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Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis

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ABSTRACT

Objective Compare paediatric COVID-19 disease characteristics, management and outcomes according to World Bank country income level and disease severity.

Design Systematic review and meta-analysis.

Setting Between 1 December 2019 and 8 January 2021, 3350 articles were identified. Two reviewers conducted study screening, data abstraction and quality assessment independently and in duplicate. Observational studies describing laboratory-confirmed paediatric (0–19 years old) COVID-19 were considered for inclusion.

Main outcomes and measures The pooled proportions of clinical findings, treatment and outcomes were compared according to World Bank country income level and reported disease severity.

Results 129 studies were included from 31 countries comprising 10 251 children of which 57.4% were hospitalised. Mean age was 7.0 years (SD 3.6), and 27.1% had a comorbidity. Fever (63.3%) and cough (33.7%) were common. Of 3670 cases, 44.1% had radiographic abnormalities. The majority of cases recovered (88.9%); however, 96 hospitalised children died. Compared with high-income countries, in low-income and middle-income countries, a lower proportion of cases were admitted to intensive care units (ICUs) (9.9% vs 26.0%) yet pooled proportion of deaths among hospitalised children was higher (relative risk 2.14, 95% CI 1.43 to 3.20). Children with severe disease received antimicrobials, inotropes and anti-inflammatory agents more frequently than those with non-severe disease. Subgroup analyses showed that a higher proportion of children with multisystem inflammatory syndrome (MIS-C) were admitted to ICU (47.1% vs 22.9%) and a higher proportion of hospitalised children with MIS-C died (4.8% vs 3.6%) compared with the overall sample.

Conclusion Paediatric COVID-19 has a favourable prognosis. Further severe disease characterisation in children is needed globally.

INTRODUCTION

The coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 has spread from a local outbreak in China to a global pandemic within months. On 31 December 2019, a cluster of cases with pneumonia of unknown cause emerged from Wuhan, China. On 30 January 2020, the WHO declared the coronavirus outbreak a Public Health Emergency of International Concern, and on 11 March 2020, a pandemic. As of 21 January 2021, there have been over 95.6 million confirmed COVID-19 cases and over 2.0 million associated deaths from 216 countries, areas or territories.[1] Children under-19 years of age comprise a small proportion (1%–10%) of the total reported cases[2–5] with a lower risk of developing critical illness from COVID-19 infection compared with adults.[6] Prior systematic reviews of paediatric COVID-19 have described a mild disease in children with good outcomes.[4 7 8] Since the publication of these reviews, the pandemic has spread extensively around the globe. In addition to pulmonary manifestations of COVID-19 in children, reports from Europe, North America, Latin America and Asia have emerged, describing a multisystem inflammatory syndrome children (MIS-C) related to COVID-19 infection.[9–12] COVID-19 has also disrupted essential maternal and child health interventions, including outpatient visits and vaccinations for young children in most countries, further worsening the existing burden on healthcare provision and delivery.[13]

The objective of this review, in addition to providing a comprehensive update of the evolving paediatric COVID-19 literature, is a unique comparison of reported cases in low-income and middle-income countries (LMICs) to high-income countries (HICs) and of children with severe versus non-severe disease. Furthermore, the review provides a subgroup analysis of children presenting with symptoms of MIS-C and neonatal cases.

METHODS

The protocol of the review is registered with PROSPERO (CRD42020183134). This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

SEARCH METHODS

The review includes a comprehensive search of MEDLINE, Embase, WHO COVID-19 Database, Chinese COVID-19 Databases (CNKI and Wangfang), Latin-American and Caribbean Health Sciences Literature (LILACS) from 1 December 2019 to 8 January 2021. Complementary searches were conducted in Google Scholar, John Hopkins Health Resource, WHO news and the Chinese and US CDC Library. MedRxiv, BioRxiv and ChinaXiv

were searched for preprints. No language restrictions were applied.

A search strategy was formulated and administered as shown in online supplemental table 1.

STUDY SELECTION

Observational studies reporting children (0–19 years old) with laboratory-confirmed COVID-19 (serology or RT-PCR) were considered for inclusion. Studies with a subset of children 0–19 years were included if disaggregated data for children were provided. Studies were screened for any overlap in paediatric cases by reviewing institution details and the period reported. Review articles, case reports, commentaries and letters not presenting any original data were excluded. Case reports were excluded to reduce risk of selection bias and over-representation of extreme cases. Covidence Software (2016) was used for screening by two reviewers independently and in duplicate. Key reference lists were screened for additional studies.

DATA EXTRACTION

Two reviewers conducted data extraction using a prepiloted data form. Data extracted included authors' names, date of publication, study-design, city, country, number of cases, gender, comorbidities, travel and contact history, diagnostic tests for COVID-19, clinical details, laboratory tests, radiological findings, management and outcomes. Disaggregated data by age groups (0–5 years, 5–10 years and >10 years old) and reported disease severity was extracted where available. Criteria for severe disease were as defined within each individual study and included admission to intensive care units (ICUs), use of mechanical ventilation, multiorgan failure and presence of hypoxia (oxygen saturation <92%).

QUALITY ASSESSMENT

Individual study quality was evaluated independently by the review authors using quality assessment tools developed by the National Heart Lung and Brain Institute (NHLBI)[14] (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Study quality was scored out of 8, based on clarity of study objectives, case definition, consecutive inclusion of cases, comparability of included patients, definition and measurement of outcomes, length of follow-up, statistical methods and results. Studies with score 6–8 were considered to be good quality, 4–5 considered fair quality and <4 considered poor quality.

DATA SYNTHESIS

Categorical data were summarised as counts and proportions. The pooled proportions of reported findings were calculated using Comprehensive Meta-Analysis 2.2.027 using random-effects model. I^2 was calculated to examine statistical heterogeneity (I^2>50% considered high heterogeneity). The clinical features and outcomes were compared according to (1) World Bank country income level (HICs versus LMICs)[15] and (2) reported disease severity (severe versus non-severe) using pooled proportions and their 95% CIs, supplemented by relative-risk (RR). Subgroup analyses of children with MIS-C and neonatal cases were conducted.

RESULTS

After removal of duplicates, 3350 citations were screened for inclusion. Full texts of 198 studies were screened and 129 studies[2 3 9–12 16–138] were included (online supplemental figure 1). Sixty-nine studies were excluded as they either presented overlapping data, did not provide age-disaggregated data for children or were commentaries, editorials or reviews. In terms of study setting, 13 studies were population-based national surveillance studies, 94 studies included only children admitted to hospital and 22 studies reported patients presenting to outpatient clinics or emergency departments (hospitalisation rate of 24.2%, 385/1590).

Sixty studies were from HICs (n=6528) and 69 studies from LMICs (n=3723). Almost one-third of included studies were from China (36/129, 28.0%),[2 16–33 35 37–43 45 52 53 55–57 71 74 138] one-fifth were from the USA (24/129, 18.6%)[3 9 10 47 58 60 64 68–70 79 81 82 85–87 93 98 109 110 115 120 133 136] together comprising almost half of the included sample size (n=4758, 46.4.%). The country of origin of included studies and study characteristics are summarised in online supplemental figure 2, tables 2 and 3.

DEMOGRAPHICS AND EPIDEMIOLOGY

A total of 9335 children from the 129 case series were included in the meta-analysis. Of 8455 children for whom initial disposition was reported, 4851 were hospitalised (57.4%). Among them, 55.5% were men. The patient's ages ranged from 0 to 17 years with mean age of 7.0±3.6 years. Ninety-one of the 129 studies reported age-disaggregated data for infection incidence as shown in online supplemental table 4. Nearly half of the cases were >10 years of age. Contact exposure to COVID-19 was reported in 64.0% of cases. Travel history to an epicentre was reported in 13.0% cases. At-least one underlying comorbidity was reported in 27.1% of cases. The most common reported comorbidities were immunosuppression (15.8%) and lung disease (12.5%).

CLINICAL MANIFESTATIONS

Table 1 summarises the clinical manifestations reported in the studies. There were 13.1% asymptomatic cases (95% CI 10.4% to 16.3%) who presented primarily through contact exposure in family-clusters (parents, siblings and other relatives). The most common presenting symptoms were fever (63.3%, 95% CI 58.6% to 68.4%) and cough (33.7%, 95% CI 29.6% to 38.1%) followed by nausea or vomiting (20.0%, 95% CI 16.5% to 24.0%) and diarrhoea (19.6%, 95% CI 16.1% to 23.7%). Other symptoms included dyspnoea, nasal-symptoms, rashes, kawasaki-like symptoms, conjunctivitis, fatigue, abdominal pain and neurological symptoms. Sixty-seven of the 129 studies reported age disaggregated data for clinical features (online supplemental table 5). Clinical features were similar in the three age groups: ≤5 years, >5 to ≤10 years, >10 years with higher prevalence of abdominal symptoms in children>5 years.

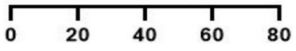
RADIOLOGICAL AND LABORATORY FINDINGS

One thousand five hundred and thirty cases out of 3670 (44.1%, 95% CI 39.5% to 48.9%) cases had radiological abnormalities; ground glass opacities (27.4%) were the most commonly reported abnormality.

Sixty-six studies provided details on laboratory-markers (table 2). Pooled analysis revealed increased C-Reactive Protein (CRP) (54.2%, 95% CI 41.5% to 66.3%), serum-ferritin (46.7%, 95% CI 32.3% to 61.7%), lactate dehydrogenase (LDH) (36.5%, 95% CI 26.5% to 47.8%) and d-dimers (35.2%, 95% CI 22.1% to 51.0%) as the most common abnormalities. Other reported abnormalities included elevated erythrocyte sedimentation rate (ESR), lymphopaenia, procalcitonin and biomarkers for organ

Table 1 Clinical symptoms among reported paediatric COVID-19 cases

Characteristics	Events/total patients	Mean proportion % (95% CI)	Heterogeneity I^2 (%)
Comorbidity	1590/6086	27.1 (23.1 to 31.5)	37.6
Fever	3576/6296	63.3 (58.6 to 68.4)	34.9
Cough	1807/5261	33.7 (29.6 to 38.1)	34.4
Nausea/vomiting	880/4243	20.0 (16.5 to 24.0)	25.7
Diarrhoea	796/4884	19.6 (16.1 to 23.7)	13.4
Dyspnoea	879/5332	17.5 (14.4 to 21.1)	23.7
Nasal symptoms	1080/5406	16.6 (13.9 to 19.7)	10.6
Rashes	744/4387	15.5 (11.9 to 19.9)	25.9
Fatigue	709/4474	15.5 (12.6 to 19.3)	26.3
Abdominal pain	626/4135	15.3 (11.9 to 19.4)	26.5
Kawasaki shock/sign	821/4365	13.3 (9.8 to 17.9)	30.6
Asymptomatic	1114/6084	13.1 (10.4 to 16.3)	15.4
Neurological symptoms	693/5475	12.1 (10.1 to 14.6)	17.6
Conjunctivitis	529/4998	10.5 (7.8 to 14.0)	21.0
Pharyngeal erythema	428/3638	9.0 (6.7 to 12.0)	0.0



injury including elevated levels of pro B-type natriuretic peptide, troponin and creatine kinase-MB as shown in table 2.

MANAGEMENT

Details of clinical management are as shown in table 3. Commonly used therapies among hospitalised children were antimicrobials (32.2%, 95% CI 25.2% to 40.1%), intravenous immunoglobulin (IVIG) (19.5%, 95% CI 13.5% to 27.2%) and systemic-steroids (19.3, 95% CI 14.9% to 24.9%). Other treatment regimens included aspirin, inotropic drugs, inhaled interferon-α (IFN-α), antimalarials and antivirals (ribavirin, oseltamivir, lopinavir, ritonavir and litonavir). Mechanical ventilation was provided to 490 patients (12.2%, 95% CI 9.7% to 15.3%).

PROGNOSIS AND SEVERE CASES

One thousand three hundred and fifty-nine patients (22.9%, 95% CI 17.6% to 29.2%) were admitted to ICUs (table 3). Thirty-eight studies provided disaggregated data for severe cases (table 4). A higher proportion of children with severe disease had symptoms consistent with MIS-C and received antimicrobials, inotropes and anti-inflammatory agents compared with those with non-severe disease. There were no deaths among children

Table 2 Laboratory and radiological features among reported paediatric COVID-19 cases

Characteristics	Events/total patients	Mean proportion % (95% CI)	Heterogeneity I^2 (%)
Inflammatory marker			
CRP ↑	556/1165	54.2 (41.5 to 66.3)	21.4
Ferritin ↑	247/525	46.7 (32.3 to 61.7)	46.5
LDH ↑	356/922	36.5 (26.5 to 47.8)	35.6
Procalcitonin ↑	137/879	21.3 (12.2 to 34.5)	24.9
Leukocytes ↑	138/953	19.9 (13.3 to 28.8)	21.4
Lymphocytes ↓	359/1347	19.0 (12.8 to 27.1)	0.0
ESR ↑	248/838	18.9 (11.8 to 28.9)	0.0
IL-6 ↑	41/341	13.1 (5.5 to 28.2)	7.1
Leucopaenia (+)	77/1037	10.7 (7.7 to 14.6)	0.0
Lymphocytes ↑	66/1264	8.2 (4.9 to 13.5)	0.0
Neutrophils ↑	22/574	7.8 (4.8 to 12.4)	0.0
Biomarkers for organ injury			
proBNP ↑	211/441	45.5 (28.5 to 63.5)	49.5
Troponin ↑	239/703	39.7 (24.7 to 57.0)	30.5
LFTs ↑	287/816	29.8 (20.3 to 41.6)	10.8
CKMB ↑	82/293	25.5 (13.4 to 43.0)	31.1
RFTs ↑	86/344	17.6 (7.6 to 35.6)	23.6
Coagulopathy markers			
D-dimers ↑	272/711	35.2 (22.1 to 51.0)	19.1
Fibrinogen ↑	168/438	17.5 (7.6 to 35.4)	0.0
Radiological test			
Abnormal CXR/CT	1530/3670	44.1 (39.5 to 48.9)	35.0

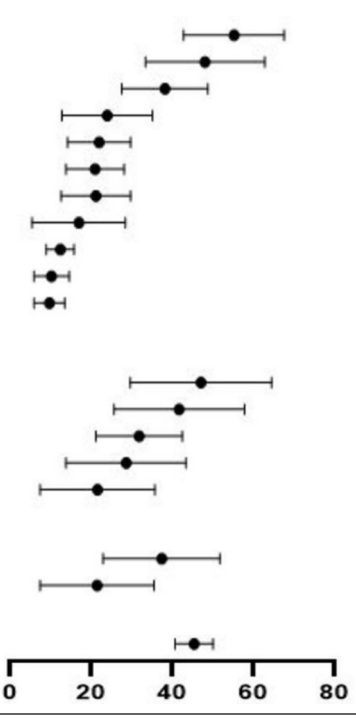
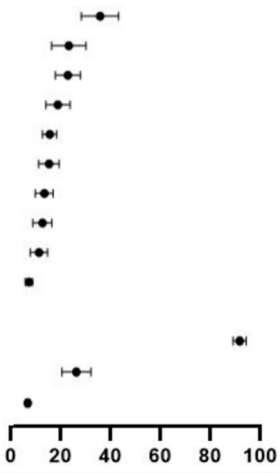


Table 3 Clinical management and outcomes among reported paediatric COVID-19 cases

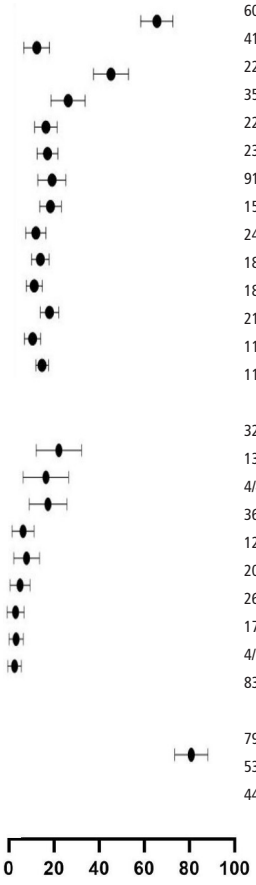
Characteristics	Events/total patients	Mean proportion % (95% CI)	Heterogeneity I^2 (%)
Clinical management			
Antibiotics	1345/3610	32.2 (25.2 to 40.1)	41.9
IVIG	698/3522	19.5 (13.5 to 27.2)	18.4
Systemic steroids	801/4229	19.3 (14.9 to 24.9)	23.7
Antiviral	527/4019	15.3 (11.1 to 20.7)	4.5
Mechanical ventilation	490/5406	12.2 (9.7 to 15.3)	15.5
Inotropes	354/3856	11.8 (8.3 to 16.4)	11.5
Antimalarial	336/3299	9.9 (6.9 to 14.0)	0.0
Aspirin	238/2588	9.0 (5.9 to 13.6)	78.1
Interferon	138/2598	7.7 (4.9 to 11.8)	0.0
Traditional medicine	22/4229	4.0 (2.8 to 5.6)	38.7
Clinical outcomes			
Recovered	8704/9335	88.9 (86.0 to 91.2)	36.3
ICU admission	1359/9335	22.9 (17.6 to 29.2)	37.2
Deaths	96/6902	3.6 (2.8 to 4.5)	24.3

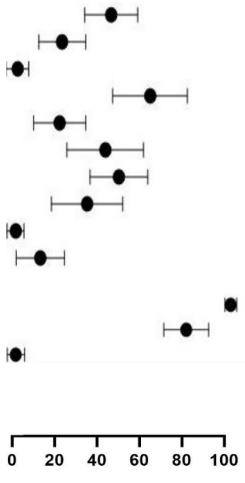


ICU, intensive care unit; IVIG, intravenous immunoglobulin.

Table 4 Comparison of clinical symptoms, management and outcomes among reported paediatric COVID-19 non-severe (n=2402 cases, 64 studies) and severe (n=796 cases, 38 studies) cases

	Non-severe cases			Severe cases		
Characteristics	Events/total patients	Mean proportion % (95% CI)		Events/total patients	Mean proportion % (95% CI)	RR severe vs non-severe (95% CI)
Clinical symptoms						
Fever	1394/2404	51.4 (45.7 to 57.0)		608/756	80.2 (73.6 to 85.5)	1.39 (1.32 to 1.46)
Pharyngeal erythema	541/1149	8.6 (5.1 to 14.0)		41/585	8.8 (5.1 to 14.8)	0.15 (0.11 to 0.20)
Cough	587/1521	35.1 (29.2 to 41.5)		225/618	34.0 (24.6 to 44.9)	0.94 (0.84 to 1.07)
Comorbidity	541/2283	19.8 (14.5 to 26.4)		351/764	44.1 (34.9 to 53.8)	1.94 (1.74 to 2.16)
Nausea/vomiting	206/1291	12.1 (8.7 to 16.6)		224/632	41.0 (36.7 to 45.5)	2.27 (1.93 to 2.67)
Dyspnoea	260/1646	12.7 (9.5 to 16.8)		237/701	36.4 (26.5 to 47.5)	2.14 (1.84 to 2.49)
Nasal symptoms	402/1659	14.1 (9.9 to 19.7)		91/652	15.8 (10.6 to 23.0)	0.58 (0.47 to 0.71)
Fatigue	192/1319	13.8 (10.4 to 18.0)		151/505	20.3 (15.3 to 33.4)	2.05 (1.70 to 2.48)
Kawasaki shock/sign	135/1243	8.5 (5.6 to 12.6)		242/695	30.7 (19.3 to 45.0)	3.21 (2.65 to 3.87)
Rashes	168/1587	10.3 (7.6 to 13.7)		180/660	32.3 (22.3 to 44.2)	2.58 (2.13 to 3.11)
Abdominal pain	95/1193	8.1 (5.8 to 11.3)		184/621	28.4 (18.8 to 40.4)	3.72 (2.96 to 4.67)
Diarrhoea	144/1326	13.5 (10.6 to 17.1)		217/632	35.3 (26.3 to 45.4)	3.16 (2.62 to 3.82)
Conjunctivitis	111/1621	7.5 (5.1 to 10.8)		116/657	22.6 (15.1 to 32.4)	2.58 (2.02 to 3.29)
Neurological symptoms	200/2230	11.0 (9.0 to 13.4)		118/703	17.4 (11.9 to 24.6)	1.87 (1.52 to 2.31)
Clinical management						
Mechanical ventilation	–	–		322/735	43.8 (33.8 to 54.3)	–
Antiviral	217/715	26.5 (17.5 to 38.1)		136/567	24.1 (16.2 to 34.3)	0.79 (0.66 to 0.95)
Interferon	127/685	20.2 (11.6 to 32.3)		4/445	6.8 (3.6 to 12.3)	0.05 (0.02 to 0.13)
Antibiotics	180/363	21.6 (14.2 to 31.3)		365/566	59.6 (44.3 to 73.3)	1.30 (1.15 to 1.47)
Antimalarial	73/717	10.1 (6.4 to 16.4)		123/537	22.9 (14.3 to 34.6)	2.25 (1.72 to 2.94)
IVIG	54/721	11.8 (7.2 to 18.8)		202/498	41.1 (27.0 to 56.8)	5.42 (4.10 to 7.15)
Systemic steroids	46/721	8.9 (5.4 to 14.4)		265/575	46.8 (35.7 to 58.2)	7.22 (5.39 to 9.69)
Inotropes	24/718	6.8 (4.1 to 11.7)		171/498	33.6 (21.2 to 48.9)	10.27 (6.81 to 15.50)
Traditional medicine	18/723	7.4 (4.8 to 11.3)		4/575	6.3 (3.8 to 10.3)	0.28 (0.10 to 0.82)
Aspirin	11/683	6.7 (4.3 to 10.4)		83/445	14.9 (7.9 to 26.4)	11.58 (6.25 to 21.47)
Clinical outcomes						
ICU	–	–		793/796	95.0 (92.1 to 96.8)	–
Recovered	1700/1925	85.4 (76.5 to 91.2)		532/796	77.6 (67.5 to 85.3)	0.76 (0.72 to 0.80)
Deaths	0/1925			44/796	8.0 (5.2 to 12.1)	

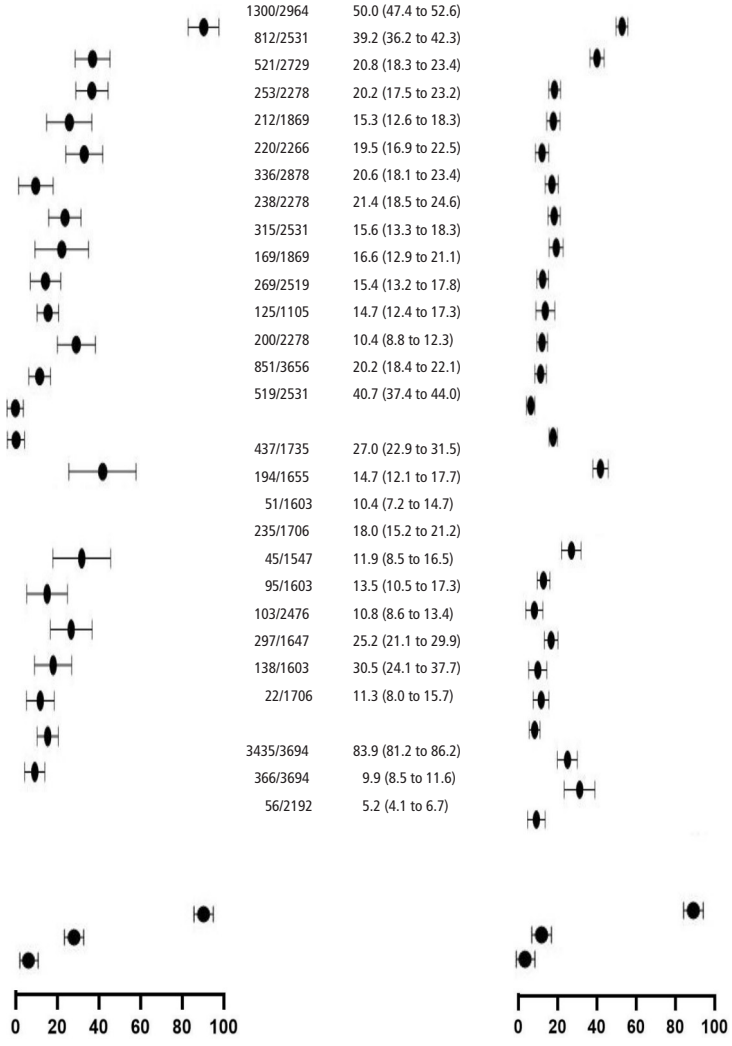




ICU, intensive care unit; IVIG, intravenous immunoglobulin.

Table 5 Comparison of clinical symptoms, management and outcomes among reported paediatric COVID-19 cases in HICs (n=5641 cases, 60 studies) and LMICs (n=3694, 69 studies)

	HICs		LMICs		
Characteristics	Events/total patients	Mean proportion % (95% CI)	Events/total patients	Mean proportion % (95% CI)	RR LMICs vs HICs, (95% CI)
Clinical symptoms					
Fever	2276/3332	72.0 (66.3 to 77.0)	1300/2964	50.0 (47.4 to 52.6)	0.64 (0.61 to 0.67)
Cough	995/2730	33.2 (27.5 to 39.5)	812/2531	39.2 (36.2 to 42.3)	0.88 (0.82 to 0.95)
Comorbidity	1069/3357	33.7 (27.4 to 38.5)	521/2729	20.8 (18.3 to 23.4)	0.60 (0.55 to 0.66)
Rashes	491/2109	24.9 (17.9 to 33.5)	253/2278	20.2 (17.5 to 23.2)	0.48 (0.41 to 0.55)
Nausea/vomiting	668/2374	30.3 (24.3 to 37.0)	212/1869	15.3 (12.6 to 18.3)	0.40 (0.35 to 0.46)
Conjunctivitis	309/2732	13.1 (8.4 to 20.1)	220/2266	19.5 (16.9 to 22.5)	0.86 (0.73 to 1.01)
Dyspnoea	543/2454	23.6 (18.5 to 29.6)	336/2878	20.6 (18.1 to 23.4)	0.53 (0.47 to 0.60)
Kawasaki shock/sign	583/2087	21.9 (14.1 to 32.5)	238/2278	21.4 (18.5 to 24.6)	0.37 (0.33 to 0.43)
Fatigue	394/1943	16.8 (12.2 to 22.6)	315/2531	15.6 (13.3 to 18.3)	0.61 (0.54 to 0.70)
Abdominal pain	457/2266	22.7 (16.4 to 30.5)	169/1869	16.6 (12.9 to 21.1)	0.45 (0.38 to 0.53)
Nasal symptoms	425/2549	17.8 (14.4 to 21.8)	269/2519	15.4 (13.2 to 17.8)	0.64 (0.56 to 0.74)
Diarrhoea	527/2365	27.5 (21.5 to 34.6)	125/1105	14.7 (12.4 to 17.3)	0.51 (0.42 to 0.61)
Neurological symptoms	493/3197	15.0 (11.6 to 19.0)	200/2278	10.4 (8.8 to 12.3)	0.57 (0.49 to 0.67)
Asymptomatic	263/2428	6.4 (4.2 to 9.7)	851/3656	20.2 (18.4 to 22.1)	2.15 (1.89 to 2.44)
Pharyngeal erythema	73/1494	6.7 (4.3 to 10.1)	519/2531	40.7 (37.4 to 44.0)	4.20 (3.31 to 5.32)
Clinical management					
Antibiotics	908/1875	36.4 (25.6 to 48.7)	437/1735	27.0 (22.9 to 31.5)	0.52 (0.47 to 0.57)
IVIG	504/1867	31.6 (20.3 to 45.5)	194/1655	14.7 (12.1 to 17.7)	0.43 (0.37 to 0.51)
Aspirin	187/985	16.0 (9.1 to 26.8)	51/1603	10.4 (7.2 to 14.7)	0.17 (0.12 to 0.23)
Systemic steroids	566/2523	27.2 (19.0 to 37.3)	235/1706	18.0 (15.2 to 21.2)	0.61 (0.53 to 0.71)
Inotropes	309/2309	19.1 (12.3 to 28.5)	45/1547	11.9 (8.5 to 16.5)	0.22 (0.16 to 0.30)
Antimalarial	241/1696	13.6 (8.7 to 20.8)	95/1603	13.5 (10.5 to 17.3)	0.42 (0.33 to 0.52)
Mechanical ventilation	387/2930	17.2 (13.1 to 22.3)	103/2476	10.8 (8.6 to 13.4)	0.32 (0.26 to 0.39)
Antiviral	230/2372	11.4 (7.7 to 16.6)	297/1647	25.2 (21.1 to 29.9)	1.86 (1.58 to 2.18)
Interferon	0/995	–	138/1603	30.5 (24.1 to 37.7)	–
Traditional medicine	0/2523	–	22/1706	11.3 (8.0 to 15.7)	–
Clinical outcomes					
Recovered	5269/5641	91.0 (87.7 to 93.4)	3435/3694	83.9 (81.2 to 86.2)	0.99 (0.98 to 1.01)
ICU admission	993/5641	26.0 (24.0 to 28.0)	366/3694	9.9 (8.5 to 11.6)	0.56 (0.50 to 0.63)
Deaths	40/4710	2.9 (2.1 to 4.1)	56/2192	5.2 (4.1 to 6.7)	2.14 (1.43 to 3.20)



HICs, high-income countries; ICU, intensive care unit; IVIG, intravenous immunoglobulin; LMICs, low-income and middle-income countries; RR, relative risk.

categorised as non-severe and 44 deaths among severe cases, where disaggregated data were provided. Hospital outcomes were reported for 9335 children; 8704 cases (88.9%, 95% CI 86.0% to 91.2%) were definitively discharged, 96 died and remaining children either remained hospitalised at the time of reporting or were readmitted.

COMPARISON OF OUTCOMES ACCORDING TO WORLD BANK COUNTRY CLASSIFICATION

Of the included studies that reported clinical characteristics and outcomes, 60 studies were from HICs (n=6528) and 69 studies from LMICs (n=3723) as show in table 5. Studies in LMICs included a higher proportion of hospitalised children (1981/3723, 53.2%) compared with HIC studies (2897/6528, 44.4%). Abdominal symptoms and symptoms consistent with MIS-C were more frequently reported in HICs. A lower proportion of children in LMICs were admitted to the ICU (RR 0.56, 95% CI 0.50 to 0.63, p<0.05), mechanically ventilated (RR 0.32, 95% CI 0.26 to 0.39, p<0.05) and treated with different therapies; inotropes, antimicrobials, steroids, aspirin and IVIG. Only children in LMICs received inhaled IFN-α. Among the hospitalised cases, 40 deaths were reported in HICs compared with 56 in LMICs (pooled proportion 2.9% vs 5.2%). Risk-adjusted mortality according to severity of illness could not be calculated due to lack of data (table 5).

SUBGROUP ANALYSES OF CHILDREN PRESENTING WITH MIS-C, AND COVID-19 IN NEONATES

Thirty-one studies (n=1208) with 22 from HIC (n=602), reported series of children presenting with MIS-C. Fever, abdominal pain and diarrhoea were the most common symptoms. Nearly half of children (638/1208) who met criteria for MIS-C were admitted to ICU (449/638, 70.3% of which were from HIC) compared with 22.9% in the overall analysis (online supplemental tables 6 and 7).

Disaggregated data were available on 184 neonates with fever; inability to feed/lethargy and dyspnoea were the most commonly

reported symptoms. Twenty-one neonates (16.6%, 95% CI 11.2% to 23.9%) were asymptomatic at the time of diagnosis.

QUALITY ASSESSMENT OF INCLUDED STUDIES

One hundred and twenty-one studies were determined to be of good quality while eight were of fair quality (online supplemental table 8). Studies were primarily downgraded for incomplete case definition,[29 31 44 46 48–50 130 135 138] incomplete case follow-up,[10 23 24 26 29 32 35 44 51 53 77 82 85 90 94 99 106 112–114 120 130 135–137] missing data[2 3 19–21 29 35 42–44 52 57 74 89 92–94 117 128] and non-consecutive patient enrolment,[9 11 12 16 18–26 28 30–35 37–39 50 57 61–73 80 82 87 89–91 93 95 102 109 110 112 114 123 125 126 129 134–136] which raises concern that the included sample could be biased towards more severe presentations.

DISCUSSION

Global knowledge of COVID-19 epidemiology, clinical characteristics and management has continued to evolve since the onset of the pandemic. Children have been noted to have relatively lower rates of severe illness and low mortality; however, they have been impacted by MIS-C.[4 139]

The findings of our review, the largest in terms of published systematic reviews on paediatric COVID-19, are consistent with previous reviews that identified predominance of infection in school-age children, slight male predisposition, prevalence of comorbidities among children with COVID-19 and low hospitalisation and mortality rates.[2 4 140] The clinical presentation in children is heterogeneous, including a wide spectrum of clinical features. Fever and cough were the most commonly reported presenting symptoms, in line with the previously published systematic reviews.[4 141]A U-shaped curve of severity has been demonstrated in children diagnosed with COVID-19 with infants under 1 year of age and adolescents 10–14 years of age at higher risk of developing severe COVID-19.[3 47 75] Due to lack of age-disaggregated data, we could not reliably compare the frequency of severe cases by age group in this review. Reported risk factors for severe disease among children include age, viral load[142] and presence of comorbidities.[3] There is a possibility that children with comorbidities may have been hospitalised related to their underlying chronic condition and incidentally determined to have COVID-19 infection or investigated more extensively. Some of the common comorbidities reported in children with COVID-19 infection include asthma, immunosuppression, congenital heart disease, kidney disease and obesity.[3 4 47]

Regional differences were identified in the comparison of clinical features, treatment and outcomes between HICs and LMICs. Pooled estimates of hospital mortality were higher in LMICs compared with HICs. Given that it was not possible to calculate risk-adjusted mortality rates for COVID-19, it is unclear whether observed differences in mortality are related to selection bias (eg, differences in severity of illness of included patients or differences in case definitions and inclusion criteria) or differences in available hospital resources. Nevertheless, there is ongoing concern that, in LMICs with high burden of illness and health system limitations, children with severe disease and MIS-C may be at greater risk for adverse outcomes and death than perceived to date. The differences in frequency of observed clinical features may be related to increasing recognition of MIS-C over the course of the pandemic and their inclusion in more recent COVID-19 case series, but is likely similar between HICs and LMICs.

Comparisons of clinical features and outcomes according to severity of illness were limited by heterogeneous reporting across the included case series. A higher proportion of children with severe disease demonstrated symptoms consistent with MIS-C (fever, abdominal symptoms, rash, neurological symptoms, conjunctivitis) and received IVIG, steroids and inotropes.

Compared with previous reviews, several at an earlier stage of the pandemic,[4 7 8 140 143] this review has several strengths. Using a broad search strategy implemented in English, Chinese and Spanish databases, we summarise evidence from 129 studies from 31 different countries, the largest sample to-date. We excluded case reports to minimise selective reporting of extreme and atypical cases. We also attempted to reduce possible overlap in cases to prevent duplications. We identified differences in features from studies in HICs compared with LMICs, and between severe and non-severe cases, although with limited available data. Finally, we report subgroup analyses for neonates, and children presenting with MIS-C.

The review is limited primarily by the small sample sizes of individual studies, limitations in study reporting, and study quality limitations due to non-consecutive patient enrolment, unclear case definition and incomplete follow-up to hospital discharge. Our approach of pooling proportions is subject to bias and wide confidence-intervals due to small study sample size. We could not undertake multivariate analysis to identify risk factors for severe infection or adverse outcome in children due to lack of individual-patient-data. The inclusion of asymptomatic cases could have contributed to underestimation of the prevalence of clinical characteristics and optimism in the reporting of outcomes. Finally, it should be noted that a large number (36/129, 28.0%) of the included studies were from China. While the Chinese healthcare system is well-resourced in certain regions, many of the Chinese studies included were conducted in the city of Wuhan or in Hubei Province (n=9, 32.1%), where the gross domestic product per capita is less than half of that of Beijing and Shanghai.[144] Therefore, the findings of studies from China may be generalisable to the socioeconomic and health development status of other middle-income countries.

This review contributes to the global understanding of paediatric COVID-19 disease and supports priority setting in research for current pandemic and future outbreaks. This body of literature would be improved by complete reporting of larger series with consecutive recruitment of patients, specific case definitions and complete long-term follow-up to determine global epidemiological trends, age-specific burden of disease and illness trajectory following COVID-19 infection. Improved characterisation of disease severity and increased reports from low-income countries are needed to better understand differences in clinical manifestations, resource utilisation and outcome by region, which can be integrated in future updated analyses. The concern for selection bias remains as it is possible that in LMICs, the population of hospitalised children was sicker and at higher baseline risk of death, independent of resources. Individual-patient-data meta-analysis would be of benefit to characterise risk factors for severe disease, clinical features in different age groups and account for observed differences in outcome. With respect to clinical management, none of the therapies instituted in the treatment of children with severe COVID-19 disease have been demonstrated to improve outcome in randomised trials; therefore, a recommendation regarding their use is challenging. Given that children appear less likely to develop severe respiratory disease, but are at risk of multiorgan dysfunction due to MIS-C, further studies are needed to characterise the clinical trajectory of this novel syndrome and determine the optimal treatment for it. Finally, there remains paucity of studies reporting long-term prognosis of COVID-19 in children.[145]

CONCLUSION

Our review suggests that children predominantly contracted mild form of infection but could be at risk of more severe outcomes. It is crucial to take into consideration risk factors including contact-exposure, underlying comorbidities, young age and male sex which may increase the risk of severe disease. While we have identified several elements that highlight the disease spectrum and higher risk of adverse outcomes in certain settings, such as LMICs, there is the need for much closer scrutiny of this illness globally with individual patient data analysis.

Contributors ZB conceptualised the study and secured funding. ZSL and OI drafted the study protocol, conducted the literature search, study screening, selection and data extraction and drafted the manuscript. LJ and KT designed the data collection instruments, collected data, carried out data analyses and reviewed and revised the manuscript. FM drafted the initial manuscript and reviewed and revised the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript as submitted. ZB is the guarantor.

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