



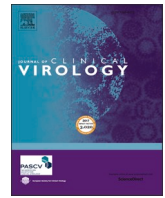
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Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: A systematic review and meta-analysis

Sujan Badal^a, Kalpana Thapa Bajgain^b, Sujeena Badal^c, Rama Thapa^d, Bishnu B. Bajgain^{e,*}, Maria Jose Santana^e

^a School of Medicine, University of Minnesota, 420 Delaware St. SE, Minneapolis, MN, 55455, USA

^b AabKa Research & Consulting, Calgary, Alberta, Canada

^c BLH Technologies, INC, Rockville, MD, USA

^d Faculty of Health Sciences, University of Lethbridge, 4401 University Drive, Lethbridge, Alberta, T1K 3M4, Canada

^e Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, T2N 1N4, Canada

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ABSTRACT

Introduction: The novel coronavirus pandemic is an ongoing challenge faced by the public and health care systems around the globe. Majority of information and evidence gathered so far regarding COVID-19 has been derived from data and studies in adult populations. Crucial information regarding the characterization, clinical symptomatology, sequelae, and overall outcomes in the pediatric population is lacking. As such, we aimed to conduct a comprehensive meta-analysis and systematic review to collect and analyze current evidence about COVID-19 in the pediatric population.

Method: A systematic search and review of scientific literatures was conducted following the PRISMA guidelines using PubMed, Embase, Scopus, Medline, and Google Scholar databases. All relevant studies until June 16, 2020 were included. Studies were reviewed for methodological quality, and random-effects model was used to conduct the primary meta-analysis. I^2 value and Egger's test was used to estimate heterogeneity and publication bias respectively.

Results: We reviewed 20 eligible studies that included 1810 pediatric patient population (<21 yo) with PCR tested COVID-19 positivity. In pooled data, majority (25 % [CI 18–32], I^2 59 %) of overall COVID-19 positive patients fell in the 6–10 yr age group. 13 % ([CI 11–14], I^2 78 %) of the patients were asymptomatic, with headache (67 % [CI 60–74], I^2 46 %), fever (55 % [CI 52–58], I^2 61 %), and cough (45 % [CI 42–49], I^2 79 %) accounting for the most prevalent physical signs seen in symptomatic patients. Leukopenia (12 % [CI 9–15], I^2 50 %) and lymphopenia (15 % [CI 13–19], I^2 85 %) was common. Elevated Ferritin (26 % [CI 16–40], I^2 73 %), Procal (25 % [CI 21–29 %], I^2 83 %), and CRP (19 % [CI 16–22 %], I^2 74 %) were other laboratory abnormalities commonly observed. Common radiological features were ground-glass opacities (36 % [CI 32–39 %], I^2 92 %), normal finding (33 % [CI 30–36 %], I^2 81 %), and consolidation. 29 % ([CI 26–33], I^2 85 %) of the patient cases was non-severe, whereas only 5 % ([CI 1–8], I^2 87 %) was severe. Mortality was observed in 0.3 % ([CI 0.1–0.4], I^2 0%) of the overall cases.

Conclusion: COVID-19 is prevalent across all pediatric age-groups and presents with varying degree of symptomatology. However, children have a milder course of the disease with extremely favorable prognosis. Laboratory and radiological features are inconsistent and require further investigations. Additional studies are needed on this topic to corroborate findings and establish evidence-based and consistent characterization of COVID-19 in the pediatric population.

* Corresponding author at: Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary, Alberta, T2N 1N4, Canada.

E-mail addresses: badal014@umn.edu (S. Badal), k.thapab@aabka.ca (K. Thapa Bajgain), sbadal@blhtech.com (S. Badal), rama.thapa@uleth.ca (R. Thapa), bishnu.bajgain@ucalgary.ca (B.B. Bajgain), mjsantan@ucalgary.ca (M.J. Santana).

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1. Background

In late 2019, an outbreak of pneumonia cases of unknown origin appeared in Wuhan, China. In the span of a few months the coronavirus disease (COVID-19), the source of that outbreak, was declared a global pandemic by the World Health Organization (WHO) [1]. The novel COVID-19 caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has since become a growing public health emergency of international concern. As of November 19, 2020, it has affected more than 56 million individuals with 1,355,143 reported deaths in 191 countries [2]. Initially, the majority of infected patients were correlated to the Wuhan Sea-food market, implying primarily and predominantly zoonotic transmission. However, no clear animal source has been identified to date and human to human transmission is now the predominant mode of transmission of new infections [3].

Studies have demonstrated that people of all ages are vulnerable to SARS-CoV-2, particularly with higher severity and mortality in older age populations and in individuals with underlying comorbidities [4]. Children, especially infants, are usually more susceptible to certain infectious diseases as compared to adults, due to their developing immune system [5]. However based on current observations, in children the susceptibility to COVID-19 seems to be much lower, with less frequency of severe cases and only rare cases of fatality [6]. Also, in pediatric COVID-19 infections the spectrum of clinical characteristics and outcomes seem to vary considerably in the limited number of studies currently available [7]. Although children typically experience a milder

form of the disease, they can still be a major source of transmission, possibly more so than adults, given the lack of and varying degree of signs and symptoms. With scarce data and lack of large-scale studies, the characterization of COVID-19 in children remains an active and necessary area of study.

In this systematic review and meta-analysis, we aim to collect updated evidence regarding COVID-19 in children and investigate prevalence of clinical symptoms, laboratory and radiological findings, and clinical outcomes. Further understanding and characterization of COVID-19 in children can better inform the ongoing efforts to control this global pandemic.

2. Methods

2.1. Search strategy and study selection criteria

Our systematic review and meta-analysis was conducted according to the PRISMA guidelines [8]. A comprehensive search spanning 2019 – June 16, 2020 was conducted in PubMed, Embase, Scopus, Medline, and Google Scholar using various combinations of keywords: “coronavirus or COVID-19 or 2019-nCoV or SARS-CoV-2” and “pediatric or neonate or newborn or infant or children or adolescence” (Appendix 1). A total of 1154 publications were identified in various databases. We included studies that offered epidemiological, clinical information and one or more outcome data on pediatric (<21 years) COVID-19 cases diagnosed with PCR. Excluded articles included those that did not contain relevant

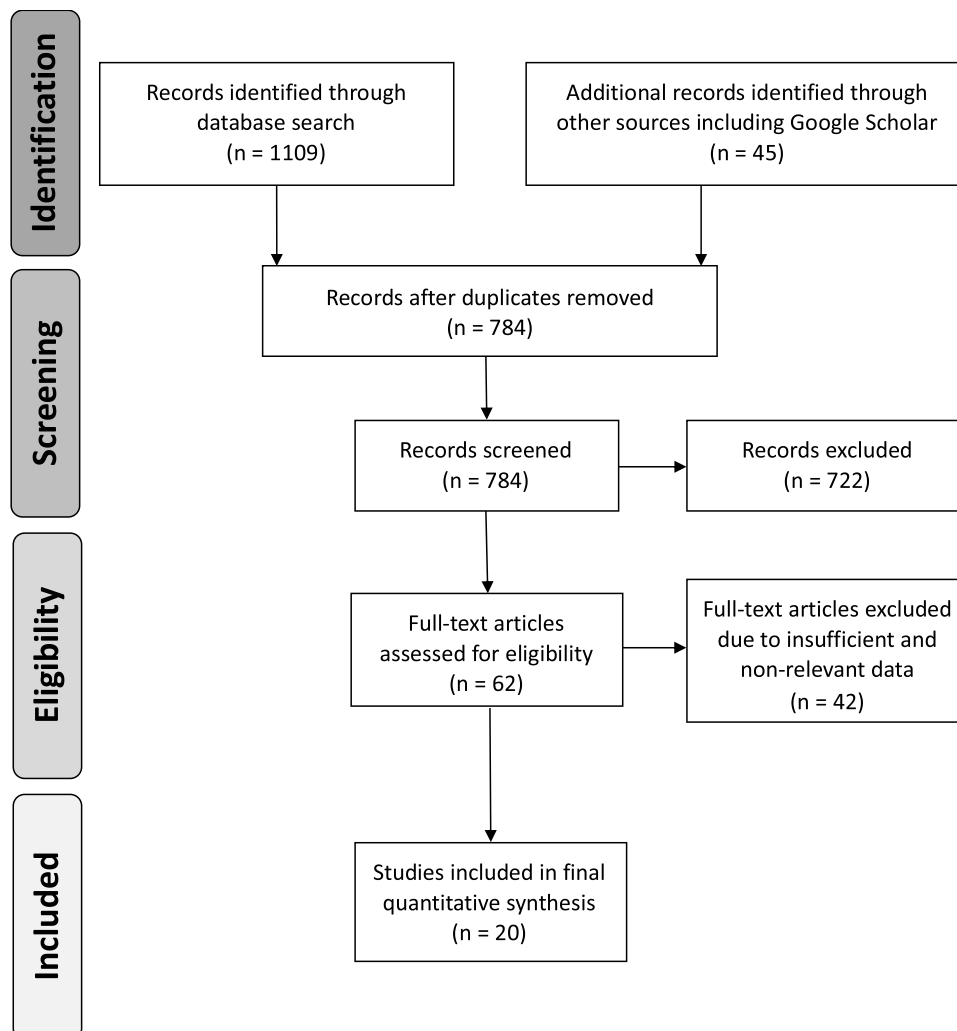


Fig. 1. PRISMA flow chart of the systematic literature review and article identification process.

and adequate data concerning prevalence, clinical features, and outcomes; exclusively neonatal or specific age group studies; comorbidity specific studies; and non-English publications (Fig. 1).

2.2. Data extraction and quality assessment

Two independent reviewers extracted all relevant data following full-text screening for eligibility. The following items were extracted from each study: author, publication date, study design, participant demographics, timeline, and if available, clinical symptoms, laboratory markers, radiological features, mortality/severity outcomes, length of hospital stay and clearance of disease. Any variations between authors were resolved through a consensus-based detailed discussion. The quality of included studies was assessed independently by two authors using the Newcastle-Ottawa Scale (NOS) [9].

2.3. Data synthesis and analysis

The primary outcomes of the study were prevalence of - COVID-19 in various age groups; clinical symptoms, laboratory markers, radiological features; and severe/mortal outcomes. Length of hospital stay (LOHS) and clearance of virus outcomes was also analyzed from available reports. Disease severity was categorized into four types: mild, moderate, severe, and critical according to published guidelines [10]. Severity outcomes were further classified into non-severe and severe groups consisting of mild/moderate cases and severe/critical cases respectively for pooled analysis. Random effects model was used to calculate pooled estimates of prevalence with 95 % confidence intervals. Freeman-Tukey double arcsine transformation was used to stabilize the variance of specific prevalence rates. I^2 index was used to assess heterogeneity with values 25 %, 50 %, and 75 % representing low, moderate, and high heterogeneity respectively [11]. If analysis included more than three studies, egger precision weighted linear regression tests and funnel plots were used to test potential publication bias, with p-value <0.05 considered significant for publication bias. If publication bias was present, the trim and fill method was performed to evaluate the effect. Meta-analysis was performed using metapackages in R (version 3.6.0).

3. Results

3.1. Study selection, quality, and epidemiological characteristics

A total of 1154 articles were identified in the initial search. After removing duplicates and performing detailed selection process, a total of 20 retrospective studies were finalized (Fig. 1) [12–31]. The quality of study assessed using the NOS ranged from good to high quality (Table 1; Supp. Table A). The total number of study population was 1810, with majority of cases coming from China (N = 1286). The general timeline of these studies ranged from December 2019 to April 2020. The median age of the patient population was approximately 8 yr [6–10], with male to female ratio of 1.34 (Table 1).

3.2. Meta-analysis results

Eleven of the eligible studies included data on COVID-19 positive population categorized across various pediatric age groups. These data were structured into age ranges in four years interval and analysis was performed to determine prevalence of the disease (Fig. 2). Overall, prevalence of COVID-19 across various age groups were, 17 % in <2 yr (CI 10–24); 21 % in 2–6yr (CI 16–25); 25 % in 6–10yr (CI 18–32); 23 % in 10–14yr (CI 17–25); 15 % in 8–24yr (CI 8–24). Further meta-analysis was conducted on 12 clinical symptoms, 11 laboratory markers, and 3 radiological features (Fig. 3). Overall, 13 % (CI 11–14) of the patient population were asymptomatic, with headache (67 % [60–74]), fever (55 % [52–58]), and cough (45 % [42–49]), being the most common symptoms. The remaining clinical symptoms had an overall estimated prevalence of <20 %. Among commonly reported laboratory findings, elevated inflammatory markers including ferritin (26 % [16–40]), Procal (25 % [21–29]), and CRP (19 % [16–22]) were the most common. Decreased lymphocytes (15 % [13–19]) and leukocytes (12 % [9–15]) were also more common than elevated counts of these immunological markers. Regarding radiological features, only small differences in prevalence was found between normal (33 % [30–36]), consolidation (29 % [26–33]), and ground glass opacification (GGO) (36 % [32–39]) findings. In analysis of the clinical outcomes including mortality and severity, prevalence of mortality was 0.3 % (CI 0.1–0.4), while severe and non-severe groups had 5% (1–8) and 84 % (92–97) estimated prevalence respectively (Table 2). Average LOH from available reports

Table 1
Main characteristics and quality of reviewed studies.

Study (n = 20)	Timeline (mm.dd)	Location	N = 1810	Age (yr) ^a	Gender (M/F)	Quality [†]
Dong, Y. et al.	Jan 06 - Feb 08	China	728	10 [4–15]	418/310	*****
Peng, H. et al.	Dec 08 - Feb 29	Wuhan, China	75	6.06 ± 4.78	44/31	*****
Bai, K. et al.	Jan 19 - Mar 12	Chongqing, China	25	11 [6.3–14.5]	14/11	*****
Du, H. et al.	Jan 28 - Feb 28	Wuhan, China	182	6 [0.01–15]	120/62	*****
Qiu, H. et al.	Jan 17 - Mar 01	Zhejiang, China	36	8.3 ± 3.5	23/13	*****
Shen, Q. et al.	Jan 08 - Feb 26	China	9	8 [1–12]	3/6	*****
Song, W. et al.	Jan 01 - Mar 17	Hubei, China	16	8.5 [1.5–14]	10/6	*****
Tan, Y.P. et al.	Jan 27 - Mar 10	Changsha, China	10	7 [1–12]	3/7	*****
Zheng, F. et al.	Feb 01 - Feb 10	Hubei, China	25	3 [2–9]	14/11	*****
Zhu, L. et al.	Jan 24 - Feb 22	China	10	9.5 [6.25–11.75]	5/5	*****
Cai, J. et al.	Jan 19 - Feb 03	China	10	6.5 [4.25–8.75]	4/6	*****
Lu, Y. et al.	Jan 30 - Mar 10	Wuhan, China	110	6 [2–9]	59/51	*****
Ma, H. et al.	Jan 21 - Feb 14	Wuhan, China	50	2.5 [0.9–7.0]	28/22	*****
Garazzino, S. et al.	Mar 25 - Apr 10	Italy	168	2.3 [0.3–9.6]	94/74	*****
Parri, N. et al.	Mar 03-Mar 26	Italy	130	6 (0–11)	73/57	*****
Garcia-Salido, A. et al. [†]	Mar 01 - Apr 15	Spain	7	8.35 [4.46–11.11]	4/3	*****
Foster, C.E. et al.	Mar 10 - Apr 18	Texas	57	10.7 [0.1–20.2]	32/25	*****
Zachariah, P. et al.	Mar 01 - Apr 15	New York City	50	9 [0.5–21]; 14 [8–19] ^b	27/23	*****
Mannheim, J. et al.	Mar 05 - Apr 08	Chicago, Illinois	64	11 [7–16]	36/28	*****
Shekerdemian, L. S. [†]	Mar 14 - Apr 10	USA/Canada	48	13 [4.2–16.6]	25/23	*****

[†] Data from PICU cases only.

[†] Newcastle-Ottawa Scale (NOS) quality assessment rating.

^a Mean ± SD or Median [IQR].

^b Age reported separately as Median [IQR] for severe and non-severe cases respectively.

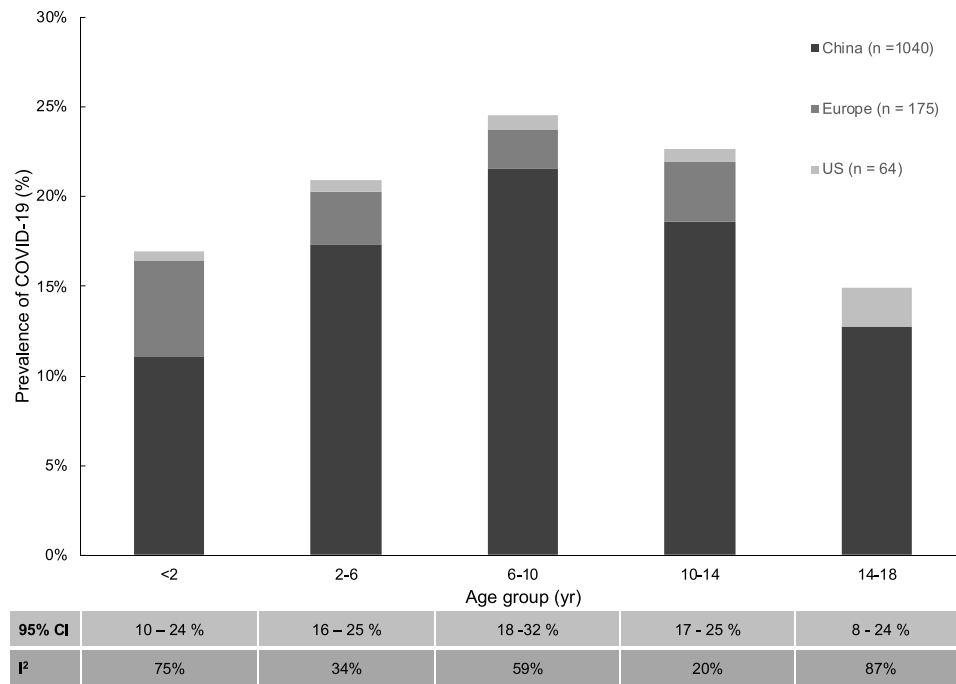


Fig. 2. Prevalence (%) of COVID-19 across various pediatric age groups. Pooled studies (N = 11) included data from China, Europe and US with varying total number of cases (n) for each age group as demonstrated. (Estimated p-values <0.05 for each age group).

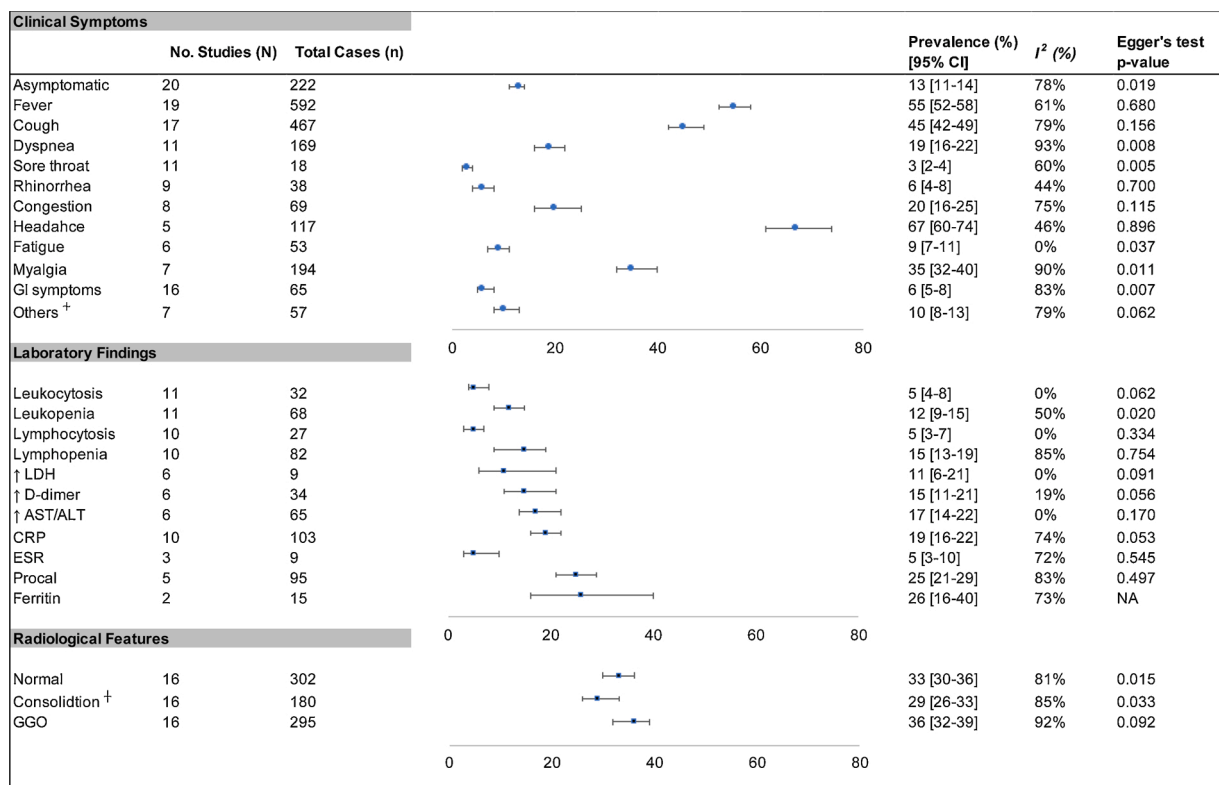


Fig. 3. Meta-analysis of the prevalence of clinical symptoms, laboratory findings and radiological features in pediatric COVID-19 patients. † Includes Unilateral and/or bilateral findings; □ Includes other Neurological, Hematological, and Musculoskeletal symptoms. Abbreviations: GI: Gastrointestinal; GGO: Ground Glass Opacity; LDH: Lactate Dehydrogenase; AST: Aspartate transaminase; ALT: Alanine transaminase; ESR: Erythrocyte Sedimentation Rate; Procal: Procalcitonin.

was 10.3 days and clearance of virus occurred at an average of 9.4 days.

3.3. Sensitivity and publication bias

Substantial heterogeneity was found among most sub-groups (Figs. 2 and 3, Table 2). In sensitivity analysis performed to assess stability of pooled results, no significant changes in overall results were found after sequential omission of studies. The Egger's regression test showed significant symmetry in certain results signifying publication bias ($p < 0.05$) (Fig. 3). In these cases, non-parametric trim and fill analysis was performed, which largely indicated little impact of publication bias (data not shown) [32].

4. Discussion

Following the COVID-19 outbreak and its subsequent global spread, the epidemiology, clinical characteristics, and patient outcomes in affected individuals has been an urgent and active area of study. Gradually, information and evidence regarding SARS-Cov-2 pathogenesis, effective diagnostic measures, and treatment options have come into light. However, current knowledge and evidence regarding COVID-19 is primarily based on studies derived from adult cases. The high prevalence of this disease in adult and elderly populations has indeed played a major role in formulating our understanding of this disease [33]. Further, lack of available data and sporadic literature reports from major worldwide epicenters regarding pediatric COVID-19 cases continues to contribute to unclear characterization of this disease in children [34–36]. More reporting of pediatric data in combination with high powered and multi-national studies are needed, in this regard, to improve our knowledge of COVID-19 in children. Our systematic review and meta-analysis of 20 studies involves 1810 pediatric patient population from multiple global epicenters, and provides an overview of epidemiological characteristics, clinical symptoms, laboratory findings, radiological features, and outcomes of COVID-19 (Table 1).

COVID-19 is present across all age ranges. Based on current evidence, there does not appear to be any age restriction for COVID-19 susceptibility [37]. However, substantial evidence has established that compared to adults, children only account for a small number of COVID-19 case [33,

38]. In our meta-analysis of COVID-19 prevalence across various pediatric age groups the distribution of cases varied but was highly frequent (21–25 %) in the 6–14 year-old age range (Fig. 2). Similar observations were made by Göttinger et al. in a large European study [39]. Similarly, in regard to common clinical indicators, fever, cough, and headache accounted for the most dominant symptoms while sore throat, rhinorrhea, and GI symptoms were rare. This strongly substantiates major results seen in other studies, while adding further information regarding prevalence of several other clinical signs and symptoms (Fig. 3) [37,38]. The most frequently evaluated laboratory markers for COVID-19 in adults and children include various immunological and inflammatory factors (Fig. 3). The primary mechanism of SARS-CoV2 pathogenesis is thought to involve its interaction with human ACE-2 receptors leading to T-cell activation and subsequent inflammatory response [40]. This pro-inflammatory state with further vascular and multi-organ injury likely contributes to the variety of laboratory abnormalities commonly seen in infected patients. Previous studies including infections caused by other novel coronaviruses have reported typically normal or reduced immunological markers with normal to elevated LDH and D-dimer levels [7]. Our findings were consistent with higher prevalence of leukopenia and lymphopenia as well as elevated levels of D-dimer and LDH. However, the most common laboratory markers seen in our study were elevated Procalcitonin and Ferritin levels consistent with a highly inflammatory state. These clinical markers alone however are non-specific, thus limiting their clinical utility in absence of a strong clinical correlation to the patient's history and physical symptoms. In this regard, radiological features can provide helpful evidence in diagnosis of a primary respiratory process, commonly seen in coronavirus infections.⁷ Radiological findings of bilateral patchy infiltrates and GGO have been observed on imaging of COVID-19 patients [7]. Our meta-analysis is consistent with these findings, however unspecific to a predominant imaging finding as the overall prevalence of abnormal findings was similar to that of a normal radiological evaluation (Fig. 3). Overall, these clinical symptoms, laboratory markers, and radiological features are highly non-specific and provide little evidence of COVID-19 infection when assessed individually. Clinicians should not diagnose or rule out COVID-19 infection solely based on any one of these findings, but synthesize information based on prevalence of common features as evidenced in ours and other studies.

Table 2
Summary of clinical outcomes of reviewed studies.

Study (n = 20)	N	Mortality	Severity n (%)				LOHS (days)	Clearance (days) [†]
			Mild	Mod.	Severe	Critical		
Dong, Y. et al.	728	1 ^a	409 (56)	298 (41)	18 (2)	3 (0.4)	—	—
Peng, H. et al.	75	0	22 (29)	51 (68)	1 (1)	1 (1)	10.6	6.4
Bai, K. et al.	25	0	25 (100)	0	0	0	15.2	15.2
Du, H. et al.	182	1 ^b	178 (98)	0	4 (2)	0	12	7
Qiu, H. et al.	36	0	17 (47)	19 (53)	0	0	13	9
Shen, Q. et al.	9	0	9 (100)	0	0	0	15	—
Song, W. et al.	16	0	16 (100)	0	0	0	14	—
Tan, Y.P. et al.	10	0	10 (100)	0	0	0	17.2	—
Zheng, F. et al.	25	0	23 (92)	0	0	2 (8)	—	—
Zhu, L. et al.	10	0	10 (100)	0	0	0	—	—
Cai, J. et al.	10	0	10 (100)	0	0	0	—	—
Lu, Y. et al.	110	0	110 (100)	0	0	0	10	—
Ma, H. et al.	50	0	48 (96)	0	0	2 (4)	—	—
Garazzino, S. et al.	168	0	152 (90)	0	14 (8)	2 (1)	—	—
Parri, N. et al.	130	0	99 (76)	11 (8)	11 (8)	9 (7)	—	—
Garcia-Salido, A. et al.	7	0	0	0	0	7 (100)	—	—
Foster, C.E. et al.	57	0	57 (100)	0	0	0	2	—
Zachariah, P. et al.	50	1 ^c	34 (68)	0	16 (32)	0	3	—
Mannheim, J. et al.	64	0	54 (84)	0	0	10 (16)	4	—
Shekerdemian, L. S.	48	2 ^d	14 (29)	1 (2)	16 (33)	17 (35)	7	—
Total (%)	1810	5 (0.23)	1297 (72)	380 (21)	80 (4)	53 (3)	10.3	9.4
Prevalence [95 % CI][†]		0.3 [0.1–0.4]	Non-Severe: 84 [72–97]		Severe: 5 [1–8]			
I2 †		0%	91 %		87 %			

Mortality Cases: ^aUnknown Complications; ^b10 mo F with intestinal necrosis, septic shock, multiorgan failure; ^cSudden Cardiac Arrest; ^dUnknown Complications, [†] Days from onset to RNA turning negative; † Pooled estimates of study results; Non-severe: mild/moderate cases, Severe: Severe/critical cases.

Outcomes of COVID-19 in children are generally favorable with rare reported cases of fatality [12,15,29,31]. This is consistent with typically milder form of the disease seen in children as evidenced in several studies [37,38]. In our study, only 5% of cases were found to be severe with majority of cases falling in the non-severe (84 %) category. A total of five deaths observed in various studies accounted for an estimated case fatality rate (CFR) of 0.3 % (Table 2). Apart from rare cases of severe disease, usually seen in children with prior health conditions, and in some newer cases of hyperinflammatory syndrome, majority of pediatric cases seem to have a milder course as compared to adults [41]. Based on our current understanding of the clinicopathogenesis of COVID-19, several reasons could account for the low severity and mortality of COVID-19 in children. Some studies have suggested that the expression of ACE-2 receptor, primary binding site for SARS-CoV2, may be less developed in children [5,40]. Reversely, long-term exposure to air pollutants and smoking in adults might contribute to higher expression of ACE-2 in the lung epithelium leading to increased disease complications [42]. Additionally, higher prevalence of comorbidities in adults as compared to children likely contributes to poorer prognosis. Overall, our findings were consistent with other studies in the observation of milder clinical course of disease in children as well as rare mortality outcome. However, the pathogenesis of COVID-19 in children as well as adults still remains unclear, and more detailed and powerful studies are needed to elucidate the marked differences seen in terms of presentation, clinical course and outcome of COVID-19 in these population groups.

Given the milder presentation of disease with inconsistent clinical markers usually seen in children, serious thought must be given in terms of precautionary and preventative measures regarding children in fighting this pandemic. Studies show similar level of susceptibility across all age groups, however, with mild to none symptoms, children can be a major source of SARS-CoV2 viral transmission [37]. As academic institutions reopen, extensively planned strategies might be needed to limit the spread of COVID-19. In communities with widespread transmission experts advocate for the cancellation of gatherings including school closures, playground limitations, and alternate education strategies [43]. Further, clinicians and policymakers should consider working on limiting non-urgent children visits to the clinic, while developing appropriate plans to allow for newborn care and wellness visits. COVID-19 is an ongoing and evolving pandemic and lack of appropriate measures in any sector of community or age group can easily lead to an uprising in new cases. Preventative measures for public locations, workplace, and academic institutions must be applied universally and diligently in order to reduce the spread of this disease.

This study has several limitations and strengths. It was conducted during a 3-month period on an ongoing pandemic. One principal limitation was that the majority of data was derived from China, and sample sizes varied considerably across studies. Exclusion of non-English sources might have limited addition of certain pediatric cohorts. Also, data on multisystem inflammatory syndrome (MIS-C) and coagulation disorders in children were lacking, which resulted in these topics being unexplored. We found substantial heterogeneity between studies and significant publication bias in several pooled analysis. Therefore, interpretation of data must be done with caution and in this context. This study includes latest scientific publications and a relatively large composite sample size. To our knowledge our study is the first to include data with detailed analysis from multiple COVID-19 epicenters outside of China, including European countries and cities within the USA. This allowed for patients of diverse socio-cultural, and ethnic backgrounds to be included in the study, which allows our findings to be generalized.

5. Conclusions

In conclusion, our study shows that all pediatric age groups are prone to COVID-19 infection with the disease usually having a mild clinical presentation and sequelae. Critical illness and death are extremely rare.

Fever, cough, and headache are the most frequently observed symptoms, while laboratory and radiological markers are inconsistent and unlikely predictive of disease. RNA PCR remains the diagnostic gold standard, especially given the largely variable presentation in children. Overall, prognosis of COVID-19 in the pediatric age group is favorable. However, these disparate features of COVID-19 in children have implications for unchecked viral transmission and infection control. Therefore, appropriate guidelines for testing and quarantine in children are needed. Effective strategies to ensure contact precautions and maintenance of access to routine preventative care is highly recommended for appropriate management of this pandemic in the pediatric population.

Author contributions

The concept of the study was developed together and in consensus by all the listed authors. SB and BBB designed the initial protocol, searched the database, and performed the quality assessment. Data extraction was carried out by all included authors. SB conducted the statistical analysis and drafted the results section. All the authors equally contributed in developing the initial manuscript draft. MJS provided guidance in refining the concept and assisted with edit and revision of the final manuscript. All the authors were involved in editing and finalizing the complete version of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jcv.2020.104715>.

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