

Clinical Features and Outcome of SARS-CoV-2 Infection in Children: *A Systematic Review and Meta-analysis*

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Objective: Knowledge about COVID-19 in children is limited due to the paucity of reported data. The pediatric age group comprises only less than 5% of total COVID-19 worldwide, therefore, large studies in this population are unlikely in the immediate future. Hence, we planned to synthesize the current data that will help in a better understanding of COVID-19 in children.

Evidence acquisition: Four different electronic databases (MEDLINE, EMBASE, Web of Science, and CENTRAL) were searched for articles related to COVID-19 in the pediatric population. We included studies reporting disease characteristics and outcomes of COVID-19 in patients aged less than 19 years. We performed a random-effect meta-analysis to provide pooled estimates of various disease characteristics.

Results: 27 studies (4857 patients) fulfilling the eligibility criteria were included in this systematic review, from a total of 883 records. About half of the patients had each of fever and cough, 11% (6-17%) had fast breathing, and 6-13% had gastrointestinal manifestations. Most of the patients had mild to moderate disease, and only 4% had a severe or critical illness. Leukopenia was the commonest reported laboratory abnormality.

Conclusion: Even among the symptomatic COVID-19 cases, severe manifestations are seen in very few children. Though fever and respiratory symptoms are most common, many children also have gastrointestinal manifestations.

Keywords: COVID-19, Gastrointestinal symptoms, Mortality, Severity.

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With the rapidly evolving severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) pandemic, the knowledge about the disease manifestations and severity has also evolved quickly. Due to its resemblance to SARS, influenza, and other respiratory viruses, children were initially thought to be more susceptible than adults. However, less than 5% of total coronavirus disease (COVID-19) cases belong to the pediatric age group, and the severity has been milder as compared to adults [3,4]. Information regarding clinical manifestations and outcomes of COVID-19 in adults is available due to a huge number of reported cases, but the scenario for the pediatric population is different as our knowledge about clinical and laboratory characteristics as well as prognosis of COVID-19 is very limited.

Due to this difference in the manifestations of COVID-19 among pediatric patients from adults, there is a need to clarify the disease manifestations and course among children. We performed this systematic review to synthesize the information on clinical manifestations, laboratory findings, and outcome of COVID-19 among the pediatric population.

METHODS

We performed this systematic review to describe the currently available literature on clinical features and outcomes of COVID-19 in children between 1 month-19 years. Our primary aim was to provide a pooled estimate of various clinical manifestations, disease severity, and outcomes in children with SARS-CoV-2 infection.

This study was conducted following the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [5]. A predefined search strategy was developed, and three investigators independently performed a literature search in MEDLINE, EMBASE, Web of Science, and CENTRAL (Cochrane central register of controlled trials) for the original articles published between December 01, 2019, to May 10, 2020. The search strategy was targeted for patients aged less than 19 years with SARS-CoV-2 infection or COVID-19 and was based on two basic groups of terminologies: study population [pediatric / children / child / infant / adolescent], and terms related to or describing COVID-19 and novel coronavirus (nCoV) infection. Terms used for literature search were: COVID-19, coronavirus, SARS-CoV-2, 2019 nCoV, severe acute respiratory syndrome

coronavirus 2, pediatric, children, adolescent, and infant. Specific search strategies were created for each search engine, by using the MeSH term and above-described terms. The electronic search was also supplemented by a hand search of bibliography of the included studies and relevant review articles. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines [6]. No language restrictions were used.

Study selection: A predefined set of the criteria were used for study selection for this systematic review. Studies enrolling children and clearly reporting data on their clinical features were considered eligible for the review. Initially, two researchers independently screened the title and abstract for the eligibility. Later all the authors examined full-text articles for inclusion and exclusion criteria. Studies were included if they met the following criteria: (i) Patients aged less than 19 years with confirmed SARS-CoV-2 infection, (ii) the study reporting clinical manifestations, disease severity, and/or laboratory investigations and/or outcome of SARS-CoV-2 in children, and (iii) all types of study design: cohort, cross-sectional studies, case-control studies, and case series. Correspondences or letters fulfilling the above criteria were also included. We excluded: (i) case series reporting nine or fewer cases, (ii) studies reporting only neonatal data, (iii) studies reporting about other serotypes of coronavirus, (iv) narrative or systematic review, (v). Conference proceedings, (vi) editorial, perspective, etc. not meeting the inclusion criteria.

Data extraction and quality assessment: A well-structured, standardized proforma was used for data extraction. Four investigators independently extracted data from the full text of the eligible studies. Extracted data included first author name, year, country, journal, study design, study population information for risk of bias assessment of the study, method, and type of sample used for confirmation of SARS-CoV-2 infection, age and gender distribution of cases, clinical and laboratory manifestations, major radiological abnormalities, the severity of the disease, and reported outcomes in studies. Any disagreement between two investigators was resolved through discussion with another investigator. An independent researcher rechecked the extracted data for its accuracy and completeness. Every effort was made to avoid duplicity of data by screening full-text articles of the included studies for author name, location, setting, date and duration of the study, number of participants, and baseline data. There is a possibility that the small case series/case report might be a part of larger retrospective cohort. To address this issue, we excluded case reports and small case series (up to nine patients).

The quality of the included studies in this systematic review was assessed using the Newcastle Ottawa scale [7]. We used the following scoring system: Good quality: 3 or 4 stars in selection domain, and 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; fair quality: 2 stars in selection domain and 1 or 2 stars in comparability domain, and 2 or 3 stars, in outcome/exposure domain; and poor quality: 0 or 1 star in selection domain or 0 stars in comparability domain or 1 star in outcome/exposure domain. Three investigators independently assigned an overall risk of bias to each eligible study, and if they disagreed, another researcher resolved the discrepancy.

Data synthesis and statistical analysis: We present the data with descriptive statistics and provide pooled estimates of various parameters, wherever it was feasible to meta-analyze the data. We categorized the disease severity into five categories (asymptomatic, mild, moderate, severe, and critical) as described by Dong, et al. [8]. We provide the pooled estimates of various categories of disease severity from studies in which severity classification was reported. Percentages and mean values were calculated to describe categorical and continuous variables, respectively.

Meta-analyzed parameters were presented as pooled estimates with a 95% confidence interval (CI). Meta-analysis was performed using STATA version 14.2 (Stata Corp LLC, College Station, Texas, USA).

We pooled data from individual studies using a random effect model with the assumption that the frequency of clinical features and other parameters will be variable across the studies. Heterogeneity in studies was explored by inspection of forest plot as well as using the chi-square test on Cochran's Q statistics. Study heterogeneity was assessed by using the Higgins and Thompson I² method [9]. Publication bias was assessed by Egger's test.

RESULTS

Using the above-described search strategy we found 883 articles, out of which 27 studies (4857 patients) (**Fig. 1**) that met inclusion and exclusion criteria were included for final qualitative synthesis, and 25 studies for quantitative synthesis (**Web Table 1**). A publication bias was found [bias (95% CI) = -2.9 (-4.5 to -1.3); *P* = 0.01].

Among 27 included studies, 21 were from China [8,10-29], two each from Italy [30,31] and the Republic of Korea [32,33], and one each from the United States of America [4], and Spain [34]. Among the included studies, five were good, thirteen were fair, and nine were of poor quality as assessed by the Newcastle Ottawa scale [7].

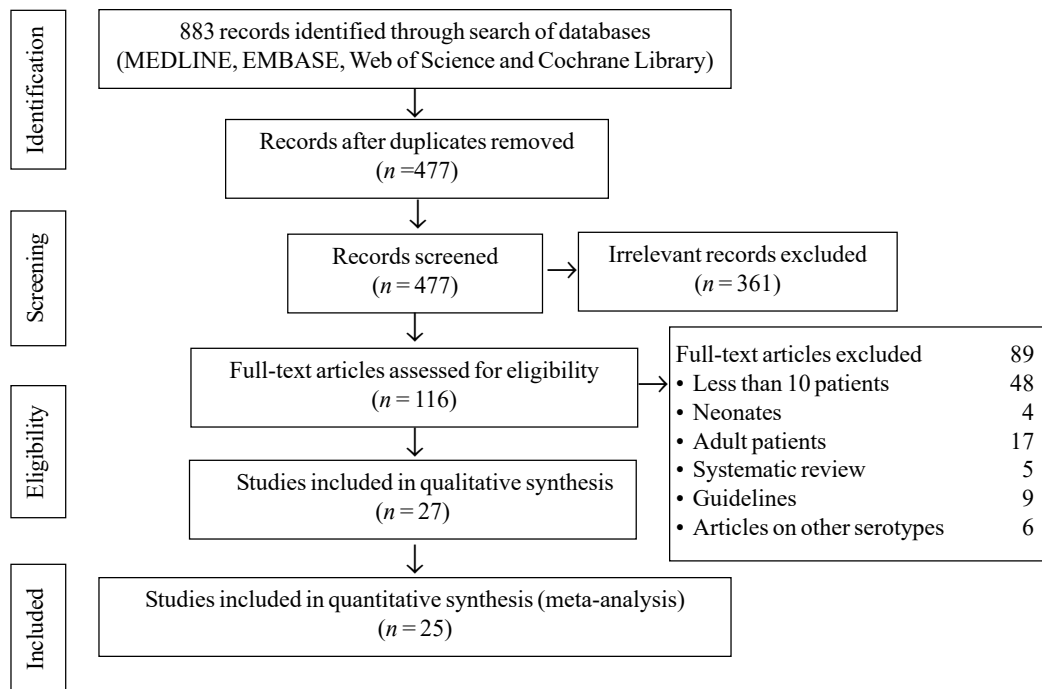


Fig. 1 Flow diagram of the study selection process.

A total of 4857 pediatric cases were reported in 27 eligible studies. The mean (SD) age of the participants was 6.4 (3.4) years (reported in eight studies) whereas the range varied from one month to 19 years. Twenty-three studies [8,10-25,27-32,34] (1777 patients) reported separate data for gender; 1014 (57%) of all the patients were male. Twenty-three studies [4,10-16,18-25,27-32,34] described the frequency of specific symptoms in patients, of which only seventeen reported disease severity.

Clinical manifestations and disease severity: Sixteen studies reported data on the history of exposure to a SARS-CoV-2 infected patient and 91% (87-95%) of children had a history of contact [10,11,14,15,17-25,27,28,30,34]. Among the included studies, only 17 studies reported data on asymptomatic SARS-CoV-2 infection [8,11,12,15,16,19,21-25,27-32]. Almost one-fourth, 23% (17-30%) of patients were asymptomatic. Since we included studies describing clinical features, this number is not representative of the overall proportion of asymptomatic cases in COVID-19 children. Twenty-three studies ($n=1330$) reported data on specific symptoms [4,10-16,18-25,27-32,34].

Fever was the commonest clinical feature and was seen in almost half of the patients (**Table I**). Similarly, 45% of symptomatic patients had cough, 11% had fast breathing, and 4-9% had gastrointestinal manifestations.

Of the all included studies, fifteen ($n=1666$) provided specific information on disease severity [8,11-13,15-20,22,24,25,30,31] (**Table II**). Most of these patients had mild to moderate disease (96%), with a very small proportion of patients having a severe manifestation (3%) like hypoxia, dyspnea, and cyanosis (**Table I**). Only 1% of all the symptomatic pediatric cases were critically sick (acute respiratory distress syndrome, respiratory failure, shock, encephalopathy, myocardial injury or heart failure, acute kidney injury *etc.*).

To explore high heterogeneity, we did sensitivity and subgroup (only for the quality of the studies) analysis and we did not find any meaningful significant difference in the pooled estimates of any of the clinical or laboratory feature. None except one study provided data on relationship of severity of the illness with the age of the patients. Dong, *et al.* [35] assessed the severity of illness by age and reported that the young children, particularly infants are more vulnerable to SARS-CoV-2 infection and had more severe disease. Data on relationship of disease severity and gender was not reported in children.

Laboratory and radiological abnormalities: Among the laboratory findings (**Table III**), leukopenia was the most commonly detected abnormality and was seen in almost one-fifth of the patients. Twelve percent also had lymphopenia. On the other hand, leucocytosis was

Table I Clinical Features in Children with SARS-CoV-2 Infection

Symptoms	Studies (patients)*	Pooled estimates [#]	Heterogeneity [‡]	P value
Fever	23 (1330)	49 (41-58)	90	<0.001
Cough	23 (1330)	45 (39-51)	79	<0.001
Fast breathing	10 (966)	11 (6-17)	87	<0.001
Coryza	15 (1095)	20 (13-26)	87	<0.001
Sore throat	15 (1012)	14 (7-21)	92	<0.001
Vomiting	13 (1067)	6 (4-9)	48	0.03
Diarrhea	15 (1102)	9 (6-13)	80	<0.001
Abdominal pain	7 (604)	4 (1-6)	52	0.05
Myalgia	6 (418)	10 (1-18)	83	<0.001
Headache	6 (546)	10 (1-19)	92	<0.001
Hypoxia	6 (405)	2 (1-3)	0.0	0.84

*Number of studies (patients); [#]in % (95%) CI; [‡]in I²%; P value for I².

Table II Severity of COVID-19 in Children

Disease severity	Studies (patients)*	Pooled estimates [#]	Heterogeneity [‡]
Mild	10 (1224)	40 (26-52)	94
Moderate	10 (1224)	56 (40-72)	95
Severe	19 (1677)	3 (1-5)	68
Critically sick	19 (1677)	1 (0.1-2)	31

*Number of studies (patients); [#]in % (95%) CI; [‡]in I²%; P value for I².

detected in 12% (6-17%) patients. A significant proportion (9-25%) of the cases had raised inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and procalcitonin). From the 15 studies which reported data on organ dysfunction, seven patients had acute kidney injury and deranged liver function was documented in 10-15% of patients [10-16,18,20-23,27,28,30]. Thirteen studies reported data on radiological imaging (X-ray, Computerized tomography scan), and the common radiological findings on CT scan were ground-glass opacity (41%) and consolidation (16%) [12,14-16,19-25,28,29,32].

Outcomes: Due to low event rate of outcome in studies we did not meta-analyze this data. Mortality data was provided in twenty-two studies (4476 patients) and overall, five deaths have been reported [4,8,10-16,18-21,24-28,30,32-34] in these studies. Nineteen studies [4,10-14,16,18-22,24,25,27,30-32,34] reported details on hospital stay in 1670 children and of these 35 (2.1%) patients required intensive care support for management and mechanical ventilator support was needed for twelve patients (0.7%).

DISCUSSION

This review summarizes the clinical features, laboratory findings, disease severity and prognosis from the available studies about pediatric COVID-19 in the age group of one month to 19 years. The total number of reported pediatric cases is much less than that reported in adults.

Similar to adults, the commonest clinical features are fever and cough; however, their frequency is much lower in children (60-100% in adults vs. 40-60% in children) [37,38]. On the other hand, features like dyspnea, hypoxemia, and sputum production are more frequently seen in adults. Like adults, the gastrointestinal manifestations (diarrhoea, vomiting) are frequently seen in children and sometimes may be the sole manifestation of COVID-19 [37-39]. Overall, respiratory symptoms followed by gastrointestinal symptoms are the predominant manifestations in children as well as adults [37,38]. These findings play an important role in devising a screening strategy for COVID-19 in children. The screening algorithms in adults rely primarily upon fever and cough as these are present in more than 80% of the patients; however, the same approach for the pediatric population is likely to miss out 40-50% of the cases. Therefore, the screening strategy for children should incorporate both respiratory and gastrointestinal features.

Similar to adults, one-third of children with COVID-19 children will have abnormal complete blood count [37,38]. Unlike other infections, leukopenia is more frequently encountered than leukocytosis even in milder cases and should raise a high index of suspicion for cases being evaluated for COVID-19. Around 15-25% of pediatric cases may have raised C-reactive protein and

Table III Laboratory Findings in Children with COVID-19

Laboratory parameter*	No. of studies (patients)	Pooled estimates % (95% CI)	Heterogeneity (I^2 %)	P value for I^2
Leukopenia	17 (743)	16 (11-22)	81	<0.001
Leucocytosis	17 (743)	12 (7-17)	71	<0.001
Lymphopenia	19 (808)	12 (8-17)	75	<0.001
Elevated aspartate transaminase	14 (665)	15 (9-21)	70	<0.001
Elevated alanine transaminase	14 (665)	10 (7-12)	0.0	0.71
Elevated C-reactive protein	13 (620)	16 (10-22)	79	<0.001
Elevated procalcitonin	9 (476)	25 (9-42)	97	<0.001
Elevated erythrocyte sedimentation rate	4 (125)	9 (4-14)	0.0	0.47

*The normal values of the laboratory parameters were as per the authors of the given study.

procalcitonin in alike other infections, and therefore inflammatory markers may not differentiate COVID-19 from other infections. Serial procalcitonin measurements in COVID-19 are shown to be useful in predicting disease severity in adults, but similar data for the pediatric population is lacking [40]. Like adults, 10-25% of pediatric COVID-19 cases may have elevated liver enzymes (AST, ALT), however, its impact on disease severity is unknown [41].

Most of the infections are asymptomatic in children as well as adults and many of them are not reported. Therefore, we confined ourselves to symptomatic cases only. Unlike other influenza-like viral infections (MERS-CoV, H1N1) the children have less severe COVID-19 affection as compared to adults [42]. Among the symptomatic ones, mostly have a mild cough, cold, fever, and upper respiratory tract infections only. The severe disease and the critical disease (acute respiratory distress syndrome, respiratory failure, shock, myocardial failure, and multiorgan dysfunction) are less frequent in children (1-3%) as compared to adults (10-30%) [37,38-43]. Similarly, the mortality associated with COVID-19 is much lower in the pediatric population (less than 0.1 %) than that reported in adults (5-15%).

We excluded neonates to avoid clinical heterogeneity as the clinical manifestations, mode of transmission, and outcome in the neonatal population are quite different from the pediatric population and are difficult to differentiate from the other neonatal illness. We included studies published until May 10, 2020 and enrolled patients tested positive for SARS-CoV-2 by RT-PCR. Also, it comprises information from observational studies done in six different countries and is likely to be the true representation of the clinical picture. The studies included in previous reviews were exclusively from

China and were primarily case reports and small case series due to the non-availability of larger studies at that time [36,44,45].

This study had several limitations. The pandemic is still spreading and the available data are derived over a short duration. The clinical features, laboratory abnormalities, and radiological findings are limited to the studies describing symptomatic patients admitted in the hospital. Therefore, it may not fully characterize mild/asymptomatic patients not requiring hospitalization. Also, we did not evaluate the impact of pre-existing comorbidities over the clinical outcome; however, this is likely to be significantly less than adults. As most of the studies are small, retrospective with lot of heterogeneity and publication bias, the overall evidence (GRADE) is very low. Therefore, the results should be interpreted cautiously.

Most of the children with COVID-19 were asymptomatic. Amongst the symptomatic patients, the majority will have a mild infection with very few requiring intensive unit care. Though fever and other respiratory symptoms make up the commonest clinical presentation, many may present with gastrointestinal symptoms. Therefore, a comprehensive screening strategy including respiratory as well as gastrointestinal features may be more useful.

Contributors: JM: conceptualized and designed the study, formulated search strategy, collected data and analyzed the data, and drafted the manuscript; JY: Acquisition and analysis of the data, and critically revised the manuscript; LS: Acquisition and analysis of the data, and critically revised the manuscript; AY: Supervised the search strategy, data retrieval, and completeness of the data. Performed hand search of the bibliographies and critically revised the manuscript; JK: Conceptualized and designed the study, formulated search strategy, collected and analyzed the data, and drafted the manuscript. All the authors

WHAT IS ALREADY KNOWN?

- Most children with COVID-19 present with mild symptoms, and carry good prognosis.

WHAT THIS STUDY ADDS?

- Though fever and cough are the most common clinical presentation, many children may present with gastrointestinal symptoms.
- A comprehensive screening strategy including respiratory as well as gastrointestinal features (diarrhea and vomiting) may be more useful.

approved the final version of the manuscript and will be accountable for all aspects of the work.

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Web Table I Details of Studies Included in the Systematic Review

<i>Author</i>	<i>Country</i>	<i>Patients (n)</i>	<i>Study design</i>	<i>Age (range)</i>	<i>Study quality</i>
CDC COVID-19 Response Team [4]	United States of America	2572	Retrospective case series	0-18 y	Good
Chen, <i>et al.</i> [43]	China	12	Retrospective case series	6 mo-17 y	Poor
Cai, <i>et al.</i> [14]	China	10	Retrospective case series	3 mo-10.9 y	Poor
Dong, <i>et al.</i> [35]	China	728	Retrospective case series	4-15 y	Good
Du, <i>et al.</i> [11]	China	14	Retrospective case series	0-16 y	Fair
Garazzino, <i>et al.</i> [31]	Italy	168	Retrospective cohort	1 d -17 y	Good
Kai, <i>et al.</i> [32]	Republic of Korea	15	Retrospective case series	4-14 y	Poor
Korea CDC [33]	Republic of Korea	480	Retrospective case series	0-19 y	Poor
Li B, <i>et al.</i> [29]	China	22	Retrospective case series	2-8 y	Fair
Li H, <i>et al.</i> [13]	China	40	Retrospective cohort	16 d -14.2 y	Poor
Lu, <i>et al.</i> [16]	China	171	Retrospective case series	1d to 15 y	Fair
Ma, <i>et al.</i> [12]	China	50	Retrospective case series	0-16 y	Fair
Parri, <i>et al.</i> [30]	Italy	100	Cohort	0-17.5 y	Fair
Qiu, <i>et al.</i> [15]	China	36	Retrospective cohort	1-16 y	Good
Shi, <i>et al.</i> [17]	China	10	Retrospective case series	7 mo-11y	Fair
Shen, <i>et al.</i> [26]	China	28	Retrospective case series	1mo-17y	Poor
Song, <i>et al.</i> [19]	China	16	Retrospective case series	11mo-14 y	Poor
Tagarro, <i>et al.</i> [34]	Spain	41	Case series	0-15 y	Poor
Tan, <i>et al.</i> [28]	China	10	Retrospective case series	13 mo- 11y 8 mo	Fair
Wang, <i>et al.</i> [27]	China	31	Retrospective case series	6 mo-17 y	Fair
Wu, <i>et al.</i> [25]	China	74	Retrospective case series	1mo -15 y	Good
Xia, <i>et al.</i> [20]	China	20	Retrospective case series	1d-14 y	Fair
Xin, <i>et al.</i> [24]	China	13	Retrospective case series	2-17 y	Fair
Xu, <i>et al.</i> [21]	China	10	Retrospective case series	2 mo-16 y	Poor
Yaoling, <i>et al.</i> [22]	China	115	Retrospective case series	1 mo-15 y	Fair
Zheng, <i>et al.</i> [18]	China	25	Cross-sectional	1mo -14 y	Fair
Zhang, <i>et al.</i> [23]	China	46	Retrospective cohort	7 mo-18 y	Fair