimated at 72% (95% CI: 64%-80%; I^2 = 90.1%; P = .000).

3.2.2 | Illness severity

Figure 3 presents a summary of the illness severity of all patients. Patients were divided into six groups as indicated based on disease

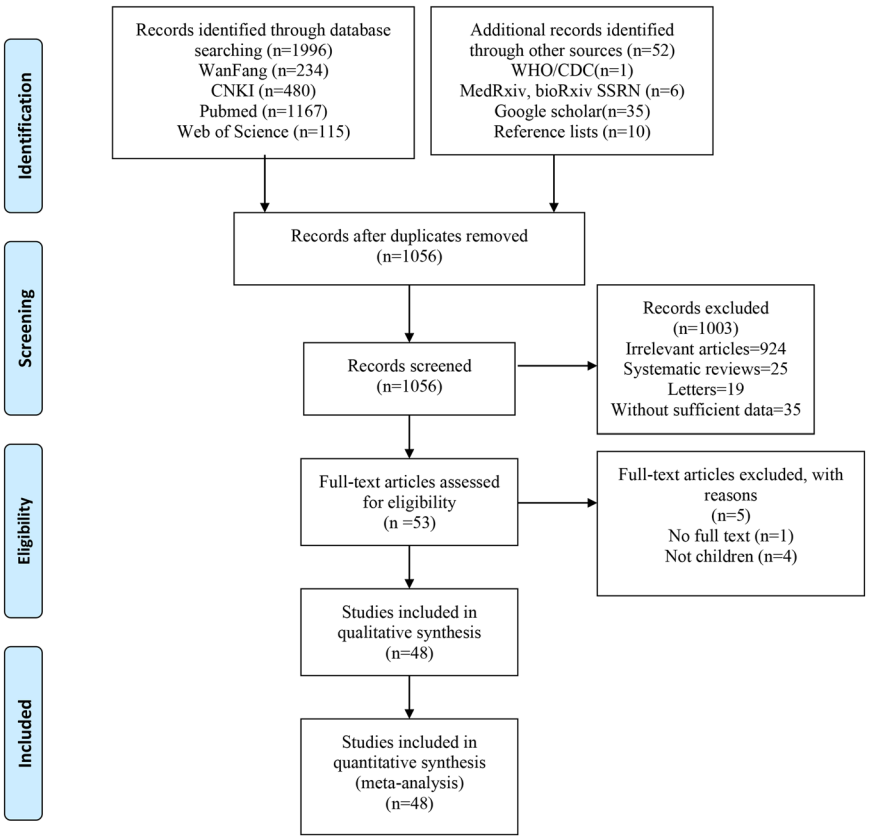

FIGURE 1 Flow diagram for the included studies

severity from light to severe, mainly including: asymptomatic, mild, moderate, severe, critical, and death. Included patients were classified by their clinicians as asymptomatic 20% (95% CI: 14%-26%; I^2 = 91.4%), mildly 33% (95% CI: 23%-43%; I^2 = 95.6%), moderate 51% (95% CI: 42%-61%; I^2 = 93.4%), severely 7% (95% CI: 4%-11%; I^2 = 90.2%), critically 5% (95% CI: 2%-9%; I^2 = 84.5%), and death 0% (95% CI: 0%-0%; I^2 = 94.9%).

Among children under 1-year old cases, asymptomatic 6% (95% CI: 5%-13%; I^2 = 24.3%), mildly 54% (95% CI: 49%-59%; I^2 = 0.0%), moderate 36% (95% CI: 27%-45%; I^2 = 4.0%), severely 7% (95% CI: 4%-11%; I^2 = 34.3%), and critically 14% (95% CI: 13%-34%; I^2 = 37.3%) (Table 2).

3.2.3 | Clinical presentation

Figure 4 presents a summary of the clinical presentation of all children. The most common clinical manifestations were fever 51% (95% CI: 45%-57%; I^2 = 78.9%), cough 41% (95% CI: 35%-47%; I^2 = 81.0%), sore throat 16% (95% CI: 7%-25%; I^2 = 91.6%), tachycardia 12% (95% CI: 3%-21%; I^2 = 93.9%), rhinorrhea 14% (95% CI: 8%-19%; I^2 = 75.4%), nasal congestion 17% (95% CI: 6%-27%; I^2 = 87.2%), tachypnea 9% (95% CI: 4%-14%; I^2 = 87.4%), diarrhea 8% (95% CI: 6%-11%; I^2 = 47.0%), vomiting 7% (95% CI: 5%-10%; I^2 = 50.4%), myalgia or fatigue 12% (95% CI: 7%-17%; I^2 = 77.7%), hypoxemia 3% (95% CI: 1%-4%; I^2 = 0.0%) and chest pain 3% (95% CI: 0%-5%; I^2 = 0.0%).

Among children under 1-year old cases, fever 53% (95% CI: 30%-76%; I^2 = 0.0%), cough 30% (95% CI: 2%-58%; I^2 = 0.0%), rhinorrhea 21% (95% CI: 5%-43%; I^2 = 0.0%), nasal congestion 50% (95% CI: 20%-99%; I^2 = 0.0%), tachypnea 33% (95% CI: 20%-57%; I^2 = 0.0%) and vomiting 33% (95% CI: 18%-67%, I^2 = 0.0%) (Table 2).

3.2.4 | Laboratory examination

Laboratory examination results, which including blood routine test, liver function tests, renal function measurement, cardiac function, inflammatory factors, and D-dimer, are shown in Figure 5. With respect to laboratory findings, the proportion of normal white blood cells in COVID-19 patients in children was 69% (95% CI: 64%-75%; I^2 = 58.5%). Leukocytosis (>12 × 10^9/L) was observed in 10% (95% CI: 7%-14%; I^2 = 63.1%) of patients, and 19% (95% CI: 14%-25%; I^2 = 80.9%) patient had leukopenia (<5.5 × 10^9/L). The proportion of patients with lymphopenia was 16% (95% CI: 11%-21%; I^2 = 76.9%). The proportion of patients with high PCT 36% (95% CI: 21%- 51%; I^2 = 97.0%), CRP 19% (95% CI: 13%-26%; I^2 = 79.3%) and LDH 29% (95% CI: 20%-39%; I^2 = 69.8%), respectively. ALT and AST are indicative parameters for liver function, the high ALT and AST patients was 11% (95% CI: 7%-15%; I^2 = 38.5%) and 18% (95% CI: 13%-23%; I^2 = 48.6%), respectively. Creatine-kinase (CK) and CK-MB are indicative parameters for cardiac function, the high CK and CK-MB was 9% (95% CI: 1%-17%; I^2 = 33.2%) and 37% (95%

TABLE 1 Characteristics of included studies

Author	Journal	Case number (N)	Male (n)	Female (n)	Study location	Study design	Total score
Bialek et al[59]	MMWR Morb Mortal Wkly Rep	2490	1408	1082	America	Case series	6
Dong et al[2]	Pediatrics	2143	1213	930	China	Case series	7
Ma et al[13]	Chin J Contemp Pediatr	115	73	42	Wuhan	Case series	6
Wang et al[14]	Chin J Pediatr	34	14	20	Shenzhen	Case series	5
Wang et al[15]	Chin J Pediatr	31	NA	NA	Six provinces in north China	Case series	7
Cai et al[16]	Clin Infect Dis	10	4	6	Shanghai	Case report	4
Feng et al[17]	Chin J Pediatr	15	5	10	Shenzhen	Case report	7
Su et al[18]	Emerg Microbes Infect	9	3	6	Jinan	Case report	7
Zhou et al[19]	Chin J Contemp Pediatr	9	4	5	Shenzhen	Case report	6
Wei et al[20]	JAMA	9	2	7	Wuhan	Case report	5
Liu et al[21]	NEJM	6	2	4	Wuhan	Case report	7
Cai et al[22]	Chin J Pediatr	1	1	0	Shanghai	Case report	3
Zhang et al[23]	Chin J Pediatr	1	0	1	Hubei	Case report	3
Ji et al[24]	World J Pediatr	2	2	0	Zhejiang	Case report	4
Zhang et al[25]	Chin J Contemp Pediatr	2	0	2	Hunan	Case report	3
Wang et al[26]	Chin J Contemp Pediatr	1	1	0	Wuhan	Case report	5
Zhao et al[27]	Zhejiang Medicine	1	1	0	Zhejiang	Case report	4
Zeng et al[28]	Chin J Pediatr	1	1	0	Wuhan	Case report	4
Zhang et al[29]	J Med Virol	3	3	0	Tianjin	Case report	4
Zeng et al[30]	JAMA Pediatrics	3	3	0	Wuhan	Case report	7
Kam et al[31]	Clin Infect Dis	1	1	0	Singapore	Case report	4
Wu et al[32]	Pediatrics	74	44	30	Shandong	Case series	6
Xing et al[33]	J Mircobiol Immunol Infect	3	2	1	Shandong	Case report	6
Park et al[34]	J Korean Med Sci	1	0	1	Korea	Case report	3
Xia et al[35]	Pediatr Pulmonol	20	13	7	Wuhan	Case series	5
Tagarro et al[36]	JAMA Pediatr	41	18	23	Spain	Case series	6
Zhu et al[37]	Pediatr Pulmonol	10	5	5	Suzhou	Case report	6
Qiu et al[38]	Lancet Infect Dis	36	23	13	Zhejiang	Cohort study	7
Yu et al[39]	Pre-print	82	51	31	Wuhan	Case series	6
liu et al[40]	Chin J Nosocomiol	91	56	35	Wuhan	Case series	7
Ma et al[41]	BMC Med	50	28	22	Wuhan	Cohort study	7
Wang et al[42]	Pre-print	74	38	36	Wuhan	Case series	7
Li et al[43]	Radiol Practice	30	18	12	Wuhan	Case series	6
Lu et al[44]	Pediatr Infect Dis J	110	59	51	Wuhan	Cohort study	8
Tang et al[45]	Pre-print	26	17	9	Shenzhen	Case series	7
Zheng et al[46]	Curr Med Sci	25	14	11	Wuhan	Case series	8

(Continues)

TABLE 1 (Continued)

Author	Journal	Case number (N)	Male (n)	Female (n)	Study location	Study design	Total score
Shen et al[47]	Pediatr Pulmonol	9	3	6	Huna	Case report	6
Sun et al[48]	World J Pediatr	8	6	2	Wuhan	Case report	5
Golnar et al[49]	J Pediatr Rev	9	6	3	Iranian	Case report	4
Liu et al[50]	J Infect	4	2	2	Wuhan	Case report	7
Wu et al[51]	Chin J Contemp Pediatr	23	9	14	Jiangxi	Case series	8
Tan et al[52]	Chin J Contemp Pediatr	13	4	9	Changsha	Case report	6
Yang et al[53]	Journal of Shandong University (Health Sciences)	10	3	7	Shandong	Case report	6
Zhang et al[54]	Journal of Shandong University (Health Sciences)	10	3	7	Shandong	Case report	6
Xu et al[55]	Nat Med	10	6	4	Guangzhou	Case report	6
Zhang et al[56]	World Latest Medicine Information	1	0	1	Yunnan	Case report	6
Chen et al[57]	Chin J Pediatr	1	1	0	Wuhan	Case report	4
Lu et al[58]	NEJM	171	104	67	Wuhan	Case series	6

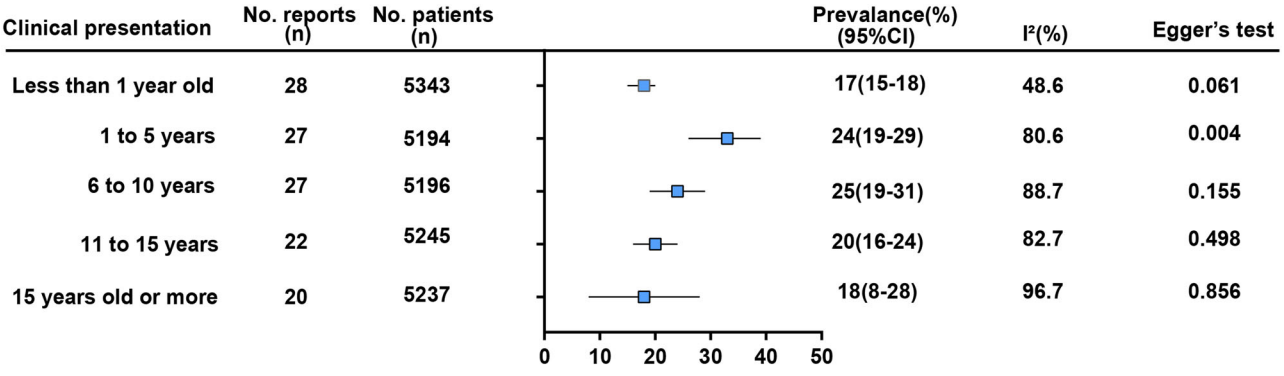

FIGURE 2 Summary results of the age distribution of all participants

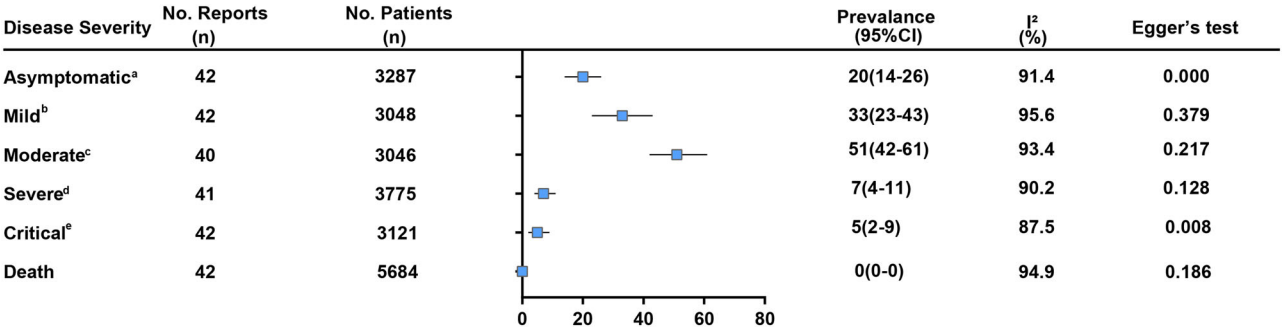

FIGURE 3 Summary results of illness severity in children with COVID-19. The definition of illness severity was mentioned as follows: (A) without any clinical symptoms and signs. Chest imaging examination was normal, while the 2019-nCoV nucleic acid test is positive. B, The main manifestations were acute upper respiratory tract infection and some children may have only digestive symptoms. Physical examination shows no auscultatory abnormalities. C, With pneumonia, some cases may have no clinical symptoms and signs, but chest CT shows lung lesions, which are subclinical. D, The disease usually progresses in about 1 week, and dyspnea occurs, oxygen saturation is less than 92%. E, Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, multiple organ dysfunction can be life-threatening. COVID-19, coronavirus disease 2019; CT, computed tomography

TABLE 2 Comparison of meta-analysis results among different ages patients with COVID-19

	Present study <1 y				Present study 0-18 y				Rodriguez-Morales AJ[4] >18 y				Michael C Grant[60] >16 y			
Study	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)
Male	11	27	46 (22-66)	33.7	36	5838	55 (53-58)	33.4	22	2874	55.9 (51.6-60.1)	66.1	NA	NA	NA	NA
Asymptomatic	11	433	6 (5-13)	24.3	42	3287	20 (14-26)	91.4	NA	NA	NA	NA	NA	NA	NA	NA
Mild	10	395	54 (49-59)	0	42	3048	33 (23-43)	95.6	NA	NA	NA	NA	NA	NA	NA	NA
Moderate	10	395	36 (27-45)	4	40	3046	51 (42-61)	93.4	NA	NA	NA	NA	NA	NA	NA	NA
Severe	12	499	7 (4-11)	34.3	41	3775	7 (4-11)	90.2	NA	NA	NA	NA	NA	NA	NA	NA
Critical	11	404	14 (13-34)	37.3	42	3121	5 (2-9)	87.5	NA	NA	NA	NA	NA	NA	NA	NA
Death	0	0	NA	NA	42	5684	0 (0-0)	94.9	7	632	13.9 (6.2-21.5)	91.4	NA	NA	NA	NA
Fever	11	24	53 (30-76)	0	48	1494	51 (45-57)	78.9	13	735	92.8 (89.4-96.2)	82.4	138	21701	78 (75-81)	94
Cough	9	19	30 (2-58)	0	45	1435	41 (35-47)	81	13	735	63.4 (48.0-78.8)	97.1	138	21682	57 (54-60)	94
Sore throat	7	10	NA	NA	38	1040	16 (7-25)	91.6	5	308	11 (2.8-19.2)	85.4	78	11721	12 (10-14)	88
Tachycardia	5	7	NA	NA	35	950	12 (3-21)	93.9	NA	NA	NA	NA	NA	NA	NA	NA
Rhinorrhea	8	17	21 (5-43)	0	36	990	14 (8-19)	75.4	NA	NA	NA	NA	36	10656	8 (5-12)	97
Nasal congestion	6	9	50 (20-99)	0	33	623	17 (6-27)	87.2	NA	NA	NA	NA	10	2584	5 (3-7)	78
Tachypnea	6	10	33 (20-57)	0	29	1034	9 (4-14)	87.4	NA	NA	NA	NA	NA	NA	NA	NA
Diarrhea	7	10	NA	NA	42	1250	8 (6-11)	47	6	457	6.1 (2.4-9.7)	62.1	93	11707	10 (8-12)	93
Vomiting	7	12	33 (18-67)	0	42	1238	7 (5-10)	50.4	NA	NA	NA	NA	26	4959	4 (2-8)	94
Myalgia or Fatigue	6	9	NA	NA	42	1253	12 (7-17)	77.7	11	446	29.4 (19.8-39.0)	80.7	78	13385	31 (27-35)	95
Hypoxemia	5	7	NA	NA	33	623	3 (1-4)	0	8	656	45.6 (10.9-80.4)	99.5	NA	NA	NA	NA
Chest pain	5	7	NA	NA	34	673	3 (0-5)	0	NA	NA	NA	NA	30	3510	7 (4-10)	92
Leukocytosis	NA	NA	NA	NA	38	907	10 (7-14)	63.1	7	487	16.8 (5.5-28.0)	93.1	NA	NA	NA	NA
Leukopenia	NA	NA	NA	NA	42	978	19 (14-25)	80.9	8	517	18.7 (8.5-28.8)	94.5	NA	NA	NA	NA
Lymphopenia	5	9	33 (24-47)	0	39	795	16 (11-21)	76.9	8	511	43.1 (18.9-67.3)	98	NA	NA	NA	NA
High PCT	7	10	NA	NA	29	709	36 (21-51)	97.0	NA	NA	NA	NA	NA	NA	NA	NA
High CRP	9	15	42 (6-78)	0	32	651	19 (13-26)	79.3	6	332	58.3 (21.8-94.7)	98.9	NA	NA	NA	NA
High LDH	4	7	50 (15-69)	0	24	301	29 (20-39)	69.8	5	341	57.0 (38.0-76.0)	92.6	NA	NA	NA	NA

(Continues)

TABLE 2 (Continued)

Study	Present study <1 y				Present study 0-18 y				Rodriguez-Morales AJ[4] >18 y				Michael C Grant[60] >16 y			
	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)	No. reports	No. patients	Prevalence (%)	I^2 (%)
High ALT	7	25	47 (25-69)	0	32	686	11 (7-15)	38.5	2	128	24.1 (13.5-34.6)	42.8	NA	NA	NA	NA
High AST	7	14	33 (20-67)	0	28	529	18 (13-23)	48.6	3	169	33.3 (26.3-40.4)	0	NA	NA	NA	NA
High Creatinine	5	20	NA	NA	NA	NA	NA	NA	3	169	4.5 (1.0-8.0)	10.2	NA	NA	NA	NA
High Blood urea nitrogen	4	18	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
High CK	2	3	NA	NA	17	109	9 (1-17)	33.2	2	140	21.3 (3.2-39.4)	81.4	NA	NA	NA	NA
High CK-MB	4	21	88 (71-94)	8.5	23	228	37 (25-48)	59.0	NA	NA	NA	NA	NA	NA	NA	NA
High D-dimer	4	5	NA	NA	24	194	11 (8-14)	0	NA	NA	NA	NA	NA	NA	NA	NA
Normal Imaging	8	13	42 (6-78)	0	38	902	41 (30-52)	93.4	NA	NA	NA	NA	NA	NA	NA	NA
Ground-glass opacity	8	14	50 (20-80)	0	39	898	36 (25-47)	92.9	10	584	68.5 (51.8-85.2)	99.1	NA	NA	NA	NA
Local patchy shadow	7	11	42 (6-78)	0	35	928	26 (21-32)	58.2	7	316	25 (5.2-44.8)	96.4	NA	NA	NA	NA
Bilateral patchy shadow	7	11	40 (13-55)	0	34	814	28 (21-35)	73.8	7	508	70.7 (50.4-91.0)	98.7	NA	NA	NA	NA
White lung change	NA	NA	NA	NA	32	653	2 (0-4)	0	NA	NA	NA	NA	NA	NA	NA	NA
Pleural effusion	NA	NA	NA	NA	35	769	2 (0-3)	0	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviation: COVID-19, coronavirus disease 2019.

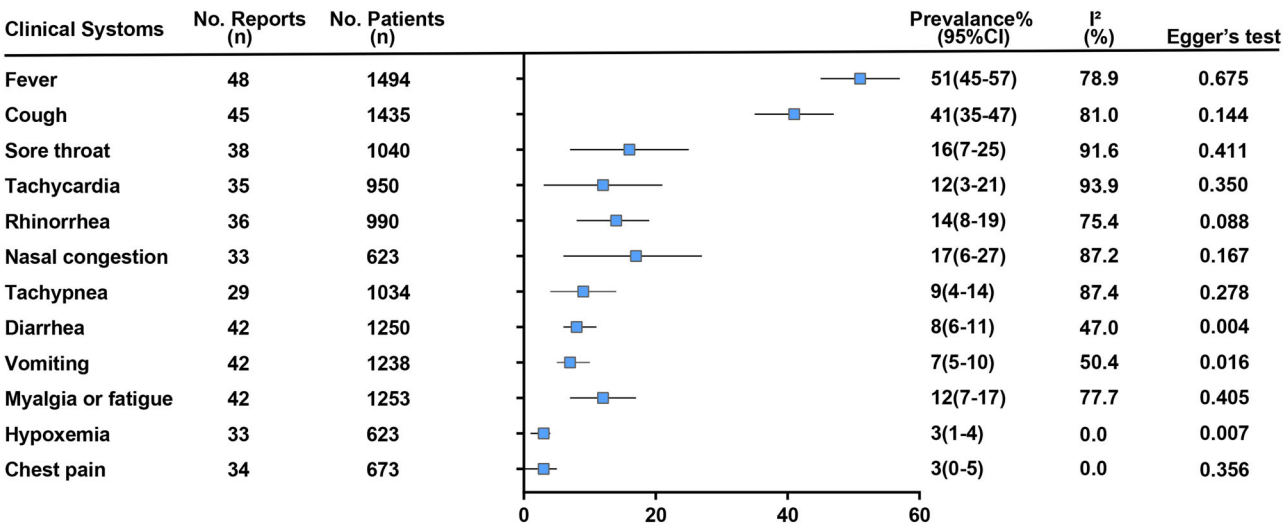

FIGURE 4 Aggregated results of clinical presentation in children with COVID-19. COVID-19, coronavirus disease 2019

CI: 25%-48%; $I^2 = 59.0\%$), respectively. We also evaluated the patients had elevated D-dimer, result revealed that nearly 11% (95% CI: 8%-14%; $I^2 = 0.0\%$).

Among children under 1-year old cases, the proportion of lymphopenia was 33% (95% CI: 24%-47%; $I^2 = 0.0\%$). The ratio of elevated CRP and LDH were 42% (95% CI: 6%-78%; $I^2 = 0.0\%$) and 50% (95% CI: 15%-69%; $I^2 = 0.0\%$), respectively. The high ALT and AST patients were 47% (95% CI: 25%-69%; $I^2 = 0.0\%$) and 33% (95% CI: 20%-67%; $I^2 = 0.0\%$), respectively. The proportion of elevated CK-MB was 88% (95% CI: 71%-94%; $I^2 = 8.5\%$) (Table 2).

3.2.5 | Imaging features

Imaging features for patients were summarized in Figure 6. All pediatric patients with normal imaging was 41% (95% CI: 30%-52%; $I^2 = 93.4\%$), GGO 36% (95% CI: 25%-47%; $I^2 = 92.9\%$), local patchy shadowing 26% (95% CI: 21%-32%; $I^2 = 58.2\%$), bilateral patchy shadowing 28% (95% CI: 21%-35%; $I^2 = 73.8\%$), white lung change was 2% (95% CI: 0%-4%; $I^2 = 0.0\%$) and pleural effusion 2% (95% CI: 0%-3%; $I^2 = 0.0\%$).

Among children under 1-year old cases, the proportion of normal imaging was 42% (95% CI: 6%-78%, $I^2 = 0.0\%$). The GGO accounted for 50% (95% CI: 20%-80%; $I^2 = 0.0\%$) of lung abnormality. Local and bilateral patchy shadowing were 42% (95% CI: 6%-78%; $I^2 = 0.0\%$) and 40% (95% CI: 13%-55%; $I^2 = 0.0\%$), respectively (Table 2).

3.2.6 | Publication bias

Publication bias was evaluated by Begg's test, which suggested that there was no notable evidence of publication bias except for 1 to 5 year ($P = .004$); asymptomatic ($P = .000$); critical ($P = .008$); diarrhea ($P = .004$); vomiting ($P = .016$); hypoxemia ($P = .007$); normal white blood cell ($P = .002$); leukocytosis ($P = .002$); leukopenia ($P = .000$); high CRP ($P = .009$) and pleural effusion ($P = .001$).

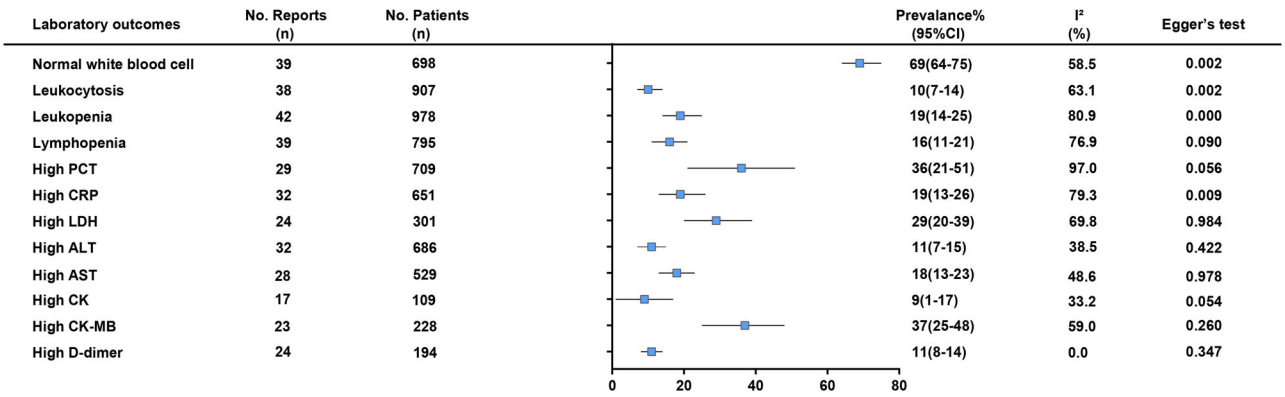

FIGURE 5 Summary results of laboratory examination in children with COVID-19. COVID-19, coronavirus disease 2019

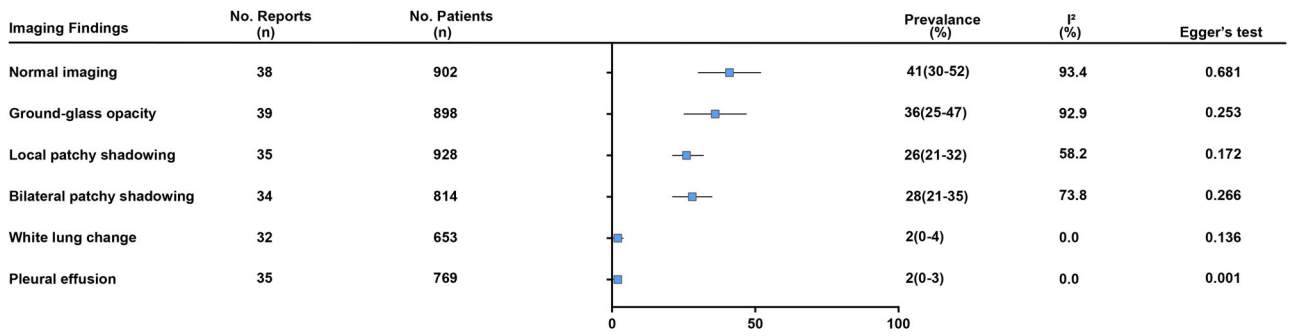

FIGURE 6 Pooled results of imaging features in children with COVID-19. COVID-19, coronavirus disease 2019

3.2.7 | Subgroup analysis

Tables S2 to S6 present the results of subgroup analyses. Noncase reports included case series and cohort studies, case reports only referred to the study design of the case report. The findings were consistent in all subgroup analyses except for the 6 to 10 years, critical and tachycardia subgroups.

4 | DISCUSSION

We comprehensively examined the demographic, clinical characteristics, laboratory, and imaging features among pediatric patients with COVID-19 and further made a meta-analysis with literature studies. We also compared the characteristics of SARS-CoV-2 infection in children under 1 year old, children between 0 and 18 years old, as well as in adults (Table 2). The main findings are as follows: first, SARS-CoV-2 was susceptible to all age groups of children, the most common clinical manifestations were fever and cough and the majority of them had experienced asymptomatic, mild and moderate illness; second, children were more likely to have normal leukocyte counts, whereas lymphocytosis occurred infrequently; Third, the incidence of critical illness and vomiting symptoms was high in children under 1 year old.

The pandemic of COVID-19 affected all age groups in children based on the current studies.[3,6,61] Our result was consistent with those previous studies that there was no significant difference in age distribution of SARS-CoV-2 infection among children. The most common clinical manifestations of COVID-19 pediatric patients were fever (51%) and cough (41%) from our meta-analysis, which were lower than the fever (78.0%-92.8%) and cough (57.0%-63.4%) in adults.[4,5,60] These findings further suggested that children's clinical symptoms were not typical when compared with adults. The frequency of severe illness was 7% in children with COVID-19, which was lower than that in adults (25.6%).[5] One possible reason might be that children are less likely to have underlying diseases such as diabetes, hypertension, or cardiovascular disease. In addition to the above reason, the fact that innate immune response declines with age could also be important for the difference.[62] The percentage of asymptomatic in children with COVID-19 was 20% and deserves full attention to control the ongoing pandemic.

For the laboratory examination, normal leukocyte counts were up to 70% in children, which was as similar as 69.7% in adults.[63] The reduction of lymphocytes in children was only 16%, but in adults, it went up to 43.1%,[4] 57.4%,[5] and 56%,[63] respectively, reported by previous meta-analysis. The reason for these differences may be related to the immune response of different organisms to novel coronavirus. The level of CK-MB was raised in 37% of all children, which is one of the classical biomarkers of cardiotoxicity. Subgroup analysis further revealed CK-MB was elevated in nearly 88% in children under 1 year old. These results suggested that we should pay special attention to the myocardial damage in children, especially for those under 1year old. It should be noted that the activity of CK-MB was detected by immunosuppressive method, which is easy to be affected by the peripheral blood creatine-kinase BB (CK-BB). In addition, the blood-brain barrier in children, especially in infants, is not fully developed, and more CK-BB will appear in the peripheral blood, resulting in the high level of CK-MB activity.[64-66] In the future, specific studies are still needed to explain the causes and effects of CK-MB elevation in children.

The CT manifestations of COVID-19 in pediatric patients are diverse and lack specificity depending on the severity of disease or clinical classification. Normal imaging occurred in 41% pediatric patients in our meta-analysis, which are similar to the other two reports with the largest number of pediatric cases so far, the proportion of normal lung CT was 35% (60/171) and 57% (66/115), respectively,[13,58] but, it was infrequent in adults, the rate of normal imaging was only 10%.[67] GGO was the most common performance in children presenting lung abnormality, which most located in the lower lung, outer band, near the pleura, and the scope was small compared with adults.[13,15,17,29,35,68,69] Pediatric patients with GGO was 36%, significantly lower than adults with 80% to 83%.[5,67] This may be related to the fact that COVID-19 in children shows milder than adults.

The rate of critical illness in children under 1 year old was 14%, higher than 5% in all children. These results suggested that clinicians should pay more attention to changes in disease activity in children under 1 year old. A total of 33% and 7% suffer from vomiting in children under 1 year old and all children, respectively. Based on all the above facts, it was worth noting that the proportion of infants developing critical cases is relatively high, and the initial symptom often include vomiting. However, due to the

limited sample size, large, well-designed studies are still needed to confirm these findings.

5 | LIMITATION

This meta-analysis has several limitations that should be addressed. First, few cohort studies available for inclusion, and most of them come from China. Second, it's hard to standardize the results of laboratory testing and radiographic imaging from different data sources. Third, more detailed patient information in children under 1 year old is not available in large sample studies at the time of analysis, the results need to be further updated.

6 | CONCLUSION

The COVID-19 pandemic affects all age groups in children and appears to be a mild illness. The common presenting complaints with COVID-19 are nonspecific symptoms, such as fever and cough. Normal leukocyte counts and infrequent of lymphopenia tend to be the laboratory characteristics. High incidence of critical illness and vomiting symptoms were as the main features in children under 1 year old. Characteristics of COVID-19 in children and adults are different and thus special criteria is still needed for more studies to identify.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Grant number: 81771589), the Key Project of Tianjin Health Care Professionals (Grant number: 16KG166), and the Program of Tianjin Science and Technology Plan (Grant number 18ZXDBSY00170).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the intellectual content of this manuscript and approved the final manuscript as submitted. (a) Conception and design: Chunquan Cai, Yongming Shen; (b) collection, assembly of data: Xiaojian Cui, Tongqiang Zhang; (c) administrative support: Ping Si, Yongsheng Xu; (d) data analysis and interpretation: Zhihu Zhao, Wei Guo, Wenwei Guo, Jiayi Zhang; (e) search literatures: Cuicui Dong, Jiafeng Zheng, Ren Na, Lisheng Zheng, Wenliang Li, Zihui Liu, Jinhu Wang, Jia Ma; (f) manuscript writing: all authors; (g) final approval of manuscript: all authors.

DATA AVAILABILITY STATEMENT

The original data can be requested reasonably.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with coronavirus disease 2019 (COVID-19). *J Med Virol*. 2021;93: 1057–1069. https://doi.org/10.1002/jmv.26398