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SPECIAL ARTICLE: Risk factors for severity in children with coronavirus-19 disease (COVID-19): A comprehensive literature review

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Abstract

The ongoing coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people, including infants and children. We carried out a comprehensive literature review to identify the underlying mechanisms and risk factors for severe COVID-19 in children, in comparison with the other two coronavirus outbreaks in the past, SARS and MERS.

Search in the Pubmed and Scopus databases to identify publications between February 26, 2020 and June 10, 2020 identified 23 relevant papers in English. Children have so far accounted for 1.7-2% of the diagnosed cases of COVID-19. They often have milder disease than adults, and child deaths have been rare. The documented risk factors for severe disease in children are young age and underlying comorbidities, although the potentially fatal multisystem inflammatory syndrome (MIS) occurs in older children. It is unclear whether male gender and certain laboratory and imaging findings can also be considered as risk factors, due to current insufficiency of evidence. Reports on other potential factors, such as vitamin D level, responsiveness of the immune system, co-infections and genetic polymorphisms have not yet been published.

Key Words: Children, coronavirus, COVID-19, risk factor, severity

Abbreviations:

ACE2: angiotensin-converting enzyme 2
COVID-19: coronavirus disease 2019
CoVs: coronaviruses
ICU: intensive care unit
MERS-CoV: Middle East respiratory syndrome coronavirus
MIS: multisystem inflammatory syndrome
RSV: respiratory syncytial virus
SARS-CoV: severe acute respiratory syndrome coronavirus

KEY POINTS

- The ongoing coronavirus disease 2019 (COVID-19) pandemic has affected hundreds of thousands of people.
- Children have so far accounted for 1.7-2% of diagnosed cases of COVID-19.
- Children often have milder disease than adults, and child deaths have been rare.
- Risk factors for severe disease from COVID-19 in children are reported to be young age and underlying comorbidities, although not confirmed in all studies.
- It is unclear whether male gender, and certain laboratory and imaging findings can also be considered as risk factors, due to insufficient data.
INTRODUCTION

Until recently, six different coronaviruses (CoVs) had been identified in humans (HCoVs): HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1, SARS-CoVs and MERS-CoVs. Endemic HCoV-OC43 and HCoV-229E were described in the 1960s, and HCoV-NL63 and HCoV-HKU1 in 2004 and 2005, respectively.\(^1,2\) The first serious CoV disease outbreak occurred in China in 2002, when the novel severe acute respiratory syndrome CoV (SARS-CoV), emerged, which was thought to have been transmitted from civet cats or bats to humans.\(^3,4\) The second novel CoV emerged in Saudi Arabia in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV),\(^5\) which is transmitted from dromedary camels to humans.\(^6\) Collectively, these two CoV diseases did not affect children widely, because of the short-term nature of the epidemic of SARS and the rigid transmission route of MERS.

Since December 2019, SARS-CoV-2 has been recognised as the causal factor of severe pneumonia and potential damage to vital organs in humans. The first cases of SARS-CoV-2 originated in Wuhan in the Hubei province of China, and subsequently spread to other countries throughout the world.\(^7\) In February 2020, the World Health Organization (WHO) designated the disease coronavirus disease 2019 (COVID-19).

A substantial number of studies have already been published on adults with COVID-19, but reports on children with COVID-19 are scarce. In this review, we aimed to analyse the current knowledge on the risk factors for the progression and severity of COVID-19 in infants and children. The possible mechanisms of aberrant clinical features of COVID-19 in children are also presented. To the best of our knowledge, this is the first review addressing the risk factors associated with the progression and severity of COVID-19 in children.

METHODS
Original research studies published in English between February 26, 2020 and June 10, 2020 were identified using PubMed and Scopus. The search used combinations of the key words ‘COVID-19’, ‘SARS-CoV2’, ‘mechanism’, ‘risk factor’, ‘severity’ and ‘child’. In addition, the reference lists of the retrieved articles were checked for other relevant articles. The initial search yielded 293 articles, of which, after screening of their titles, 72 studies were considered relevant to the aim of our review. Studies on adults and neonates were not included, and 7 studies were excluded because they were in Chinese. Pediatric case reports of COVID-19 were included only if they provided information about risk factors for severe disease. Thus, 23 studies were finally selected, as shown in Figure 1, and are discussed here. The factors that may introduce bias into the findings of this review are restriction to articles in English, together with database and citation bias.

Most of the studies originated in China, the United States of America (USA), Italy, Spain and South Korea, despite the large number of patients diagnosed with COVID-19 throughout the world. Some published studies relating to COVID-19 in children do not provide detailed information on the mechanisms, triggering factors and/or clinical features which led to the deterioration of the status of the patients. In addition, the current studies do not provide a uniform definition of severe or critical disease. The information from all the studies related to the risk factors for severe COVID-19 in infants and children is summarized in Table 1.

**Epidemiology of COVID-19**

Cases of COVID-19 worldwide are less common in children than in adults. A review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of the cases were in children younger than 10 years and 1% of the cases were in children aged 10 to 19 years. In the USA, among 149,082 reported cases of COVID-19, 1.7% were in
children aged under 18 years. From the currently available data it appears that children tend to have asymptomatic or mild disease more commonly than adults, but severe cases and even deaths have been reported worldwide in patients younger than 18 years. In a cohort study of 32,583 confirmed cases of COVID-19 from Wuhan, China, 4.1% of severe and critical cases were in patients aged < 20 years.

According to a large retrospective study conducted in China, 4 HCoVs, HCoV-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1, were more common in children, as their prevalence was 4.3%, and the highest prevalence was among infants aged 7-12 months. Infection by these 4 strains usually causes acute respiratory disease, with severe manifestations in some children. Regarding SARS-CoV, only 6 case series have been reported, including a total of 135 pediatric cases, from Canada, Hong Kong, Taiwan and Singapore. A milder form of the disease was observed in children compared with adults, and no child death was recorded. In the MERS-CoV epidemic, pediatric cases were even fewer, as only two small case series of children were reported, both originating from Saudi Arabia, one of 31 children with a mean age of 10 years and one of 7 children with a mean age of 8 years. In both studies, 42% of the infected children were asymptomatic, and in one, 2 of the 7 had severe disease, while in the other, 2 of the 31 children died (6%).

**RISK FACTORS FOR SEVERITY IN COVID-19 AND OTHER COVS INFECTION**

I. The impact of age

SARS-CoV-2

In a series of 2,135 children with suspected and confirmed COVID-19 from China, severe disease was defined as the occurrence of dyspnea, central cyanosis and oxygen saturation of less than 92%. Critical disease was defined as progression to acute respiratory
distress syndrome, shock, encephalopathy, myocardial injury, coagulation dysfunction and acute kidney injury. Severe and critical cases were reported in 10.6% of the children aged <1 year, 7.3% of those aged 1-5 years, 4.1% of those aged 6-10 years and 3% of the children aged >16 years. One 14-year-old boy died, but no further information was provided about this patient, and the study gave no data on underlying comorbidity or other possible risk factors. It is of note that of the 2,135 children, only 728 had laboratory confirmation, and the severe symptoms in the suspected cases may have been due to pathogens other than SARS-CoV-2. Two case reports from the same country, China, referred to children with severe disease, a 55-day-old female infant and a 3-year-old girl with no apparent risk factor apart from the young age.\textsuperscript{18,19}

Cases have been reported of infants in China and in Vietnam that, despite their young age had mild disease, including 10 diagnosed with COVID-19, who were otherwise healthy, with mild or no symptoms.\textsuperscript{20,21} In a study of 177 children from the Children’s National Hospital in Washington, the adolescents and young adults were more commonly critically ill than the younger children.\textsuperscript{22} Another study from the USA reported that the mean age of COVID-19 positive children was significantly higher than those testing negative (9.72 vs. 4.85 years). In that study, the ethnicity was examined, and African American children had a significantly higher rate of positive tests for COVID-19, 6.8% vs. 1.7% of white children.\textsuperscript{23} In a study in England, among 58 children, race (Black-Asian) was described as a risk factor for COVID-19.\textsuperscript{24}

Other CoVs

In the USA, in the case of other CoVs, specifically 229E, HKU1, NL63, and OC43, age < 2 years has been reported as a risk factor for severe disease, defined as the need for respiratory support.\textsuperscript{25} Conversely in a series of 44 children in China with SARS-CoV, an age
of >12 years was associated with severe illness, requiring methylprednisolone therapy and oxygen supplementation.\textsuperscript{15}

In adults, older age has been reported to be an independent risk factor for severity and mortality, not only in SARS-CoV-2 but also in the previous epidemics of SARS and MERS.\textsuperscript{26,27}

\textit{II. The impact of male gender}

Male gender is a risk factor for severe CoV disease in adults.\textsuperscript{28} A predominance of males was reported in all age subgroups among 2,490 pediatric cases of COVID-19 in a series in the USA, but no details were given about the impact of gender on the severity of the disease.\textsuperscript{9}

Among 2,143 Chinese children with COVID-19 in the study of Dong and colleagues, no significant difference was reported in the number of cases between boys and girls, and no detailed information was given on the gender of the severe and critical cases.\textsuperscript{10} In a cross-sectional study of 48 children with COVID-19 admitted to US and Canadian ICUs, 52\% were males.\textsuperscript{29} Severe cases have been reported in girls and the current data suggest that in children, male gender is not an independent risk factor of severe COVID-19 disease.

\textit{III. Underlying medical comorbidity}

\textit{SARS-CoV-2}

In a series of 171 children with COVID-19 from the city in China, Wuhan, where SARS-CoV-2 was first described, 3 patients required ICU support and invasive mechanical ventilation, all of which had underlying comorbidities. One was a 10-month-old male infant with intussusception who developed multiorgan failure and died 4 weeks after admission.\textsuperscript{30} The second child had leukemia, in the maintenance chemotherapy phase, and the third, aged 13 months, had bilateral hydronephrosis and calculus of the left kidney.\textsuperscript{30,31} It was not reported whether any of the 168 children who did not need ICU admission had an underlying condition.
In the recently published CONFIDENCE study from Italy, which included 100 children, 27% had an underlying medical condition. Of the 9 children needing respiratory support, 5 were aged under one year and 6 had an underlying condition. The severe (1) and critical (1) cases were both in children with underlying medical conditions.\(^{32}\)

Among 25 pediatric cases of COVID-19 from Hubei province in China, two 1-year-old boys needed invasive mechanical ventilation, both of which had congenital heart disease. One of them also had malnutrition and a suspected hereditary metabolic disease, and the other had co-infection with \textit{Enterobacter aerogenes}.\(^{33}\)

The first report from the USA concerning children with COVID-19 is of 2,572 pediatric cases. Among the children for whom hospitalization status was known, 20% were hospitalized. Due to lack of information on specific disease features, hospitalization was considered to be an indicator of serious illness, and it was most often reported in children younger than 1 year. An underlying medical condition was noted in 77% of hospitalized children, in contrast to 12% of those not hospitalized. The most common comorbidities were chronic lung disease (including asthma), cardiovascular disease and immune suppression. Three deaths were reported, but their association with COVID-19 is still under investigation.\(^9\) In another US study, among 48 children admitted to ICU, 83% had a significant preexisting comorbidity.\(^{29}\) Severe and critical cases have also been reported in children with no underlying comorbidity. Sun and colleagues reported 8 severe and critical cases of children in a hospital in Wuhan, 7 of whom were previously completely healthy. In this study, severe cases were defined as the coexistence of tachypnea, oxygen saturation < 93% and arterial partial pressure of oxygen $\leq$ 300 mmHg, while critical cases were defined as the presence of septic shock or the need for mechanical ventilation or ICU admission. The age range of the 8 severe cases was from 2 months to 15 years, 6 were boys and only one of them had an underlying medical condition (acute lymphocytic leukemia).\(^{34}\)
Information from a registry of 310 hospitals in Madrid, Spain, showed that of 41 children with COVID-19, 60% were hospitalized, 4 children were admitted to ICU and 4 needed respiratory support. Of these children, one had a previous condition (recurrent wheezing) and no patient died. In a recent report from Paris of 27 children with severe COVID-19, 70% had an underlying medical condition. Of the 5 children who died, 3 had no underlying comorbidity, suggesting that comorbidities may be a risk factor for severe disease and fatality, but that other mechanisms may also be implicated in the severity of the disease.

It appears, therefore, that while underlying medical comorbidity may be a risk factor for severe disease in childhood, it is not the only risk factor for progression of the disease and development of complications. It would be of interest to gather further information on the children with underlying medical problems and assess the percentages with severe or mild disease, and their other risk factors. To date, there is lack of such data in the literature, although in adults, specific co-morbidities are well documented as risk factors not only for admission to ICU but also for mortality.

*Other COVs*

Severe pediatric disease from other CoVs reported in USA, specifically 229E, HKU1, NL63, and OC43, defined as need for respiratory support or pediatric ICU admission, has been associated with underlying comorbidity, and in particular, cardiovascular, chronic respiratory and genetic/congenital conditions. Ogimi and colleagues in USA showed that both an immunocompromised state and underlying pulmonary disorder were associated with lower respiratory tract disease or severe lower respiratory tract disease from HCoV. No significant difference was demonstrated regarding the severity of illness among hospitalized children with different HCoV types.
The two deaths reported in children with MERS-CoV in Saudi Arabia were in a 2-year-old child with cystic fibrosis, and a 9-month-old infant with infantile nephrotic syndrome, while a 14-year-old girl with Down syndrome needed hospital admission, but eventually recovered.

IV. Co-infection with another pathogen

SARS-CoV-2

Co-infection with other pathogens may be a risk factor for severe disease. One child in Wuhan with a history of congenital heart disease and severe illness was found to have co-infection with Enterobacter aerogenes. In a study of 20 pediatric cases from the same region, 40% had an underlying co-infection, but there was no report on their severity. A severe case of COVID-19 has been reported in a Chinese 2-month-old infant who had co-infection with respiratory syncytial virus (RSV).

Other CoVs

The presence of co-pathogens with more than one HCoV strain (229E, HKU1, NL63, and OC43) or other respiratory pathogens, is a risk factor for febrile illness. Patients infected with a single strain of HCoV infection were more likely to present pulmonary rales than those infected by more than one HCoV strain or other respiratory pathogens. The presence of RSV has been associated with lower respiratory tract disease or severe lower respiratory tract disease from HCoV.

V. Laboratory findings
Here we report only the available laboratory information on the severe cases compared with mild cases, according to the current literature; several publications did not provide relevant data.

**SARS-CoV-2**

Based on currently available data, it is not possible to document a pattern of laboratory values in pediatric COVID-19 according to the severity of the disease. In the study of Qiu and colleagues from China, no laboratory data were reported for severe cases, but only for 36 children with moderate and mild disease. Moderate cases (19 patients) compared with mild cases (17 patients) were associated with raised body temperature, a decrease in lymphocytes, higher levels of procalcitonin and creatine kinase-MB and increased d-dimers. Laboratory data from 8 severe pediatric cases in the same country showed normal or raised leukocyte count, and high levels of C-reactive protein (CRP), procalcitonin and lactate dehydrogenase (LDH), while half had abnormal liver function tests. In a study of 67 children in the USA, admission to ICU was associated with higher levels of CRP, procalcitonin and pro-B type natriuretic peptide and a raised platelet count.

Henry and colleagues reviewed 2020 case reports and case series providing laboratory data on pediatric cases of COVID-19. In that review, 69.6% of the children had a normal leukocyte count and the authors commented that the absence of lymphopenia in children may in part be explained by the milder disease. Another assumption was that raised procalcitonin could be due to a bacterial co-infection as a complication of COVID-19. Procalcitonin was raised in 80% of Chinese pediatric cases in the study of Xia and colleagues, and in that series, 40% of the children had a co-infection.

**Other CoVs**
Neutrophilia was a predictor of severe illness among 44 children with SARS.\textsuperscript{15} Lymphopenia was detected in 10 children with SARS, of whom 4 needed oxygen therapy and 2 assisted ventilation.\textsuperscript{46}

**RISK FACTORS FOR PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME (MIS) ASSOCIATED WITH SARS-COV-2**

A syndrome of fever and multisystem inflammation (MIS) has recently been described in children with COVID-19. Some of these children presented with shock and multiorgan failure and others had characteristics of Kawasaki disease or a combination of Kawasaki-like disease and shock, named the Kawasaki-disease shock syndrome.\textsuperscript{47,48} These children presented with acute cardiac decompensation,\textsuperscript{49} and some developed coronary artery aneurysms.\textsuperscript{24} Among 44 children hospitalized in USA with MIS, 84.1\% had gastrointestinal symptoms as the presenting clinical complaint.\textsuperscript{50}

Most studies to date have reported that MIS presents in children at an older age, with median age of 8 to 10 years.\textsuperscript{24,49,51} In a retrospective study of 35 children with MIS, admitted to ICU in France and Switzerland, comorbidities were present in 28\% of the children, including asthma and being overweight,\textsuperscript{49} but most of the children in other studies reported from Europe, specifically Italy and England, were previously healthy.\textsuperscript{24,48} In a study of 8 children from the UK with MIS, 6 were Afro-Caribbean and 5 were male.\textsuperscript{47} It has been suggested that black and Asian races may be predisposed to this clinical complication.\textsuperscript{24} These limited data indicate a possible gender and race predilection for MIS.

The laboratory findings in children with MIS were characterized by a marked elevation of inflammatory markers such as C-Reactive Protein CRP and ferritin,\textsuperscript{24} and a cytokine storm, with specific increase in the level of interleukin-6 (IL-6) and macrophage activation.\textsuperscript{49,51} The patients often had a significant increase in B-type natriuretic peptide and troponin-T.\textsuperscript{48} MIS is
considered to be a result of a continuous immune response rather than injury from an acute
SARS-CoV-2 infection. The disease presented 2 to 3 weeks after the peak of the infection and
most children had negative Covid-19 PCR but positive viral serology.\textsuperscript{52}

**WHAT MECHANISMS PLAY A ROLE IN THE ATYPICAL PICTURE OF COVID-19
IN CHILDREN?**

The SARS-CoV-2 is a $\beta$ CoV of group 2B, with over 70\% similarities in genetic
sequence to SARS-nCoV.\textsuperscript{53} The established scientific evidence on SARS-nCoV has enabled
elucidation of the host defense mechanisms against SARS-CoV-2 and helped to explain the
lower susceptibility of children to the virus, and the variability between children. The reasons
for the different pattern of COVID-19 disease in children are still unclear, but several
hypotheses have been put forward.

*Environment-Epigenetics*

The effect of the environment must be considered a factor with significant impact on
infection with COVID-19. Children have healthier airway tracts, due to having less exposure to
cigarette smoke, air pollution, chemicals and industrial pollutants than adults. In adults, these
environmental factors, and especially smoking, have a negative epigenetic impact on epithelial
and immune cells, leading to increased vulnerability to all respiratory viruses, including SARS-
CoV-2.\textsuperscript{54,55} CoVs are known to alter the epigenetic cellular mechanisms of the host associated
with viral entry, replication and innate immune control.\textsuperscript{56}

Most children hospitalized with COVID-19, especially those in ICU, were below the
age of 3 years.\textsuperscript{33,35} This may be explained by the immaturity of the immune system in this age
period, and the low likelihood of wearing face masks in this age group and the subsequent high
viral load.\textsuperscript{57}
Another reason for the different clinical picture of COVID-19 in children is that they have fewer underlying disorders than adults that may predispose to severe COVID-19.\textsuperscript{58} The severity of COVID-19 is higher in children with preexisting conditions, such as asthma, malignancies, cardiovascular disorders and immunosuppression.\textsuperscript{33,35} In certain chronic diseases, including systemic lupus erythematosus (SLE), epigenetic dysregulation might enable viral entry, replication, and a disproportionate immune response to SARS-CoV-2.\textsuperscript{59}

*Entry of the virus into the cells*

Angiotensin-converting enzyme 2 (ACE2) is a zinc containing metalloenzyme located on the surface of endothelial and other cells, which counters the activity of the related angiotensin-converting enzyme (ACE) by reducing the amount of angiotensin-II.\textsuperscript{60} ACE2 serves as the entry point into cells for NL63 and SARS-CoV, and recent studies indicate that ACE2 is also likely to be the receptor for SARS-CoV-2, and the key region responsible for the interaction.\textsuperscript{61,62}

Differences in the distribution, maturation, and functioning of ACE2 in the developing phase of childhood is a possible reason for milder SARS-CoV-2 infection. Newborn infants and children have higher ACE activities, with serum levels showing an increase up until puberty and progressive reduction after maturity.\textsuperscript{63} On the other hand, ACE2 expression in rat lung has been found to decrease dramatically with age.\textsuperscript{64} Studies have provided evidence that ACE2 also protects against severe acute lung injury that can be activated by sepsis, SARS, and avian influenza A H5N1 virus infection.\textsuperscript{65} It may be that children are protected against SARS-CoV-2 because ACE2 is less mature at younger ages.

Epigenetic alteration of ACE2, which is further exacerbated by virus infections, is another potential mechanism in the severity of COVID-19 in patients with chronic diseases such as SLE.\textsuperscript{59}
Another aspect in the variability of severity is the genetic variation of ACE among different populations. The polymorphism D/I in ACE1, an enzyme with amino acid identity and function similar to ACE2, could explain the varying rate of COVID-19 infection between European countries, and specifically, the prevalence of COVID-19 infections has been shown to be correlated with the ACE D allele frequency.

*Immune antiviral response*

Frequent exposure of children to viral infections boosts the immune system and possibly enhances the response to SARS-CoV-2, and the presence of other concurrent viruses in the airway mucosa may limit the replication and the viral load of SARS-CoV2. It has been shown that the amount of viral copies is correlated with the severity of COVID-19.

The immune system undergoes significant changes from birth to adulthood, especially in lymphocyte biology, and the interaction of lymphocytes with SARS-CoV-2 may be different in children from that in adults. It is of note that, when documented, lymphocytopenia is frequent in adults with COVID-19 (83%) but not in children (3%). In the 2003 SARS epidemic, however, lymphocytopenia was reported in 77% of infected children. The changing level of T lymphocytes with age may also be a reason for the mild disease phenotype in childhood.

Interferon mediated response to HCoVs is essential for the disease course. Virus-induced suppression of interferon induced pathways leads to viral replication and disease progression, along with the production of other pro-inflammatory cytokines, such as IL-2, IL-6 and tumor necrosis factor (TNF) in the lower respiratory tract and other tissues. In some cases, the increase of cytokines is uncontrolled, leading to the detrimental cytokine syndrome, with a poor outcome. The percentage of children suffering from COVID-19 with raised levels of inflammatory markers is reported to be low, and this could be a co-factor for non-severe
disease. On the other hand, an unusual immune response accompanied by cytokine storm and macrophage activation is thought to result in MIS, which has been linked to COVID-19 in children.

Another immunological aspect that could be related to the mild disease in children is trained innate immunity, due to the routine use of various vaccines, including Bacille Calmette-Guerin (BCG). BCG vaccination induces epigenetic changes in monocytes, and increased cytokine production in response to several different pathogens. In mice, BCG also enhances nonspecific defense against influenza virus infection.

Several studies have identified links between inadequate vitamin D concentrations and the development of upper and lower respiratory tract infections in infants and young children. Although the mechanism of the vitamin D effect on immunity is complex, currently available data support the hypothesis that cathelicidins and defensins can lower viral replication rates and reduce the levels of pro-inflammatory cytokines. Studies in small children with influenza have shown that high doses of vitamin D resulted in fast relief from symptoms, a rapid decrease in viral load and early disease recovery. In addition, high daily doses of vitamin D have been shown to be effective in the prevention of seasonal influenza.

**SUMMARY**

Although children are less susceptible to COVID-19, and the clinical picture in childhood is often distinct from that in adults, in both age groups chronic underlying medical problems can predispose to severe disease. In contrast to adults, in whom older age is an independent risk factor for severity and mortality, very young age is considered a risk factor for severity in children, although this has recently been questioned, and MIS occurs in older children.
Although a distinct pattern of laboratory findings has not emerged as being associated with severity of the disease in pediatric cases of COVID-19, lymphopenia appears to be a risk factor for severe disease in children. Raised levels of the inflammatory markers procalcitonin and CRP could be due to a bacterial co-infection as a complication of COVID-19. The recently described pediatric MIS appears to be the result of continuous immune response, rather than an injury from an acute SARS-CoV-2 infection, but further studies are needed to reach definitive conclusions.

Several other aspects could be implicated in the severity of COVID-19 in children, such as co-infection with RSV, responsiveness of the immune system, vaccination history, levels of vitamin D and genetic polymorphisms, but the present paucity of data limits our ability to draw such conclusions.

It is important to further study the potential risk factors for severe disease in children and to clarify the underlying mechanisms, in order to improve the management of children with COVID-19 and to help in the development of new forms of treatment.

Contributors

TS and MA designed the study, TS, MA and KC did the literature search. AM, KC and SE were responsible for the data collection. TS and KC collected and analysed the data. TS, MA, KC and ES analysed data and wrote the report.

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Figure 1. Flow-chart of the literature search on risk factors for severe coronavirus 19 (COVID-19) in childhood (February 26, 2020 to June 10, 2020)

Table 1. Studies on severity and risk factors of coronavirus 19 (COVID-19) in children (February 26, 2020 to June 10, 2020)
| First author       | Region                                                                 | Study period                  | Number of children | Mean age (% of young children) | Underlying diseases % (diseases) | Severity                                                                 | Risk factors                                                                 |
|-------------------|------------------------------------------------------------------------|-------------------------------|--------------------|--------------------------------|----------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bialek S, et al (9) | USA (33% from New York City, 23% from the rest of New York state, 15% from New Jersey, 29% from other jurisdictions) | February 12 to April 2, 2020  | 2,572              | 11 (< 1 year 15%)               | 23% (chronic lung disease, cardiovascular disease, immunosuppression)   | 5.7-20% hospitalized, 0.58-2% admitted to ICU, aged< 1 year: 15-62% hospitalized, 3 deaths | Children aged<1-year, underlying condition                                 |
| Dong Y, et al (10) | Chinese CDC, Cases from Hubei province and Anhui, Henan, Hunan, Jiangxi, Shanxi and Chongqing | January 16 to February 8, 2020 | 2,135 suspected and confirmed cases | 7 (<1 year 17.6%) | Not available | 90% had asymptomatic to moderate disease. Severe or critical disease in 10.6% < 1 year, 7.3% 1-5 years, 4.1% 6-10 years, 3% >16 years One 14-year-old boy died | Young age                                                               |
| Lu X, et al (30)  | Wuhan Children’s Hospital, China                                       | January 28 to February 26, 2020 | 171                | 6.7 (< 1 year 18%)             | 3 patients (hydronephrosis, leukemia, intussusception)                  | 3 patients with invasive mechanical ventilation (all with underlying condition), 1 death | Underlying condition                                                       |
| DeBiasi R, et al (22) | Children’s National Hospital Washington                              | March 15 to April 30, 2020    | 177                | 9.6                            | 39% (asthma, neurological condition, DM, obesity, cardiac problem, hematological disease, oncological condition) | 9 critically ill patients | Adolescents and young adults |
| Study Authors and Details | Population and Setting | Study Period | Number of Children | Demographics | Underlying Conditions | Outcome Measures |
|---------------------------|------------------------|--------------|-------------------|--------------|----------------------|-----------------|
| Parri N, et al (32)       | Italy, 17 pediatric emergency departments, the CONFIDENCE study | March 3 to March 27, 2020 | 100 | 3.3 (40% < 1 year, 14% < 5 years) | 27%, cystic fibrosis, neurological, hematological, cardiac, immunological, oncological conditions, metabolic disease, prematurity, syndrome | 1% had severe disease, 1% were in critical condition |
| Chao J, et al (44)        | Single tertiary children’s hospital New York City | March 15 to April 13, 2020 | 67 | 13.1 | Obesity and asthma | 33 admitted to ICU |
| Whittaker E, et al (24)   | 8 hospitals in England | March 23 to May 16, 2020 | 58 | 9 | 3 had asthma, 1 neurodisability, 1 epilepsy, 1 sickle cell disease, 1 alopecia | All had multisystem inflammatory syndrome, 50% developed shock, and 14% coronary artery aneurysm |
| Shekerdemian L, et al (29) | 46 North American ICUs | March 14 to April 3, 2020 | 48 | 13 | 83% | All admitted to ICU, 23% had multiorgan failure, 2% needed extracorporeal membrane oxygenation, 4% died |
| Tagarro A, et al (35)     | 30 Hospitals in Madrid, Spain | March 2 to March 16, 2020 | 41 | 1 | 27% had underlying disease | 60% hospitalized, 9.7% admitted to ICU, 9.7% needed respiratory support (1 had underlying condition) |
| Qiu H, et al (43)         | 3 hospitals, Zhejiang, China | January 17 to March 1, 2020 | 36 | 8.3 (<5 years 28%) | Not available | All patients had mild or moderate type |

Underlying medical condition, young age

Higher levels of CRP, procalcitonin, and proBNP and platelet count

Elevated CRP and ferritin, older age, Black or Asian race

Underlying comorbidities

Perhaps young age, underlying condition

Radiographic presentation, decreased lymphocytes, elevated body temperature,
| Study | Location/Setting | Dates | Sample Size | Comorbidities | Laboratory Findings | Clinical Findings |
|-------|-----------------|-------|-------------|---------------|-------------------|-------------------|
| Belhadje Z, et al (49) | 14 ICU in France and Switzerland | March 22 to April 30, 2020 | 35 | 28% had comorbidities (asthma, overweight) | Multisystem inflammatory syndrome - acute cardiac failure | Cytokine storm and macrophage activation |
| Bandi S, et al (23) | University COVID-19 clinic, Chicago, USA | 12 March to 20 April, 2020 | 25 | Not available (Sickle cell acute pain crisis) | 20% hospitalized, 12% admitted to ICU, 1 intubated | Older age, African-American race |
| Zheng F, et al (33) | 10 hospitals, Hubei, China | February 1 to February 10, 2020 | 25 | 8% (congenital heart disease, malnutrition, suspected hereditary metabolic diseases) | Most patients had mild disease. Two had critical disease (both with underlying disorder) | Underlying disorders |
| Cheung E, et al (51) | Columbia University Irving Medical Center/New York-Presbyterian Morgan Stanley Children’s Hospital in New York City | April 18 to May 5, 2020 | 17 | 3 mild asthma | Multisystem inflammatory syndrome | Elevated inflammatory markers, troponin T and NT-proBNP levels |
| Verdoni L, et al (48) | Bergamo province, Italy | February 18 to April 20, 2020 | 10 | None | Multisystem inflammatory syndrome | Older age, features of macrophage activation |
| Riphagen S, et al (47) | ICU UK | Mid-April, 2020 | 8 | None | Multisystem inflammatory syndrome | Afro-Caribbean descent, Male gender |
| Sun D, et al (34) | ICU of Wuhan Children’s Hospital, China | January 24 to February 24, 2020 | 8 | 1 acute lymphoblastic leukemia | All admitted to ICU | Raised levels of CRP, LDH, procalcitonin, abnormal liver function, cytokine |
| Author(s)                  | Hospital Location | Date | Age | No. | Condition                                                                 | Findings/Notes                                                                 |
|---------------------------|-------------------|------|-----|-----|----------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Liu W, et al (19)         | Tongji Hospital (Wuhan), China | January 7 to January 15, 2020 | 6   | 3   | None                                                                      | All 4 patients ≤ 3 years had pneumonia, 1 admitted to ICU                   |
|                           |                   |      |     |     | 4 children ≤ 3 years                                                      | Young age                                                                      |
| Cui Y, et al (18)         | Hubei Province, China | January 28, 2020 | 1   | 55days | None                                                                      | Pneumonia, myocardial injury, acute liver injury                               |
| Shi B, et al (42)         | Hubei Province, China | February 3, 2020 | 1   | 2months | None                                                                      | Severe pneumonia, need for noninvasive ventilation                            |
|                           |                   |      |     |     | 2 months                                                                  | Young age, co-infection with RSV                                              |

**Abbreviations:** ICU: Intensive care unit, CRP: C-reactive protein, LDH: lactate dehydrogenase, NT-proBNP: N-terminal pro b-type Natriuretic Peptide, CT: computed tomography, RSV: respiratory syncytial virus, DM: diabetes mellitus
Figure 1. Flow-chart of the literature search on risk factors for severe coronavirus-19 (COVID-19) in childhood (February 26, 2020 to June 10, 2020)

- Literature search: PubMed, Scopus

- Studies identified through database search (n=293)

- Studies found appropriate on the basis of title (n=72)

- Full-text articles assessed for eligibility (n=23)

221 studies excluded
- non-English language articles
- studies on adults
- studies on neonates and pregnancy
- studies focused on treatment strategies

49 studies excluded
- studies not providing information on risk factors for severe COVID-19