SARS-CoV-2 Infection in Children and Newborns: A Systematic Review

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Abstract

A recent outbreak of a novel Coronavirus responsible for a Severe Acute Respiratory Syndrome (SARS-CoV-2) is spreading globally. The aim of this study was to systematically review the existing evidence on SARS-CoV-2 infections in pediatric age.

An electronic search was conducted in PubMed database. Papers published between the 1st of January and the 7th of April, 2020 including children aged 0-18 years were selected.

Fifty-two studies and two reviews were included, with a total sample size of 4.612 children (2.366 males, 51.3%, weighted mean age 7 years). Patients showed mainly mild (1285/2679, 48.5%) and moderate (1035/2679, 39.1%) signs of the infection. Less than 2% of children were admitted to the Pediatric Intensive Care Unit. The most commonly described symptoms were fever (49.2%) and cough (44.1%). Laboratory findings were often unremarkable. Children underwent a chest CT-scan in 85.7% of all cases, and 36% resulted normal. Overall, the estimated mortality was 0.07%. A higher proportion of newborns was severely ill (17%) and dyspnea was the commonest reported sign (40%).

Conclusion: SARS-CoV-2 affects children less severely than adults. Laboratory and radiology findings are mainly nonspecific. Larger epidemiological and clinical cohort studies are needed to better understand possible implications of COVID-19 infection in children.

Introduction

In early January 2020, a novel type of Coronavirus (CoV) was identified in the bronchoalveolar lavage sample of a subject affected by pneumonia of unknown origin[1]. The virus was provisionally named novel coronavirus (2019-nCoV)[2] to differentiate it from the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)[3] and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[4], responsible for two previous outbreaks, in 2002 and 2012 respectively[5]. Successively, the International Committee on Taxonomy of Viruses defined it as SARS-CoV-2[6] and the associated disease has been called 2019 Coronavirus Disease (COVID-19). SARS-CoV-2 rapidly spread worldwide, forcing the World Health Organization (WHO) to declare the outbreak as a pandemic on 11 March[7, 8].

As of April 7, 1.511.104 cases have been reported in 184 countries in all continents except for Antarctica, with 88.338 deaths and 328.661 recovered[9]. Children seem to be less affected than adults, but data regarding epidemiologic characteristics and clinical features of COVID-19 in pediatric age are very poor and essentially based on limited case series[10, 11]. In a report of 72.314 cases from Chinese Center for Disease Control and Prevention (CDC), about 2% of all patients were aged <19 years, but no specific clinical information was available[12].

Italy has the second largest number of COVID-19 cases in the world, with 1.2% of all patients represented by children[9, 13, 14]. The estimated overall case-fatality rate in Italy resulted higher than in China (7.2% vs 2.3%)[15], but no death in the pediatric age has been reported, confirming that the mortality remains low and no specific risk factor could be identified[16].

Neonatal SARS-CoV-2 infections are also extremely rare and, to date, there is no evidence of intrauterine infection caused by vertical transmission[17, 18]. As described in a case series by Chen et al., amniotic fluid, cord blood, neonatal throat swab and colostrum samples collected from infected mothers were negative for COVID-19[19]. However, as the virus is transmitted via droplets or direct contact, currently in China all newborns are separated from their infected mothers for at least 14 days[20].

Despite the global interest and concern about COVID-19, clinical pattern is still unclear for the pediatric health community. The aim of our review is to provide a concise and systematic overview of the available evidence on clinical, laboratory and radiological findings in children with SARS-CoV-2 infection.

Materials And Methods

This study is in compliance with the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines[21].

An electronic search was conducted on studies published from the 1st of January, 2020 to the 7th of April, 2020 in PubMed database. We used the search terms “2019 novel coronavirus OR COVID-19 OR SARS-CoV-2 AND child* OR pediatric* OR newborn OR infant” with no language restriction to include as much data as possible. However, since full texts available only in Chinese language could not be evaluated, we had to rely on English-language abstracts. For the purpose of this review, studies on children aged 0 to 18 years old were included. Case reports, case series, retrospective or observational studies were all considered eligible.

Articles were first screened by title and abstract: duplicates and those with no available English summary were excluded. Eligible full texts were then assessed for pediatric clinical, laboratory and radiological data. Papers reporting information on both children and adults were included only if pediatric data could be retrieved. To identify missing studies, we also checked the reference list for each selected paper.

Three reviewers extracted data independently. A standardized table with the following information was used for data extraction: first author, date and journal of publication, study design (cohort study, case series, case report), sample size, age, mortality and morbidity rate, clinical features, laboratory and radiological results and treatment information. All included studies were differentiated in tables for newborns and infants ≤ 3 months and for children aged > 3 months.

During the data analysis process, clinical patterns were grouped according to the pediatric scoring for patients with COVID-19 (recommendations issued by the pediatric branch of the Chinese Medical Association[22]). In particular, cases described as “upper respiratory tract infection” (i.e. pharyngeal congestion, sore throat, and fever) with no abnormal radiographic and septic presentation were included in the “mild” symptomatic category. Children with “pneumonia” and no complications were categorized as “moderate”. Patients with mild or moderate clinical patterns, plus any manifestations suggesting disease progression (i.e. tachypnoea, hypoxia, neurological deterioration, dehydration, myocardial injury, coagulation dysfunction, rhabdomyolysis) were considered “severe”. Critically-ill children were those with a rapid disease progression, plus any other of the following conditions: respiratory failure with need for mechanical ventilation (i.e. acute respiratory distress syndrome, persistent hypoxia), septic shock or multiple organ failure (MOF)[22].

Laboratory data were presented as abnormally high or low according to the reference value reported by the paper, if available. Similarly, radiological findings were categorized according to the available description.

A quantitative synthesis of the included studies was performed. For continuous variables, weighted mean (range) was calculated as appropriate, while categorical variables were expressed as percentages or frequencies in relation to the total or subtotal sample size, according to the number of missing data.

Results

We initially identified 191 papers on SARS-CoV-2 infection in children published from the 1st of January 2020 to the 7th of April 2020. After screening the title and abstract, 101 full articles were evaluated for eligibility. At the end of the selection process (Figure 1), 52[10, 11, 14, 16, 23–70] studies and two previously published reviews[71, 72] with a total sample size of 4.612 children (2.366 males, 51.3%) were included in the systematic review (Table 1). The weighted mean age of patients was 7 years, ranging from 0 to 18 years old. Children included were mainly Chinese (2700/4612; 58.6%) and Italian (1708/4612; 37%). The most extensive retrospective study[16] described clinical characteristics of 2.143 children with confirmed (n=713) or suspected (n=1430) SARS-CoV-2 infection. Overall, 3382/4612 (73.3%) were discharged after a weighted mean hospitalization of 11.6 days (range 2-23). The estimated mortality was 0.07%, with 3 reported deaths: a 10 months baby with intussusception who developed MOF[10], a 14-year-old boy from Hubei province[16], and a preterm newborn who died from complications of sepsis[59]. Significant comorbidities were reported in 11 patients: 3 who were on immunosuppressive treatment for previous liver transplantation[24], 3 with a diagnosis of congenital heart disease[26, 55], 2 with asthma[55, 56], 1 child had acute lymphoblastic leukemia (ALL)[25], 1 with duplicate kidneys[56], and 1 with nephroblastoma[55]. None of them had a severe course of the disease.

Clinical features

Clinical findings were available in 2.679 children aged 3 months-18 years (38 studies)[10, 11, 16, 24–56, 67, 68] (Table 2). Severe and critically ill children accounted for 4.5% (118/2679) and 0.7% (18/2679) of the total sample size respectively. The most commonly described symptoms in pediatric age were fever (49.2%), cough (44.1%) and sore throat (19%). Rarely children were also dyspneic (4.5%) and required oxygen supplementation for SpO₂ below 92% (10.4%)[10, 25]. Extrarespiratory symptoms were mainly represented by diarrhea (8.9%) and vomiting (5.5%). A familial history of positive contact could be identified in 85% of the cases. One child with ALL on chemotherapy contracted SARS-CoV-2 infection during hospitalization, but then recovered[25].

Laboratory investigations

Table 3 summarizes the main laboratory investigations reported in 474 children (29 studies)[10, 11, 25–28, 30–44, 49, 52–56, 67, 68]. The full blood cell count was unremarkable in most patients, with less than one-fifth of them (18.9%) showing low white blood cell (WBC) and lympho- or neutropenia (12.3%). Elevated inflammatory indexes such as C-reactive protein (CRP) and procalcitonin (PCT) were shown by 38.7% of children. Creatine kinase (CPK) and liver enzymes were also altered, as shown by 13.1% and 12.9% of all patients respectively.

Radiology findings

Of the 493 children who had radiological exams (31 studies)[10, 11, 25–28, 30–44, 47, 49, 51–56, 67, 68], up to 52.1% of them showed abnormalities, even if asymptomatic (Table 4). Most patients underwent a chest CT-scan (85.7%) that resulted normal in 163 out of 453 patients (36%), whereas typical ground-glass opacities (GGO), nonspecific unilateral and bilateral lesions were identified in 33.7%, 21% and 15.4% of patients, respectively.

Treatment

Of all patients, less than 2% were admitted in the Pediatric Intensive Care Unit (PICU) and required mechanical ventilation (MV) (Table 5)[10, 11, 25–27, 30–32, 34, 35, 37, 38, 43, 45, 47, 49, 51–56, 67, 68]. Most authors described the use of nebulized Interferon (IFN) (47.5%), and of other antiviral agents (38.5%) or antibiotics (22.3%). The use of intravenous immunoglobulin (IVIg) and corticosteroids (CCS) was less frequently described (5% and 6%, respectively).

Neonatal cases

A few case reports[43, 57, 58, 62–65, 69, 70] and case series[59, 60, 66] including a total of 25 newborns (15 males, 60%) with SARS-CoV-2 were identified (Table 6). Neonates were usually screened because of a history of primary maternal infection (80%). Similarly to older children, most of them were asymptomatic (12%) or had mild (52%) and moderate (20%) signs of clinical infection. However, a slightly higher proportion of them was severely ill

(17%). Dyspnea was the commonest reported sign in neonatal age (40%). Fever (32%) and feeding intolerance (24%) were also described. Blood tests showed high WBC (28%), CRP and/or PCT (20%), CPK (28%) and liver enzymes (20%).

Unlike older children, newborns underwent a chest X-ray in most cases (64%) (Table 7). Abnormal radiological findings could be recognized in more than half of them (56%), but specific lesions were not so frequently described: 8% had GGO, 24% unilateral patchy area, and 12% bilaterally. Poor information on treatment options was obtainable from the included reports, and most patients (48%) received only symptomatic therapies.

Discussion

This systematic review fully assesses epidemiological and clinical characteristics of SARS-CoV-2 infections reported in pediatric age.

Children are less likely to develop severe symptoms of COVID-19 than adults, with 95% of all cases ranging from asymptomatic to mild-moderate clinical patterns, as described by different case series[10, 11, 24, 27–56, 67, 68]. Moreover, less than 2% of patients were admitted to PICU or required MV[10, 25, 26]. Overall, three deaths were reported (mortality rate 0.07%): all patients developed complications[10, 16], including a preterm newborn who died from sepsis[59]. In adulthood, over two-third of those who died from COVID-19 had a comorbidity[73], while a very limited number of children with underlying disease could be identified, and none of them showed worse clinical course of the infection in comparison to previously healthy patients[10, 24, 26, 55, 56].

However, children might not be tested for SARS-CoV-2 as frequently as adults. Moreover, the current gold standard for the diagnosis of SARS-CoV-2 infection is Real Time-Polymerase Chain Reaction (RT-PCR) on respiratory tract specimen. The diagnostic accuracy of RT-PCR highly depends on the virus-specific diagnostic window, and the analytical sensitivity of this assay is potentially plagued by false SARS-CoV-2 negativity attributable to the low viral loads, especially in asymptomatic or mild symptomatic patients that might transmit the disease as well[74].

Clinical features

Infected children usually show typical symptoms of acute respiratory infections including fever (49.2%) and cough (44.1%)[10, 11, 16, 25–29, 31–33, 35–37, 41, 45, 47, 49, 53–56]. In particular, some authors reported that up to one-third of symptomatic children may have high fever[10], but generally below 39°C[32]. Differently from adults, children are more likely to present with extrapulmonary symptoms[75]: diarrhea (8.9%) and vomiting (5.5%) are the most frequently reported ones. It has been showed that, when present, gastrointestinal symptoms usually anticipate the typical respiratory pattern[76]. Previous studies on SARS-CoV cases demonstrated the viral detection in gut biopsy specimens and stool of recovered patients, indicating a possible gastrointestinal tract tropism that may partially provide explanations for extrapulmonary symptoms and persistent viral shedding through fecal-oral route[77]. There is growing evidence that this mechanism of excretion may be typical also for SARS-CoV-2[2, 31]. As described in a case series of ten infected children, SARS-CoV-2 remained detectable in rectal swabs after nasopharyngeal swabs turned negative[31]. However, the extrapulmonary detection of viral RNA does not mean infectious virus is present, but two independent laboratories from China declared that they have successfully isolated live 2019-nCoV from the stool of patients (unpublished)[76]. Moreover, given the fact that pathogenesis of human coronavirus mainly depends on the interactions between its transmembrane spike glycoprotein (S-protein) and specific cell receptors of angiotensin converting enzyme II (ACE2)[78], recent analysis revealed that ACE2 was expressed also in upper esophagus and absorptive enterocytes from ileum and colon[55].

According to evaluated studies, clinical presentation in newborns and infants below 3 months could be slightly different than in older children, with a higher proportion of them (17%) presenting with a severe pattern[59, 60]. Even if the vertical transmission for SARS-CoV-2 has not been demonstrated[19, 79], in 80% of neonatal cases the mother was infected[57–60, 63, 66]. Moreover, nosocomial infection may also occur, and strict measures to reduce this risk should be always observed[20]. However, some authors hypothesized that 2019-nCoV infection and morbidity in newborns may be related to possible hypoxemia in the infected mother that increases the risk of perinatal adverse events such as birth asphyxia and premature birth[59, 80]. Evidence remains still too limited.

Laboratory findings

Twenty-nine studies accounting for a total of 474 patients reported information on blood investigations in pediatric cases with COVID-19. Overall, no significant abnormalities were observed and this was consistent with the results of a previously published review including a total sample size of 66 children with confirmed SARS-CoV-2 infection[71]. In particular, full blood cell count was normal in most patients. Two case series reported high rates of lymphopenia (10/25, 40%[26] and 11/36, 30.1%[54] respectively). However, this finding seems to be in contrast with adult data, as low lymphocyte count has been noted in up to 80% of infected critically-ill subjects[74, 81]. The limited number of severe COVID-19 infection may in part explain the lack of significant lymphopenia in children.

Our results suggested that inflammatory indexes may be abnormal in more than one-third of children with SARS-CoV-2 infection (38.7%), while Henry et al. described only 10-13% of cases with high CRP and/or PCT[71]. This controversial finding could be explained by the high heterogeneity in defining a cut-off of abnormal values across all the included studies. However, in adults a PCT value of ≥ 0.5 ng/ml was observed to be associated with a near 5-fold increase in risk of severe clinical course of COVID-19 infection[82].

Other significant reported laboratory investigations were represented by high CPK values (13.1%) and liver enzymes (12.9%). These enzymes could be often altered during viral infections[83]. In particular, high CPK levels or aspartate aminotransferase activity correlated with more severe clinical patterns in adult patients with SARS-CoV-2 infection[84]. Abnormal transaminases levels may also express a sign of direct liver damage. Recently published data

demonstrated enrichment of ACE2 expression in cholangiocytes (59.7% of cells) suggesting that SARS-CoV-2 might lead to direct damage of intrahepatic bile ducts[85].

Radiology findings

A total of 493 children had radiological exams, with half of them showing abnormalities. The sensitivity of chest X-ray is supposed to be inferior to that of CT-scan: in adults, nonspecific patchy peripheral and peribronchovascular opacities may be shown in all lung zones, according to the severity of the infection[86]. As children usually develop milder patterns of the disease, chest X-ray may fail to identify typical lesions, and it is mainly adopted in newborns and younger infants[59, 63, 66]. CT-scan is frequently performed in children with suspected or confirmed SARS-CoV-2 infection (up to 85% of all cases reported). The most frequently recognizable lesions are represented by GGO, with unilateral or bilateral distribution [27–29]. However, it should be noted that CT-scan was performed also in asymptomatic patients[10, 27–30, 38, 39, 49, 57], and that more than one third of all patients who underwent this exam resulted completely normal. The use of CT-scan as a diagnostic screening tool in confirmed or suspected COVID-19 patients is supported by recent evidence showing that its sensitivity could be greater than that of real time-PCR in detecting the virus (98% vs. 71%, respectively)[87]. However, routine use of CT-scan has several obvious implications, in particular in a pediatric setting where concern about unnecessary exposure to radiation source should be raised. Therefore, other possible diagnostic imaging tools may be used. Lung ultrasound has been successfully adopted in adult subjects with SARS-CoV-2 infection[88], but, to date, there is no data in children.

Treatment

Currently, there is no ongoing drug trial specifically aimed at children. Symptomatic treatment alone was used in most cases, in particular in newborns[59].

The only therapeutic recommendation in pediatric age is to use nebulized IFN and oral antiviral agents (i.e., lopinavir/ritonavir), with CCS for complications (acute respiratory distress syndrome, encephalitis, hemophagocytic syndrome or septic shock) and IVIg for severe cases[22]. However, none of these therapies have shown a clear benefit in the treatment of SARS-CoV-2.

The main limitation of our review is represented by the difficulty to retrieve the full text of some Chinese studies, and we had to rely on English-language summaries, or publications that referenced papers published in Chinese. Moreover, our findings are essentially based on limited case-series and case reports, therefore laboratory parameters of interest were not consistently reported and reference ranges were not always clearly defined. Similarly, radiological patterns were difficult to compare, as the description of the included cases was not standardized.

However, despite the scarce and extremely heterogeneous evidence on pediatric patients with COVID-19, the use of systematic databases allowed us to review at a glance and interpret the majority of published studies up to 7 April 2020.

Conclusion

SARS-CoV-2 affects children less commonly and severely in comparison to adults, with an estimated very low mortality rate. This could be due either to the fact that children are less frequently exposed to the main sources of transmission (in particular, nosocomial), and that they tend to show milder symptoms, therefore may be less often tested. In symptomatic patients, laboratory and radiology findings are mainly nonspecific, but could help identifying those who are severely ill. Larger epidemiological and clinical cohort studies are needed to better understand possible implications of COVID-19 infection in children.

Declarations

Author Contribution

IL conceptualized the systematic review, performed the electronic search, evaluated articles for eligibility, extracted relevant data, interpreted the results, and drafted sections of the manuscript.

CP contributed to study design, screened search results, reviewed all included studies and reviewed and revised the manuscript.

MB and MF contributed to study design, developed search terms and performed the electronic search, and reviewed and revised the manuscript.

AN contributed to study design, reviewed and revised the manuscript, and provided mentorship;

AP, EV and PC conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with Ethical Statement:

- **Conflict of Interest:** All authors have no conflicts of interest to disclose.

- **Funding Source:** None

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Tables

Table 1. Characteristics of the included studies and main outcome measures in children with documented SARS-CoV-2 infection.

Author	Cohort	Case series	Case Report	Country	Language	N	Males	Age	Mortality	Still admitted at time of publication	Discharged	Days of hospitalization
Lu ¹⁰	✓	-	-	China	English	171	104	Median age 6.7 yrs (0 -15 yrs)	1 ^a	149	21	NR
Wang ²⁷	✓	-	-	China	Chinese	34	14	Median age 8 yrs	0	0	34	NR
Xia ²⁸	-	✓	-	China	English	20	13	Median age 2.1 (0 -14 yrs)	0	0	20	12.9 ^b
KSID ²³	✓	-	-	South Korea	English	201	NR	0-9 yrs: 16%; 9-19 yrs: 84% (45day infant-19 yrs)	0	NR	201	NR
Dong ¹⁶	✓	-	-	China	English	2143 ^c	1213	Median age 7 yrs (2-13 yrs)	1	NR	1213	NR
Liu ³³	-	✓	-	China	English	4	2	2 mo -9 yrs	0	0	4	NR
Wang ⁵⁷	-	-	✓	China	English	1	1	36 hours	0	0	1	16
Cui ⁵⁸	-	-	✓	China	English	1	0	55 days	0	0	1	11
Li ⁵¹	-	-	✓	China	English	2	1	4 yrs	0	1	1	NR
Ji ³⁵	-	-	✓	China	English	2	2	9-15 yrs	0	0	2	2
Liu ¹¹	-	✓	-	China	English	6	2	Median age 3 yrs (1-7 yrs)	0	0	6	7.5 ^d
Zhou ³⁶	-	✓	-	China	Chinese	9	NR	0-3 yrs	0	0	9	NR
Zhu ⁵⁹	-	✓	-	China	English	10	8	Newborns (60% preterm)	1 ^e	4	5	NR
Li ³⁴	-	✓	-	China	English	5	4	Median age 3.4 yrs (10 mo - 6 yrs)	0	2	3	12-14
D'Antiga ²⁴	-	✓	-	Italy	English	3 ^f	NR	NR	0	0	3	NR
Sun ²⁵	-	✓	-	China	English	8 ^g	6	2mo-15 yrs	0	3	5	NR
Zheng ²⁶	-	✓	-	China	English	25 ^h	14	3 yrs (3 mo-14 yrs)	0	24 ⁱ	1	NR
Park ³⁷	-	-	✓	South Korea	English	1	0	10 yrs	0	0	1	NR
Lu ⁶⁰	-	✓	-	China	English	3	NR	Newborns	0	0	3	NR
Liu** ³⁸	-	-	✓	China	English	1	1	10 yrs	0	0	1	NR
Chan** ³⁹	-	-	✓	China	English	1	1	10 yrs	0	0	1	NR
Cai** ⁴⁰	-	-	✓	China	Chinese	1	1	7 yrs	0	0	1	NR
Chen** ⁴¹	-	-	✓	China	Chinese	1	1	13 mo	0	0	1	NR
Zhang** ⁶¹	-	-	✓	China	Chinese	1	0	3 mo	0	0	1	NR
Zeng** ⁶²	-	-	✓	China	Chinese	1	1	2 weeks	0	0	1	NR
Cai** ³²	-	✓	-	China	English	10	4	Median age 6.2 yrs (3 mo - 10.9 yrs)	0	0	10	NR
Kam** ⁴²	-	-	✓	China	English	1	1	6 mo	0	0	1	18
Feng** ²⁹	-	✓	-	China	Chinese	15	5	4-14 yrs	0	0	15	NR
Wang** ³⁰	✓	-	-	China	Chinese	31	NR	7 yrs (6 mo-17 yrs)	0	7	24	NR
Zhang** ⁴³	-	✓	-	China	Chinese	2	0	14 mo	0	0	2	NR

Zhao** ⁴⁴	-	-	✓	China	Chinese	1	1	13 yrs	0				NR
Wei ⁴⁵	-	✓	-	China	English	9	2	1-11 mo	0	0	9		NR
Shen ⁴⁶	-	✓	-	China	English	28	NR	1 mo - 17 yrs	0	0	28		NR
Lou ⁴⁷	-	✓	-	China	English	3	1	6 mo and 6-8 yrs	0	0	3		10
Qian ⁴⁸	-	-	✓	China	English	1	0	13 mo	0	0	1		NR
Wang ⁶⁵	-	-	✓	China	Chinese	1	NR	Newborn	0	0	1		14
Su ⁴⁹	-	✓	-	China	English	9	3	Median age 3.5 yrs (11mo-9 yrs)	0	0	9 ^l		NR
Zeng ⁶⁶	-	✓	-	China	English	3	3	Newborns (1 preterm)	0	0	3		2-11
Le ⁶³	-	-	✓	Vietnam	English	1	0	3 mo	0	0	1		14
Tang ⁵⁰	-	-	✓	China	English	1	1	10 yrs	0	0	1		NR
Xu ³¹	-	✓	-	China	English	10	6						
ISS ^{14***}	✓	-	-	Italy	English	802	433	<17 yrs ^m	0	59	743		NR
Pan ⁵²	-	-	✓	China	English	1	1	3 yrs	0	0	1		NR
Chen ⁵⁶	✓	-	-	China	English	31	13	1.5-17 yrs	0	8	23		NR
Xing ⁵³	-	✓	-	China	English	3	2	Median age 4.2 yrs	0	0	3		23
Qiu ⁵⁴	✓	-	-	China	English	36	23	Mean age 8.3 yrs (1-16 yrs)	0	0	36		14
Zhang ⁵⁵	✓	-	-	China	English	34	14	Median age 33 mo (10-94 mo)	0	0	34		NR
Dong ⁶⁴	-	-	✓	China	English	1	0	Newborn	0	0	1		NR
Shen ⁶⁷	-	✓	-	China	English	9	3	Median age 8 yrs (1-12 yrs)	0	3	6		15.3
Han ⁶⁸	-	✓	-	China	English	7	4	Mean age 1.3 yrs (2mo-13 yrs)	0	0	7		10
Kamli- Aghdam ⁶⁹	-	-	✓	Iran	English	1	1	Newborn, 15 days	0	0	1		6
Canarutto ⁷⁰	-	-	✓	Italy	English	1	1	Newborn 32 days	0	0	1		5
Total	9	20	19			4612	2366	WMⁿ 7 yrs	3	297	3382	WM^o 11.6	days
						51.3%	(range 0-18 yrs)	0.07%	6.4%	73.3%	(range 2-23)		

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported.

^a10 mo. Baby with intussusception and MOF; ^bMedian; ^c713 confirmed; ^dMedian; ^eDied because of sepsis, MOF and DIC (preterm); ^f3/200 screened children on immunosuppressive treatment; ^gComplications: 2/8 MOF; 3/8 still in PICU; ^h2 CHD; ⁱ24 still admitted but recovering; ^l5 discharged children were admitted again because their stool resulted + for SARS-CoV-2; ^m(25 0-1 yr; 9 2-6; 25 >7). No child in PICU; ⁿweighted mean (N=2508); ^oweighted mean (N=102).

**Studies included in the review by Henry et al⁶⁷.

***last update, 6 April, 2020.

Table 2. Clinical features in children with documented SARS-CoV-2 infection.

Author	N	Clinical features					Common symptoms					Extrarespiratory Symptoms				Contact	
		Asymptomatic	Mild	Moderate	Severe	Critical	Fever	Cough	Sore	Runny	Dyspneic	Diarrhea	Vomiting	Fatigue/other	Family	Unknow	
								Throat	Nose					symptoms			
Lu ¹⁰	171	27	33	111	0	0	71	89	79	0	4	15	11	13	154 ^a	15	
Wang ²⁷	34	3	9	22	0	0	17	13	0	0	0	0	0	0	28	6	
Xia ²⁸	20	2	6	12	0	0	12	13	1	0	2	3	1	1	13	7	
Dong ¹⁶	2143	94	1091	831	112	13	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Liu ³³	4	1	3	0	0	0	3	3	0	0	0	0	0	1	NR	NR	
Li ⁵¹	2	0	2	0	0	0	0	2	0	2	0	0	0	0	2	0	
Ji ³⁵	2	0	2	0	0	0	1	0	1	0	0	1	0	0	2	0	
Liu ¹¹	6	0	2	4	0	0	6	6	0	0	0	0	4	0	NR	NR	
Zhou ³⁶	9	5	4	0	0	0	4	2	0	1	0	0	0	0	9	0	
Li ³⁴	5	4	1	0	0	0	1	0	1	1	0	0	0	0	4	1	
D'Antiga ²⁴	3	3	0	0	0	0	0	0	0	0	0	0	0	0	NR	NR	
Sun ²⁵	8	0	0	0	5	3	6	6	0	0	8	3	4	1 ^b	5	2 ^c	
Zheng ²⁶	25	0	8	15	0	2	13	11	0	2	2	3	2	0 ^d	21	4	
Park ³⁷	1	0	1	0	0	0	1	0	0	0	0	0	0	0	1	0	
Liu** ³⁸	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Chan** ³⁹	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Cai** ⁴⁰	1	0	1	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Chen** ⁴¹	1	0	0	0	1	0	1	1	0	0	0	0	0	0 ^e	NR	NR	
Cai** ³²	10	0	6	4	0	0	8	6	4	5	0	0	0	0	6	4	
Kam** ⁴²	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Feng** ²⁹	15	10	5	0	0	0	5	0	0	0	0	0	0	0	NR	NR	
Wang** ³⁰	31	4	13	14	0	0	20	14	0	0	0	3	0	3	28	3	
Zhang** ⁴³	2	0	2	0	0	0	2	2	0	0	0	0	0	0	2	0	
Zhao** ⁴⁴	1	0	1	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Wei ⁴⁵	9	1	6	0	0	0	4	2	0	2	0	0	0	0	9	0	
Shen ⁴⁶	28	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	28	0	
Lou ⁴⁷	3	0	3	0	0	0	3	1	0	2	0	2	0	2	3	0	
Qian ⁴⁸	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Su ⁴⁹	9	6	3	0	0	0	2	1	0	0	0	0	0	0	9	0	
Xu ³¹	10	1	9	0	0	0	7	5	4	2	0	3	0	0	7	3	
Tang ⁵⁰	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Pan ⁵²	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0	
Chen ⁵⁶	31	12	19	0	0	0	14	13	2	3	0	0	0	2	29	2	
Xing ⁵³	3	0	3	0	0	0	3	0	0	0	0	0	0	0	NR		

Qiu ⁵⁴	36	10	7	19	0	0	13	7	2	1	1	2	2	0	32	2
Zhang ⁵⁵	34	0	34	0	0	0	26	20	0	7	3	4	4	0	13	0
Shen ⁶⁷	9	2	7	0	0	0	3	1	1	0	0	2	0	0	9	0
Han ⁶⁸	7	0	4	3	0	0	5	5	1	0	3	4	0	0	7	0
Total	2679	191	1285	1035	118	18	249	223	96	28	23	45	28	23	427	49
	%	7.2^f	48.5	39.1^f	4.5^f	0.7^f	49.2^g	44.1^g	19^g	5.5^g	4.5^g	8.9^g	5.5^g	4.5^g	85.1^h	9.8^h
				^f												

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported.

^a2 others; ^bheadache (1/8) and constipation (1/8); ^c1 in-hosp infection; ^d2 abdominal pain; ^erenal failure; ^fcalculated on the total of reported symptoms (N=2647);;

^gcalculated on the total of reported symptoms (N=506); ^hcalculated on the total of reported symptoms (N=502).

**Studies included in the review by Henry et al⁶⁷.

Table 3. Lab investigations in children with documented SARS-CoV-2 infection.

Author	N	Low WBC	High WBC	Lymphopenia/neutropenia	Low Plt	High Plt	High CRP-PCT	High CPK	High transaminase
Lu ¹⁰	171	45	0	6	NR	NR	105	NR	25
Wang ²⁷	34	1	5	1	NR	NR	1	NR	NR
Xia ²⁸	20	4	2	7	NR	NR	16	5	5
Liu ³³	4	1	0	0	NR	NR	1	NR	NR
Ji ³⁵	2	0	1	0	NR	NR	1	NR	NR
Liu ¹¹	6	4	0	6	NR	NR	NR	NR	NR
Zhou ³⁶	9	0	2	0	NR	NR	NR	NR	NR
Li ³⁴	5	0	2	0	NR	NR	1	NR	NR
Sun ²⁵	8	1	6	1	2	1	4	0	2
Zheng ²⁶	25	NR	NR	10	NR	NR	NR	0	0
Park ³⁷	1	0	0	0	0	0	0	NR	NR
Liu** ³⁸	1	0	0	0	0	0	0	1	0
Chan** ³⁹	1	0	0	0	0	0	0	NR	0
Cai** ⁴⁰	1	0	1	0	1	0	1	1	0
Chen** ⁴¹	1	0	1	0	0	0	1	1	NR
Cai** ³²	10	1	3	3	1	2	3	5	2
Kam** ⁴²	1	1	0	1	1	0	NR	NR	NR
Wang** ³⁰	31	2	3	2	0	2	4	4	6
Zhang** ⁴³	2	0	2	NR	0	2	1	NR	2
Zhao** ⁴⁴	1	0	0	1	0	0	0	0	0
Xu ³¹	10	3	0	5	0	0	6	0	1
Su ⁴⁹	9	3	1	3	1	0	0	6	0
Pan ⁵²	1	0	0	0	0	0	0	0	0
Chen ⁵⁶	31	12	17	0	1	0	4	2	2
Xing ⁵³	3	0	0	1	0	2	1	0	
Qiu ⁵⁴	36	7	0	11	NR	NR	6	1	3
Zhang ⁵⁵	34	0	17	0	NR	NR	17	0	NR
Shen ⁶⁷	9	0	1	0	NR	NR	1	NR	2
Han ⁶⁸	7	0	2	0	0	1	3	4	3
Total	458	85	66	58	7	10	177	30	53
%		18.9^a	16^a	12.3^b	5.8^c	8.3^c	38.7^d	13.1^e	12.9^f

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported. WBC: white blood cell. Plt: platelet. CRP: C-reactive protein. PCT: procalcitonin. CPK: creatine kinase.

^acalculated on the total of reported labs (N=449); ^bcalculated on the total of reported labs (N=472); ^ccalculated on the total of reported labs (N=120); ^dcalculated on the total of reported laboratory investigations (N=457); ^ecalculated on the total of reported labs (N=229); ^fcalculated on the total of reported labs (N=411).

**Studies included in the review by Henry et al⁶⁷.

Table 4. Radiological findings in children with documented SARS-CoV-2 infection.

Author	N	Abnormal Radiological findings	Chest X-ray	CT-scan	GGO	Local patchy	Bilateral Patchy	Normal
Lu ¹⁰	171	51	0	111	56	32	21	60
Wang ²⁷	34	34	0	34	NR	NR	NR	NR
Xia ²⁸	20	16	0	20	12	6	6	4
Liu ³³	4	3	0	4	1	1	1	1
Li ⁵¹	2	2	0	2	0	1	1	0
Ji ³⁵	2	0	0	2	0	0	0	2
Liu ¹¹	6	4	0	6	1	3	0	2
Zhou ³⁶	9	9	0	9	6	7	0	0
Li ³⁴	5	3	0	5	3	0	0	2
Sun ²⁵	8	8	0	8	6	0	8	0
Zheng ²⁶	25	17	0	25	0	5	12	8
Park ³⁷	1	0	1	1	1	0	0	1
Liu** ³⁸	1	1	0	1	1	0	0	0
Chan** ³⁹	1	1	0	1	1	0	0	0
Cai** ⁴⁰	1	1	NR	NR	NR	NR	NR	NR
Chen** ⁴¹	1	1	NR	NR	NR	NR	NR	NR
Cai** ³²	10	4	10	0	0	4	0	6
Kam** ⁴²	15	9	0	15	9	7	2	6
Wang** ³⁰	31	14	0	31	9	0	0	0
Zhang** ⁴³	2	1	0	2	NR	NR	NR	1
Zhao** ⁴⁴	1	1	NR	NR	NR	NR	NR	NR
Lou ⁴⁷	3	3	0	3	3	0	0	0
Xu ³¹	10	5	10	10	5	0	0	5
Su ⁴⁹	9	1	0	9	1	1	0	8
Pan ⁵²	1	0	0	1	0	0	0	1
Chen ⁵⁶	31	11	0	31	11	8	3	20
Xing ⁵³	3	2	0	3	2	2	0	1
Qiu ⁵⁴	36	19	0	36	19	0	0	17
Zhang ⁵⁵	34	28	0	34	0	14	14	6
Shen ⁶⁷	9	2	0	9	2	2	0	7
Han ⁶⁸	7	2	0	7	NR	NR	NR	5
Total	493	257	21	420	149	93	68	163
%		52.1	4.3^a	85.7^a	33.7^b	21^b	15.4^b	36^c

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported. GGO: ground-glass opacities

^acalculated on the total of reported imaging (N=490); ^bcalculated on the total of reported imaging (N=442); ^ccalculated on the total of reported imaging (N=453);

**Studies included in the review by Henry et al⁶⁷.

Table 5. Treatments used in children with documented SARS-CoV-2 infection

Author	N	PICU	MV	Noninvasive Ox	Symptomatic alone	Antiviral	Antibiotic	IVIg	CCS	IFN	Other
Lu ¹⁰	171	3 ^a	3 ^a	NR	NR	NR	NR	NR	NR	NR	NR
Wang ²⁷	34	0	0	0	0	20 ^b	0	0	0	0	0
Li ⁵¹	2	0	0	2	2	0	0	0	0	0	0
Ji ³⁵	2	0	0	0	2	0	0	0	0	0	0
Liu ¹¹	6	1	1	1	0	6 ^c	0	1	4	0	0
Li ³⁴	5	0	0	0	0	2	2	5	0	2	3 ^d
Sun ²⁵	8	2	2	6	0	8	5	4	5	0	1 ^e
Zheng ²⁶	25	2	2	0	0	12	13	2	0	12	1 ^f
Park ³⁷	1	0	0	0	1	0	0	0	0	0	0
Liu** ³⁸	1	0	0	0	0	1 ^g	0	0	1	0	0
Cai** ³²	10	0	0	0	5	0	5	0	0	0	0
Wang** ³⁰	31	0	0	0	31	0	0	0	0	0	0
Zhang** ⁴³	2	0	0	0	2	0	0	0	0	0	0
Wei ⁴⁵	9	0	0	0	9	0	0	0	0	0	0
Lou ⁴⁷	3	0	0	0	1	0	0	0	0	2	0
Xu ³¹	10	0	0	0	0	0	1	1	0	10	0
Su ⁴⁹	9	0	0	0	0	1 ^h	0	0	0	9	0
Pan ⁵²	1	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Chen ⁵⁶	31	0	0	0	0	3	1	0	0	30	0
Xing ⁵³	3	0	0	0	0	3	0	0	0	3	3
Qiu ⁵⁴	36	0	0	6	0	14	0	0	0	36	0
Zhang ⁵⁵	34	0	0	3	0	28	30	0	5	28	0
Shen ⁶⁷	9	0	0	9	0	9	5	1	1	0	0
Han ⁶⁸	7	0	0	2	4	0	0	0	1	0	0
Total	450	8	8	29	57	107	62	14	17	132	8
%		1.8	1.8	10.4 ⁱ	20.5 ⁱ	38.5 ⁱ	22.3 ⁱ	5 ⁱ	6.1 ⁱ	47.5 ⁱ	2.9 ⁱ

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported. PICU: pediatric intensive care unit. MV: mechanical ventilation. Noninvasive Ox: noninvasive oxygen. IVIg: intravenous immunoglobulin. CCS: corticosteroids. IFN: interferon

^aall with coexisting conditions (hydronephrosis, leukemia, and intussusception); ^bLopinavir and ritonavir; ^cribavirin 2/6; oseltamivir 6/6; ^d3/5 montelukast; ^e1/8 plasmapheresis; ^f1 also kidney replacement; ^gribavirin; ^hribavirin; ⁱcalculated on the total of reported treatments (N=278).

**Studies included in the review by Henry et al⁶⁷.

Table 6. Clinical features and laboratory results in newborns and infants ≤ 3 months of age with documented SARS-CoV-2 infection.

Author	N	Clinical Features					Symptoms					Family	Labs						
												contact							
		Asymptomatic	Mild	Moderate	Severe	Fever	Cough	Dyspneic	Vomiting	Feeding		High	Low	Low	High	High	High	High	
											intolerance	WBC	L	Plt	Plt	CRP-	CPK	transaminase	
PCT																			
Wang ⁵⁷	1 (1 m)	1	0	0	0	0	0	0	0	0	1	NR	1	NR	NR	0	1	1	
Cui ⁵⁸	1	0	0	0	1	1	1	1	0	0	1	1	0	0	1	1	1	1	
Zhu ⁵⁹	10 (8 m)	0	8	0	2	2	0	6	0	4	10	3	0	2	0	2	2	2	
Lu ⁶⁰	3	1	1	0	1	1	0	1	1	0	3	NR	NR	NR	NR	NR	NR	NR	
Zhang** ⁶¹	1	0	0	1	0	NR	NR	NR	NR	0	NR	0	NR	0	1	1	NR	NR	
Zeng** ⁶²	1 (1 m)	0	1	0	0	NR	NR	NR	NR	0	NR	0	NR	0	1	1	NR	NR	
Wang ⁶⁵	1	0	1	0	0	0	0	0	1	1	NR	NR	NR	NR	NR	NR	NR	NR	
Zeng ⁶⁶	3 (3 m)	0	0	3	0	2	0	1	0	1	3	2	2	NR	NR	0	2	1	
Kamli- Aghdam ⁶⁹	1 (1m)	0	0	1	0	1	0	1	0	0	NR	0	0	0	0	0	NR	NR	
Canarutto ⁷⁰	1 (1m)	0	1	0	0	1	1	0	0	0	NR	0	1	0	0	0	NR	NR	
Le ⁶³	1	0	1	0	0	0	1	0	0	0	1	1	0	0	0	0	1	0	
Dong ⁶⁴	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	
Total	25 (15 m)	3	13	5	4	8	3	10	2	6	20	7	4	2	3	5	7	5	
%		12	52	20	17	32	12	40	8	24	80	28	17	8	12	20	28	20	

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported. WBC: white blood cell. L: lymphocyte. Plt: platelet. CRP: C-reactive protein. PCT: procalcitonin. CPK: creatine kinase.

**Studies included in the review by Henry et al⁶⁷.

Table 7. Radiological findings and treatments used in newborns and infants ≤ 3 months of age with documented SARS-CoV-2 infection.

Author	N	Radiology findings							Treatment						
		Abnormal	Chest X-ray	CT-scan	GGO	Local patchy	Bilateral Patchy	Normal	PICU	MV	Symptomatic alone	Antibiotic	IVIg	IFN	
Wang ⁵⁷	1 (1 m)	1	0	1	0	1	0	0							
Cui ⁵⁸	1	1	0	1	1	1	0	0	0	0	0	1	0	1	
Zhu ⁵⁹	10 (8 m)	7	10	0	1	1	3	3	0	0	9	0	1	0	
Lu ⁶⁰	3	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Zhang** ⁶¹	1 (1 m)	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Zeng** ⁶²	1(1 m)	1	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	
Wang ⁶⁵	1	NR	NR	NR	NR	NR	NR	NR	0	0	0	0	0	1	
Zeng ⁶⁶	3 (3 m)	3	3	0	0	3	0	0	1	1	2	1	0	0	
Kamli-Aghdam ⁶⁹	1 (1m)	0	1	0	0	0	0	1	1	0	0	1	0	0	
Canarutto ⁷⁰	1 (1m)	0	1	0	0	0	0	1	0	0	1	0	0	0	
Le ⁶³	1	0	1	0	0	0	0	1	0	0	0	1	0	0	
Dong ⁶⁴	1	0	0	1	0	0	0	1	0	0	0	0	0	0	
Total	25 (15 m)	14	16	3	2	6	3	7	2	1	12	4	1	2	
%		56	64	12	8	24	12	28	8	4	48	16	4	8	

SARS-CoV-2: severe acute respiratory syndrome – Coronavirus -2. NR: Not Reported. GGO: ground-glass opacities. PICU: pediatric intensive care unit. MV: mechanical ventilation. IVIg: intravenous immunoglobulin. CCS: corticosteroids. IFN: interferon

**Studies included in the review by Henry et al⁶⁷

Figures

Figure 1

PRISMA flow diagram of the included studies on children with SARS-CoV-2 infection.