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REVIEW

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COVID-19 under 19: A meta-analysis

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic continues to cause global havoc posing uncertainty to educational institutions worldwide. Understanding the clinical characteristics of COVID-19 in children is important because of the potential impact on clinical management and public health decisions.

Methods: A meta-analysis was conducted for pediatric COVID-19 studies using PubMed and Scopus. It reviewed demographics, co-morbidities, clinical manifestations, laboratory investigations, radiological investigations, treatment, and outcomes. The 95% confidence interval (CI) was utilized.

Results: Out of 3927 articles, 31 articles comprising of 1816 patients were selected from December 2019 to early October 2020 and were defined by 77 variables. Of these studies 58% originated from China and the remainder from North America, Europe and the Middle East. This meta-analysis revealed that 19.2% (CI 13.6%–26.4%) of patients were asymptomatic. Fever (57%, CI 49.7%–64%) and cough (44.1%, CI 38.3%–50.2%) were the most common symptoms. The most frequently encountered white blood count abnormalities were lymphopenia 13.5% (CI 8.2%–21.4%) and leukopenia 12.6% (CI 8.5%–18.3%). Ground glass opacities were the most common radiological finding of children with COVID-19 (35.5%, CI 28.9%–42.7%). Hospitalization rate was 96.3% (CI 92.4%–98.2%) of which 10.8% (CI 4.2%–25.3%) were ICU admissions, and 2.4% (CI 1.7%–3.4%) died.

Conclusion: The majority of pediatric patients with COVID-19 were asymptomatic or had mild manifestations. Among hospitalized patients there remains a significant number that require intensive care unit care. Overall across the literature, a considerable level of understanding of COVID-19 in children was reached, yet emerging data related to multisystemic inflammatory syndrome in children should be explored.

KEYWORDS

adolescents, children, clinical presentation, COVID-19, meta-analysis, pediatric, SARS-CoV2

Abbreviations: CDC, center for disease control; CI, confidence interval; CK, creatinine kinase; CK-MB, creatinine kinase-MB; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; GGO, ground glass opacity; ICU, intensive care unit; IVIG, intravenous immunoglobulin; JBI, Joanna-Briggs Institution; LDH, lactate dehydrogenase; LFT, liver function test; MeSH, Medical Subject Headings; MIS-C, multisystemic inflammatory syndrome in children; PMID, PubMed ID; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RT-PCR, real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; T^2, Tau square test; WBC, white blood cell; WHO, World Health Organization.

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1 | INTRODUCTION

The novel coronavirus (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] has created a global healthcare pandemonium with over 61.8 million cases and 1.4 million deaths reported worldwide as of December 1, 2020.[2] Since its inception in Wuhan, China in December 2019 as a cluster of cases presenting with influenza-like illness, the virus' uncurbed spread has spanned over 218 countries and territories resulting in the World Health Organization (WHO) announcing it as a pandemic on March 11, 2020.[3] The disease presented itself in earlier stages primarily as a respiratory illness with higher morbidity and mortality in older individuals.[4] However, the evolving trends of this novel disease highlighted the diversity of presenting features and involvement within pediatric age groups. To date, most of the available literature focuses on the adult population leaving a noticeable gap in description of pediatric COVID-19. Of assurance, COVID-19 has fared well in children with initial trends showing milder form of illness, less hospitalizations and minimal fatality as reported in various studies worldwide.[5–7] However, the evolving disease trends have depicted varied severity in children with United States Center for Disease Control (CDC) releasing a health advisory reporting a Multisystem Inflammatory Syndrome in Children (MIS-C) related to COVID-19 on May 14, 2020.[8] Our progressing knowledge about the disease in the past year necessitates a data-rich meta-analysis of pediatric COVID-19 to establish statistical significance across these studies and thereby, understanding the validity of the observed parameters.

The study aims to describe clinical presentation, laboratory and radiographic findings, treatment modalities and outcomes of pediatric patients under age 19 with COVID-19. Furthermore, the perpetual rapid escalation of cases worldwide and controversies related to re-opening of educational institutes necessitates a more inclusive look into pediatric presentations of COVID-19 to guide health and education policy-making worldwide.

2 | METHODOLOGY

2.1 | Protocol

The study protocol was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was reported using the PRISMA checklist.[9] The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42020186160 on May 17, 2020.

2.2 | Literature search and data extraction

The databases PubMed and Scopus were reviewed from December 1, 2019 to October 3, 2020, to identify all relevant COVID-19 primary publications. The keywords and Medical Subject Headings (MeSH) terms selected included "Novel coronavirus 2019," "COVID-19," and "SARS-CoV-2," and the target population was specified with the terms "pediatric," "children," "infant," "neonate," and "adolescent." The last search was performed on October 3, 2020 and the search was not limited by language (translation performed with Google Translate) or geographic region.

2.3 | Eligibility criteria and study selection

2.3.1 | Inclusion criteria for screening

Study selection methodology initially entailed screening articles using title and abstract and subsequent full-text screening. All available peer-reviewed original articles (case series, cohort studies, cross-sectional studies, etc.) pertaining to pediatric COVID-19 published in the literature in the aforementioned time frame were included in this study. Selected articles must have subjects with SARS-CoV-2 infection confirmed via real-time reverse transcriptase polymerase chain reaction (RT-PCR) using upper respiratory swabs. Alternatively, subjects who met the MIS-C criteria as defined by CDC or WHO were also included in the study.[8,10] The pediatric population was defined by ages 0–18 years (including neonates). The selected articles included variables on demographics, risk factors, clinical manifestations, laboratory investigations, radiological investigations, treatment, and outcomes.

Articles were excluded due to the inability to extract pediatric data from adult data separately. The publication types excluded were review articles and studies such as letters, correspondence or comments that had no extractable primary pediatric data. Articles with irrelevant clinical study focus (such as epidemiology, modeling, animal data, pand ost-mortem data) and nonclinical study focus (such as genetics, diagnostic techniques, or virology) were excluded as well.

2.3.2 | Inclusion criteria for meta-analysis data

Studies that qualified for initial screening for data extraction, as mentioned above, were further filtered with stringent criteria. The inclusion criteria were optimized for the selection of articles with sufficient data and sample size for data synthesis.

2.4 | Data extraction and quality assessment

Four investigators worked on title/abstract, full-text screening and data extraction in pairs (AA and ME, SG and NT) on a shared data extraction form. Any disagreements were resolved by consulting one of the investigators from the other pair. The investigators extracted data on demographics, co-morbidities, signs and symptoms, laboratory investigations, radiological investigations, treatment, and outcomes of COVID-19 in pediatric patients. The Joanna–Briggs Institute (JBI) checklists were utilized for the critical appraisal of case series and

cross-sectional studies.[11] The investigators assigned two points for "Yes," 1 point for "Unclear" and 0 points for "No/Inapplicable." The average score of the two investigators generated the final JBI score. Each checklist had a different cumulative score which was scaled out of 10 (Table 1). A score more than 7 reflected a high-quality study, 5–7 moderate-quality, and less than 5 low-quality study.

2.5 | Statistical analysis

Percentages were calculated to describe the distribution of the categorical dichotomous variables. For continuous data, the pooled prevalence with mean and 95% confidence intervals (CI) were calculated. For studies reporting the mean with 95% CI or the range of

TABLE 1 Study Characteristics of the 31 selected studies

Study number	Author	Date of publication	Country	Study design	No. ped patients	JBI scaled score
1	Cai et al.[12]	1-Mar	China	Case-series	10	8.5
2	Chen et al.[13]	22-May	China	Case-series	20	7.5
3	Cheung et al.[14]	15-May	USA	Case-series	17	8.5
4	García-Salido et al.[15]	28-May	Spain	Case-series	7	8
5	Godfred-Cato et al.[16]	16-May	USA	Cross-sectional	570	6.3
6	Harman et al.[17]	1-Jun	UK	Case-series	12	9.5
7	Kanthimathinathan et al.[18]	3-Jul	UK	Case-series	45	8.5
8	Korkmaz et al.[19]	1-Jul	Turkey	Cross-sectional	81	8.8
9	Liu et al.[20]	24-Jun	China	Cross-sectional	53	7.5
10	Lu et al.[21]	19-Mar	China	Observational	171	5.8
11	Lu et al.[22]	8-May	China	Cross-sectional	110	10
12	Ma et al.[23]	7-May	China	Cross-sectional	50	9.1
13	Mamishi et al.[24]	22-Sep	Iran	Cross-sectional	45	8.1
14	McLaren et al.[25]	3-Sep	USA	Cross-sectional	7	8.1
15	Mithal et al.[26]	5-Jun	USA	Cross-sectional	18	8.8
16	Musolino et al.[27]	20-Jun	Italy	Case-series	10	7
17	Parri et al.[28]	30-May	Italy	Cross-sectional	130	7.5
18	Pouletty et al.[29]	29-May	France	Observational	16	7.7
19	Qiu et al.[30]	30-Mar	China	Cross-sectional	36	8.8
20	Song et al.[31]	4-May	China	Case-series	16	8
21	Sun et al.[32]	7-Jun	China	Cross-sectional	36	8.8
22	Tan et al.[33]	22-Apr	China	Cross-sectional	13	4.4
23	Tan et al.[34]	18-Apr	China	Case-series	10	9
24	Toubiana et al.[35]	5-Jun	France	Cross-sectional	21	9.4
25	Wang et al.[36]	3-Mar	China	Cross-sectional	31	8
26	Wu et al.[37]	4-Jun	China	Case-series	148	8.8
27	Wu et al.[38]	22-May	China	Cross-sectional	23	7.5
28	Xia et al.[39]	7-Mar	China	Cross-sectional	20	7.8
29	Xu et al.[40]	15-Apr	China	Observational	10	7.8
30	Zhang et al.[41]	12-Aug	China	Cross-sectional	46	5.6
31	Zhang et al.[42]	17-Jun	China	Cross-sectional	34	8.8

Abbreviation: JBI, Joanna–Briggs Institute.

the data, the formula, (upper limit-lower limit)/4, was used to extract the standard deviation (*SD*).

The meta-analysis was conducted on Comprehensive Meta-Analysis version 3.3.070 software. The random-effect model was implemented to estimate the pooled prevalence and 95% CI. Pooled percentage, proportion, and corresponding 95% CI were calculated to summarize the weighted effect size for all binary variables. The measure of heterogeneity reported included the Cochran's Q statistics, I^2 index with the level of heterogeneity defined as low less than 25, moderate more than 50, and high more than 75, and the tau square (τ^2) test. Publication bias was assessed with a funnel plot and Egger's test.

3 | RESULTS

As shown by the literature retrieval flowchart in Figure 1, 3927 pediatric COVID-19 articles were searched from two databases (PubMed and Scopus) from December 2019 to October 2020 with a predefined search strategy. Out of those, 1542 duplicate studies were excluded and 1961 studies did not meet the eligibility criteria for meta-analysis, owing to inappropriate study type/focus or lack of relevant clinical pediatric data when screened with title and abstract. Of the remaining 424 full text articles that met the eligibility criteria, 31 studies comprising of 1816 patients sieved through the rigorous criteria of inclusion for meta-analysis. Remaining studies were excluded due to inadequate sample size, insufficient availability of data and other reasons described in Figure 1. The journal name, PMID and characteristics of the 31 studies selected for meta-analysis, and funnel plots and forest plots were shown in the supplementary material.

Table 1 lists the study characteristics of the 31 articles selected for meta-analysis with their author information, date of publication, country of origin, study design, number of pediatric patients and JBI scaled score. As shown in the table, these studies were published between March and September 2020. About half (58%) of the studies were from China, USA articles accounted for 13% of the studies. Other studies originated from the UK, Italy, France, Iran, Spain, and Turkey. Cross sectional studies comprised of more than half (58%) of the study design and the remaining half were distributed among case series and observational studies. Approximately half of the articles had a sample size under 20 patients and 18% had a sample size of over 80. The mean JBI scaled score is 7.9 (1.23 *SD*) out of 10. In addition, 90% of the selected articles yielded a JBI scaled score of more than or equal to 7, affirming good quality of the selected articles.

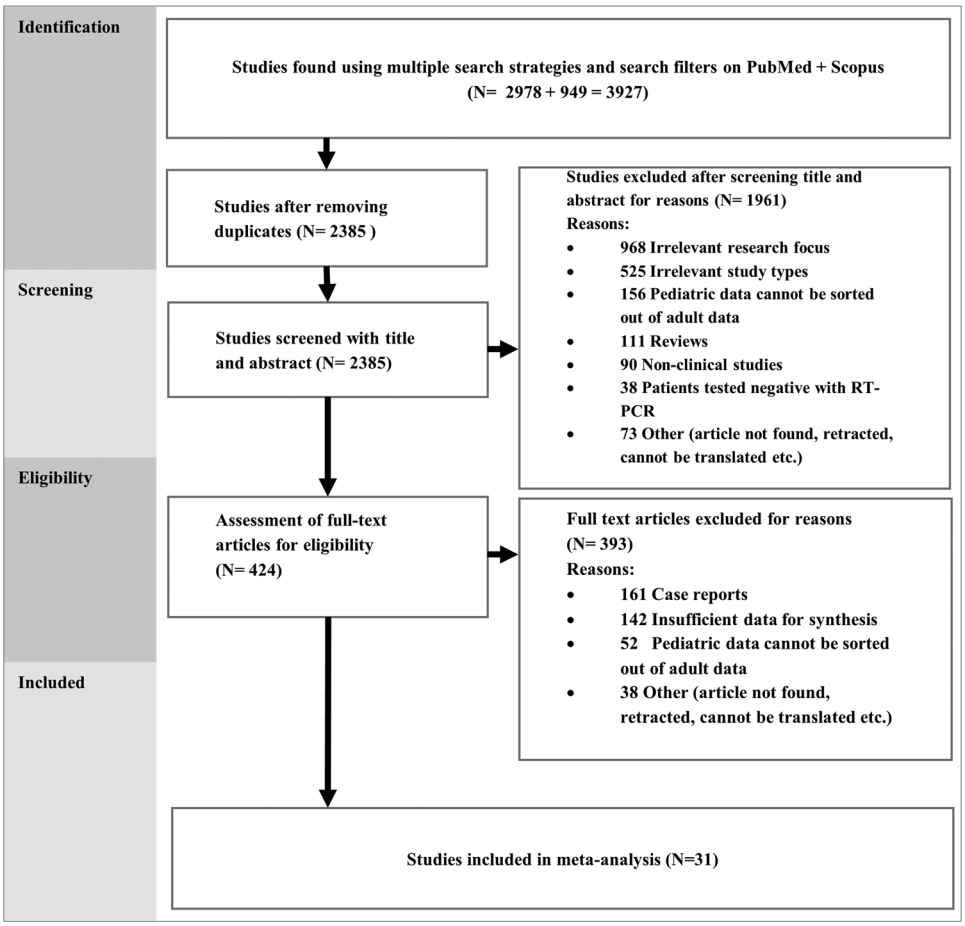

FIGURE 1 PRISMA flow diagram for study selection

4 | META-ANALYSIS RESULTS

4.1 | Demographic characteristics

Of the 1816 pediatric patients analyzed, the mean age of the patients across the studies was 6.6 years (CI 5.5–7.6). Females comprised 54% (CI 50.4–57.3%) of the population (Table 2).

4.2 | Co-morbidities

The total prevalence of co-morbidities associated with pediatric COVID-19 based on 21 studies was 16.9% (CI 11.4%–24.4%). The most common co-morbidities were asthma 3.9% (CI 2%–7.4%) and obesity 3.8% (CI 1.4%–10.1%).

4.3 | Clinical presentation

Fever was the most prevalent symptom in majority of the papers analyzed (57% with CI 49.7%–64%), followed by cough (44.1 with CI 38.3%–50.2%). Approximately one-fifth of the patients were asymptomatic (19.2% with CI 13.6%–26.4%). The spectrum of clinical manifestations included generalized (headache, fatigue, rash, and myalgia), respiratory (cough, dyspnea, rhinorrhea, nasal congestion, and sore throat), and gastrointestinal (nausea, vomiting, abdominal

TABLE 2 Results of meta-analysis: Demographics, co-morbidities, and clinical presentation

Item	No. of studies	Prevalence%	95% CI	*n*	Q	I^2	τ^2	*p* value	Egger's test *p*
Demographical characteristics and pre-morbidities									
Age (mean in years)	31	6.6	5.5–7.6	30	14179.9	99.8	2.9	<.001	.0006
Female	31	54.0	50.4–57.3	30	45.6	34.2	0.0	.034	.4097
Male	31	46.0	–	–	–	–	–	–	–
Co-morbidities									
All co-morbidities	21	16.9	11.4–24.4	20	113.6	82.4	0.7	<.001	.0034
Asthma	14	3.9	2–7.4	13	15.6	16.6	0.3	.272	.0008
Obesity	13	3.8	1.4–10.1	12	46.2	74.0	2.1	<.001	<.001
Neurological[a]	16	3.4	1.4–8	15	42.9	65.0	2.1	<.001	.0137
Congenital heart disease	11	2.6	1.2–5.5	10	12.2	17.8	0.3	0.274	.0585
Diabetes	15	2.1	1–4	14	11.8	0.0	0.0	.625	.4368
Preterm	10	2.1	1–4.3	9	9.5	5.5	0.1	.39	.5734
Cancer	16	1.7	0.9–3.2	15	8.1	0.0	0.0	.921	.6956
Clinical manifestation and symptoms									
Asymptomatic	25	19.2	13.6–26.4	24	106.7	77.5	0.6	<.001	.3119
Fever	30	57.0	49.7–64	29	123.3	76.5	0.4	<.001	.0656
Cough	27	44.1	38.3–50.2	26	106.5	75.6	0.2	<.001	.3131
Dyspnea	21	15.2	10.2–21.9	20	113.6	82.4	0.6	<.001	.0084
Expectoration	6	15.0	9.2–23.6	5	9.2	48.0	0.2	.087	.2689
Rhinorrhea	17	12.9	9–18.1	16	41.5	61.4	0.4	<.001	.2423
CNS	13	12.8	6.1–25	12	72.7	83.5	1.4	<.001	.0068
Diarrhea	22	11.1	5.9–19.8	21	227.7	90.8	1.9	<.001	.0001
Nausea/vomiting	20	10.5	4.9–21.1	19	275.6	93.1	2.7	<.001	.0004
Headache	12	10.3	5–19.7	11	75.7	85.5	1.2	<.001	.0029
Sore throat	16	9.7	4.8–18.6	15	115.8	87.0	1.8	<.001	.0007
Nasal congestion	8	9.3	4.5–18	7	14.6	52.1	0.5	.041	.8459
Abdominal pain	12	8.1	2.8–21	11	105.0	89.5	2.7	.001	<.001
Fatigue	13	5.8	3.3–10.1	12	25.9	53.7	0.5	<.001	.0174
Myalgia	9	4.7	1.3–15.4	8	56.0	85.7	3.0	<.001	.0068
Anosmia	6	3.5	1.4–8.1	5	3.7	0.0	0.0	.596	.3993
Rash	8	46.9	29.4–65.2	7	37.0	81.1	0.7	<.001	.4158

Abbreviations: CI, confidence interval; CNS, central nervous system; I^2, index for the degree of heterogeneity; *n*, degree of freedom; Q, Cochran's Q statistic for heterogeneity; τ^2, Tau-squared measure of heterogeneity.

[a]Neurological: febrile seizures, epilepsy, and cerebral palsy.

pain, and diarrhea) symptoms. Among papers regarding MIS-C, rash development was highly prevalent (46.9% with CI 29.4%–65.2%).

4.4 | Laboratory investigations

The most commonly encountered white blood cell (WBC) abnormalities were lymphopenia and leukopenia that were present in 13.5% (CI 8.2%–21.4%) and 12.6% (CI 8.5%–18.3%) of patients, respectively. From the array of abnormal laboratory findings in pediatric SARS-CoV-2 infection, more prevalent ones included elevated C-reactive protein (CRP; 28.1%, CI 19.7%–38.3%), elevated procalcitonin (39%, CI 27.5–51.8), abnormal liver function tests (LFT; 18.6%, CI 12.3%–27%), high serum lactate dehydrogenase (LDH; 22.9%, CI 14.1–35), and elevated D-dimer (16.6%, CI 7.9–31.9). In a minority of studies primarily involving MIS-C patients, abnormal cardiac biomarkers, brain natriuretic peptide (BNP; high in 70.7%, CI 34.9–91.4), troponin (high in 25.4%, CI 7.2%–59.9%), and creatinine kinase-MB (CK-MB; high in 21.3%, CI 12.4%–33.9%) were prevalent. An additional interesting finding extracted from 16 studies showed co-infections (26.4%, CI 18.3%–36.4%) in children with COVID-19, the most common being bacterial co-infections (18.4%, CI 12.5%–26.1%) followed by influenza A or B (5.2%, CI 1.9%–13.6%). Note that differences between asymptomatic and symptomatic patients in terms of laboratory, radiologic, and treatment data were often not specified in the articles and hence were not analyzed.

4.5 | Radiological findings

Computed Tomography (CT) of the chest appeared to be the imaging modality of choice over chest x-rays from the meta-analyzed studies in Table 3. The most common CT abnormality, occurring in more than one-third of the patients, was ground glass opacities (GGO; 35.5%, CI 28.9%–42.7%).

4.6 | Treatment

92.1% of patients (CI 81.5%–96.9%) received some form of treatment (includes the treatment options listed in Table 4 as well as symptomatic and herbal medications). Antiviral therapies were the most prescribed treatments at 82.7% (CI 55.7%–94.8%) and included interferon α, lopinavir/ritonavir, oseltamivir, and umifenovir (in China). A significant proportion of patients received antibiotics (41% with CI 30.8%–52%) during their course of illness. A high proportion of patients were also administered glucocorticoids (16.8%, CI 8.1%–31.6%) and intravenous immunoglobin (IVIG; 13.9%, CI 5.4%–31.4%).

4.7 | Clinical outcomes

Majority of the patients included in the meta-analysis were hospitalized out of which 10.8% (CI 4.2%–25.3%) received treatment in the intensive care unit. 92.8% (CI 87.8%–95.9%) were eventually discharged during the course of the studies. The proportion of deaths was 2.4% (CI 1.7%–3.4%).

4.8 | Bias and heterogeneity across studies

About 42 out of the 77 variables analyzed did not have significant publication bias, denoted by an Egger's p value more than .05. Approximately half of the variables were homogenous based on I^2 index more than 75.

5 | DISCUSSION

This is a meta-analysis of 31 studies with a total of 1816 pediatric patients that was conducted from December 2019 until October 2020. Of these studies 58% originated from China and the remainder from North America, Europe, and Middle East. Our study showed approximately one out of six children had some associated co-morbidity. This was unlike other meta-analyses in the literature which under or infrequently reported comorbidities in pediatric patients.[43–45] We further dissected the comorbidities and found the most common being history of asthma and obesity. The other co-morbidities associated with COVID-19 presentation in children in our study included history of prematurity, neurological diseases (epilepsy, febrile seizures), congenital heart disease, cancer, and diabetes, which is distinctive from what was found in most adult studies.[44,46] However, in comparison, adult data had much higher levels of co-morbidity, including hypertension, and diabetes mellitus.[44]

Fever and cough were the most reported symptoms in this meta-analysis, which is consistent with findings reported by other meta-analyses including both pediatric and adult data.[43–45,47] The adult meta-analysis however, described a much higher proportion of patients complaining of these symptoms. A likely explanation to this difference is the proportion of asymptomatic patients in pediatric populations. Our data shows a much higher proportion of asymptomatic children in comparison to adults but is consistent with other pediatric meta-analyses.[44,45] Dyspnea was the third most common symptom in our meta-analysis as well as what is reported by Meena et al.[47] However, according to Jutzeler et al.,[44] fatigue was the third most common symptom in adults. This may be explained by the fact that pediatric patients will often find it difficult to describe fatigue, whereas it is easier to objectively identify their fever and cough.

This study shows that children presented with more upper respiratory findings such as sore throat, nasal congestion, and rhinorrhea. An array of gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain were reported in pediatric patients with COVID-19, however, it was difficult to discern the proportion of these symptoms attributable to the disease process or among side-effects of therapeutic agents used for treatment or a combination of both.

This meta-analysis' findings revealed lymphopenia and leukopenia as the most common white cell abnormalities which is similar to other meta-analyses.[45,47] Among the three analyzed acute phase

TABLE 3 Results of meta-analysis: Laboratory and radiological investigations

Items	No. of studies	Proportion (%)	95% CI	*n*	Q	I^2	τ^2	*p* value	Egger's test *p*
Laboratory investigations									
Lymphopenia	28	13.5	8.2–21.4	27	205.8	86.9	1.6	<.001	.0039
Leukopenia	28	12.6	8.5–18.3	27	121.1	77.7	0.9	<.001	.0085
Lymphocytosis	22	10.6	6.3–17.1	21	60.2	65.1	0.9	<.001	<.0001
Thrombocytopenia	15	8.2	4.2–15.3	14	60.1	76.7	1.0	<.001	.0001
Neutrophilia	13	8.1	5.8–11.1	12	4.5	0.0	0.0	.973	.06184
Leukocytosis	21	8.0	4.3–14.1	20	92.1	78.3	1.5	<.001	.0343
Neutropenia	11	5.8	2.6–12.1	10	32.5	69.2	1.2	<.001	.0085
Elevated procalcitonin	22	39.0	27.5–51.8	21	134.9	84.4	0.9	<.001	.2034
High CRP	27	28.1	19.7–38.3	26	149.8	82.6	1.0	<.001	.5856
Elevated ESR	22	10.9	6.5–17.5	21	59.0	64.4	0.8	<.001	.0001
High LDH	13	22.9	14.1–35	12	67.1	82.1	0.9	<.001	.6586
Abnormal LFTs	21	18.6	12.3–27	20	119.9	83.3	0.9	<.001	.3428
Low albumin	6	14.3	3.5–43.4	5	57.7	90.5	3.0	<.001	.3927
Elevated D-dimer	17	16.6	7.9–31.9	16	259.3	93.8	2.3	<.001	.0058
High creatinine	10	3.7	9–14.5	9	40.3	77.7	4.1	<.001	.0002
High BNP	3	70.7	34.9–91.4	2	16.0	87.5	1.5	<.001	.02554
Elevated troponin	6	25.4	7.2–59.9	5	55.0	90.9	2.7	<.001	.9188
Elevated CKMB	10	21.3	12.4–33.9	9	43.3	79.2	0.6	<.001	.0074
Creatinine Kinase	15	12.3	6.6–21.5	14	74.6	81.2	1.1	<.001	.0001
Elevated IL-6	10	16.0	3.4–50.9	9	70.9	87.3	6.1	<.001	.7573
Elevated IL-10	6	10.2	6.8–14.9	4	6.2	19.0	0.1	.287	.0375
Total co-infection	16	26.4	18.3–36.4	15	46.3	67.6	0.5	<.001	.1078
Bacterial co-infection	12	18.4	12.5–26.1	11	21.6	49.1	0.2	.028	.0022
Viral co-infection	11	6.1	2.2–15.9	10	42.0	76.2	2.2	<.001	<.001
Mycoplasma co-infection	10	19.7	13.4–27.9	9	18.3	50.9	0.2	.031	.00908
Influenza A or B co-infection	11	5.2	1.9–13.6	10	34.5	71.0	1.9	<.001	.0892
Adenovirus co-infection	9	2.0	0.8–4.8	8	2.9	0.0	0.0	.943	.6084
Radiological investigations									
Chest CT									
Ground glass opacity	17	35.5	28.9–42.7	16	42.9	62.7	0.2	<.001	.41144
Patchy shadows	11	22.3	12–37.6	10	65.2	84.7	1.1	<.001	.4689
Consolidation	14	5.5	2.3–12.7	13	40.8	68.2	1.9	<.001	.0007
Unilateral lesion	11	32.5	28.1–37.3	10	10.0	0.0	0.0	.443	.35284
Bilateral lesion	10	25.9	17.2–37.1	9	43.4	79.3	0.5	<.001	.4012
Pleural effusion	9	5.7	2.6–12.1	8	10.9	26.4	0.4	.209	.0077
Chest x-ray									
Interstitial infiltrates	7	18.1	7.5–37.8	6	15.6	61.4	1.0	.016	.6933
Consolidation	9	14.8	7.9–26	8	13.6	41.3	0.4	.092	.2995

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; CKMB, creatinine kinase-MB; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; I^2, index for the degree of heterogeneity; IL, interleukin; *n*, degree of freedom; LDH, lactate dehydrogenase; LFT, liver function test; Q, Cochran's Q statistic for heterogeneity; τ^2, Tau-squared measure of heterogeneity.

reactants, procalcitonin was the most highly elevated followed by CRP, then ESR which is also reflected in another meta-analysis.[47] However, the elevation in Procalcitonin was not found in the study by Zhang et al.[45] This meta-analysis shows elevations in LDH, D-Dimer and creatinine kinase which are consistent with Zhang et al.[45] This meta-analysis also shows elevations in LFTs and creatinine which is consistent with Meena et al.[47] Four articles collected data on patients who developed MIS-C, which reported elevations in cardiac biomarkers (Troponin, CKMB, and BNP) as well as IL-6 and IL-10.[16]

Co-infections were found in close to one-fourth of patients, which is again a peculiar finding of pediatric COVID-19 and the most common co-infections were bacterial in origin. Ten studies reported the finding of *Mycoplasma pneumoniae* co-infection in 19.7% of

TABLE 4 Results of meta-analysis: Treatment and outcomes

Item	No. of studies	Proportion%	95% CI	*n*	Q	I^2	τ^2	*p* value	Egger's test *p*
Treatment									
Any treatment	22	92.1	81.5–96.9	21	348.7	94.0	4.2	<.001	.2209
Antiviral	18	82.7	55.7–94.8	17	162.0	89.5	7.0	<.001	.2258
Antibiotics	18	41.0	30.8–52	17	68.2	75.1	0.6	<.001	.3199
Gluco-corticoids inhaled	16	16.8	8.1–31.6	15	124.3	87.9	1.9	<.001	.0009
IVIG	18	13.9	5.4–31.4	17	179.6	90.5	3.8	<.001	.0001
Hydroxychloroquine	11	2.8	1.4–5.9	10	6.2	0.0	0.0	.797	.0239
Clinical course and outcomes									
All hospitalization	28	96.3	92.4–98.2	27	147.9	81.8	2.5	<.001	<.001
ICU admission	21	10.8	4.2–25.3	20	289.8	93.1	4.6	<.001	.0007
Oxygen/NIV	14	12.4	7.2–20.6	13	43.2	69.9	0.8	<.001	.2905
Mechanical ventilation	17	4.0	1.7–8.9	16	82.4	80.6	2.1	<.001	.03878
Shock	12	12.1	5.1–25.8	11	71.8	84.7	1.8	<.001	.0402
Discharge	26	92.8	87.8–95.9	25	86.9	71.2	1.2	<.001	.0007
MISC	31	5.2	1.8–14.3	30	146.7	80.0	8.0	<.001	.7853
Death	31	2.4	1.7–3.4	30	24.849	0.0	0.0	.732	0.3696

Abbreviations: CI, confidence interval; I^2, index for the degree of heterogeneity; ICU, intensive care unit; IVIG, intravenous immunoglobin; *n*, degree of freedom; NIV, noninvasive ventilation; Q, Cochran's Q statistic for heterogeneity; τ^2, Tau-squared measure of heterogeneity.

patients. Viral co-infections were relatively less frequent, and Influenza A/B and Adenovirus were the most common.

Ground glass opacities on CT-scan were the most common radiological finding present in more than a third of patients, resembling previous literature on pediatric COVID-19.[43,44,47] Another interesting radiological finding of this meta-analysis was the equal proportion of unilateral and bilateral lesions in CT-scans in children with COVID-19. In contrast, Mantovani et al.[48] and Zhang et al.[45] reported a higher proportion of unilateral involvement than bilateral, while most other meta-analyses have not described other radio findings other than GGOs.[43,49] This meta-analysis showed reduced manifestations of GGO on CT when compared to adult populations.[44] It is important to note that this study's confidence intervals were narrower and hence relatively more precise than other meta-analyses due to the higher sample size from data-rich articles.

About 96.3% of patients were hospitalized and 92.1% of patients received some form of treatment based on our findings. Antiviral medications were the most used therapeutic agents, apart from analgesic and herbal medicines, followed by antibiotics. It is important to note that there was expected therapeutic variability due to different protocols across the world as well as the changing trends during the pandemic. Intravenous immunoglobulin (IVIG) and glucocorticoids were unique treatment options for pediatric patients with SARS-CoV-2, especially with the emergence of MIS-C.[8] This analysis did not show frequent use of hydroxychloroquine treatment (2.8%) as expected potentially due to the evolving treatment protocols.

Of the hospitalized patients, 10.8% required intensive care admission, 4% required mechanical ventilation which were similar to published pediatric and adult data, but these variable had a significant publication bias (Egger's test p-value < .05).[44] These important outcomes are under-reported in meta-analysis literature.[43,45,49] Shock was one of the striking complications of the disease course present in about 12% of patients, as highlighted by our meta-analysis. 92.8% of patients were discharged and this value could be confounded by the time span of the studies and different protocols for patient discharge. Our meta-analysis reports higher than expected death rate (2.4%) compared with surveillance data, but this may be due to sampling and reporting bias within studies.[50]

It is possible that our results were confounded by the heterogeneity and publication bias within half of the variables. The high heterogeneity reflects the global nature of the data which contains more non-Chinese articles compared to other meta-analyses. Publication bias is also an unavoidable consequence as most studies with sufficient data to synthesize the clinical findings and outcomes would consist of more symptomatic, sick and hospitalized patients. In addition, the variations of diagnostic and therapeutic protocols in different parts of the world and its transformation with the evolving pandemic affects the outcomes reported.

6 | CONCLUSION

Studies on COVID-19 in children are vital to better understand their unique epidemiological trends, clinical course, laboratory investigations, radiological investigations, prognosis, and outcomes. Significant differences exist in all these factors compared to adults. The characteristics of COVID-19 infection in children were constantly evolving since the beginning of the pandemic, especially as more research began emerging from outside of China. We have reached a considerable level of understanding of COVID-19 infection in children, yet emerging data related to MIS-C is still accumulating and

must be explored further. Emerging information on the relatively high proportion of asymptomatic cases and its eventual effect on spread of disease will benefit healthcare providers and public health officials in designing appropriate policies.

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AUTHOR CONTRIBUTIONS

Nagham Toba: data curation (equal); methodology (supporting); project administration (equal); writing original draft (equal). **Shreya Gupta**: data curation (equal); methodology (supporting); project administration (equal); writing original draft (equal). **Abdulrahman Ali**: data curation (equal); methodology (supporting); project administration (equal); writing original draft (equal). **Mariam ElSaban**: data curation (equal); methodology (supporting); project administration (equal); writing original draft (equal). **Amar H. Khamis:** methodology and statistical analysis, writing and editing. **Samuel Ho**: conceptualization; methodology (lead); project administration; writing review & editing (lead). **Rizwana Popatia**: conceptualization; methodology and data curation; project administration (lead); validation; writing review & editing.

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REFERENCES

1. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it
2. Emergency Situational Updates. Weekly epidemiological update - 1 December 2020. 2020. https://www.who.int/publications/m/item/weekly-epidemiological-update—1-december-2020
3. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed*. 2020;91(1):157-160.
4. Bennett S, Tafuro J, Mayer J, et al. Clinical features and outcomes of adults with coronavirus disease 2019: A systematic review and pooled analysis of the literature. *Int J Clin Pract*. 2020:e13725.
5. Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. *Pediatrics*. 2020;145(6):e20200834.
6. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020;145(6):e20200702.
7. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. 2020.
8. Centers for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). https://emergency.cdc.gov/han/2020/han00432.asp. Accessed Distributed via the CDC Health Alert Network.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
10. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief. 2020. https://apps.who.int/iris/handle/10665/332095
11. Santos WMD, Secoli SR, Puschel VAA. The Joanna Briggs Institute approach for systematic reviews. *Rev Lat Am Enfermagem*. 2018;26:e3074.
12. Jiehao C, Jin X, Daojiong L, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis*. 2020;71(6):1547-1551.
13. Chen J, Wang XF, Zhang PF. [Asymptomatic SARS-CoV-2 infection in children: a clinical analysis of 20 cases]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(5):414-418.
14. Cheung EW, Zachariah P, Gorelik M, et al. Multisystem inflammatory syndrome related to COVID-19 in previously healthy children and adolescents in New York City. *JAMA*. 2020;324(3):294-296.
15. García-Salido A, Leoz-Gordillo I, Martínez de azagra-Garde A, et al. Children in critical care due to severe acute respiratory syndrome coronavirus 2 infection: experience in a Spanish hospital. *Pediatr Crit Care Med*. 2020;21(8):e576-e580.
16. Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1074-1080.
17. Harman K, Verma A, Cook J, et al. Ethnicity and COVID-19 in children with comorbidities. *Lancet Child Adolesc Health*. 2020;4(7):e24-e25.
18. Kanthimathinathan HK, Dhesi A, Hartshorn S, et al. COVID-19: a UK children's hospital experience. *Hosp Pediatr*. 2020;10(9):802-805.
19. Korkmaz MF, Ture E, Dorum BA, Kilic ZB. The epidemiological and clinical characteristics of 81 children with COVID-19 in a pandemic hospital in Turkey: an observational cohort study. *J Korean Med Sci*. 2020;35(25):e236.
20. Liu YJ, Chen P, Liu ZS, Li Y, Du H, Xu JL. [Clinical features of asymptomatic or subclinical COVID-19 in children]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(6):578-582.
21. Lu X, Zhang L, Du H, et al. SARS-CoV-2 infection in children. *N Engl J Med*. 2020;382(17):1663-1665.
22. Lu Y, Li Y, Deng W, et al. Symptomatic infection is associated with prolonged duration of viral shedding in mild coronavirus disease 2019: a retrospective study of 110 children in Wuhan. *Pediatr Infect Dis J*. 2020;39(7):e95-e99.
23. Ma H, Hu J, Tian J, et al. A single-center, retrospective study of COVID-19 features in children: a descriptive investigation. *BMC Med*. 2020;18(1):123.
24. Mamishi S, Movahedi Z, Mohammadi M, et al. Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in 45 children: a first report from Iran. *Epidemiol Infect*. 2020;148:e196.
25. McLaren SH, Dayan PS, Fenster DB, et al. Novel coronavirus infection in febrile infants aged 60 days and younger. *Pediatrics*. 2020;146(3):e20201550.
26. Mithal LB, Machut KZ, Muller WJ, Kociolek LK. SARS-CoV-2 infection in infants less than 90 days old. *J Pediatr*. 2020;224:150-152.
27. Musolino AM, Supino MC, Buonsenso D, et al. Lung ultrasound in children with COVID-19: preliminary findings. *Ultrasound Med Biol*. 2020;46(8):2094-2098.
28. Parri N, Magistà AM, Marchetti F, et al. Characteristic of COVID-19 infection in pediatric patients: early findings from two Italian Pediatric Research Networks. *Eur J Pediatr*. 2020;179(8):1315-1323.

29. Pouletty M, Borocco C, Ouldali N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis*. 2020;79(8):999-1006.
30. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis*. 2020;20(6):689-696.
31. Song W, Li J, Zou N, Guan W, Pan J, Xu W. Clinical features of pediatric patients with coronavirus disease (COVID-19). *J Clin Virol*. 2020;127:104377.
32. Sun D, Chen X, Li H, et al. SARS-CoV-2 infection in infants under 1 year of age in Wuhan City, China. *World J Pediatr*. 2020;16(3):260-266.
33. Tan X, Huang J, Zhao F, Zhou Y, Li JQ, Wang XY. [Clinical features of children with SARS-CoV-2 infection: an analysis of 13 cases from Changsha, China]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(4):294-298.
34. Tan YP, Tan BY, Pan J, Wu J, Zeng SZ, Wei HY. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. *J Clin Virol*. 2020;127:104353.
35. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094.
36. Wang D, Ju XL, Xie F, et al. [Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China]. *Zhonghua Er Ke Za Zhi*. 2020;58(4):269-274.
37. Wu H, Zhu H, Yuan C, et al. Clinical and immune features of hospitalized pediatric patients with coronavirus disease 2019 (COVID-19) in Wuhan. China. *JAMA Netw Open*. 2020;3(6):e2010895.
38. Wu HP, Li BF, Chen X, et al. [Clinical features of coronavirus disease 2019 in children aged<18 years in Jiangxi, China: an analysis of 23 cases]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2020;22(5):419-424.
39. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol*. 2020;55(5):1169-1174.
40. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med*. 2020;26(4):502-505.
41. Zhang B, Liu S, Zhang J, et al. Children hospitalized for coronavirus disease 2019 (COVID-19): a multicenter retrospective descriptive study. *J Infect*. 2020;81(2):e74-e75.
42. Zhang C, Gu J, Chen Q, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. *PLoS Med*. 2020;17(6):e1003130.
43. Grant MC, Geoghegan L, Arbyn M, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): A systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One*. 2020;15(6):e0234765.
44. Jutzeler CR, Bourguignon L, Weis CV, et al. Comorbidities, clinical signs and symptoms, laboratory findings, imaging features, treatment strategies, and outcomes in adult and pediatric patients with COVID-19: A systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;37:101825.
45. Zhang L, Peres TG, Silva MVF, Camargos P. What we know so far about Coronavirus Disease 2019 in children: a meta-analysis of 551 laboratory-confirmed cases. *Pediatr Pulmonol*. 2020;55(8):2115-2127.
46. Ding Y, Yan H, Guo W. Clinical characteristics of children With COVID-19: a meta-analysis. *Front Pediatr*. 2020;8:431.
47. Meena J, Yadav J, Saini L, Yadav A, Kumar J. Clinical features and outcome of SARS-CoV-2 infection in children: a systematic review and meta-analysis. *Indian Pediatr*. 2020;57(9):820-826.
48. Mantovani A, Rinaldi E, Zusi C, Beatrice G, Saccomani MD, Dalbeni A. Coronavirus disease 2019 (COVID-19) in children and/or adolescents: a meta-analysis. *Pediatr Res*. 2020.
49. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. *Pediatr Pulmonol*. 2020;55(10):2565-2575.
50. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization rates and characteristics of children aged<18 years hospitalized with laboratory-confirmed COVID-19 - COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(32):1081-1088.

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