Risk Factors for Severity in Children with Coronavirus Disease 2019

A Comprehensive Literature Review

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KEYWORDS

• Children • Coronavirus • COVID-19 • Risk factor • Severity

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% to 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 this is not confirmed in all studies.
- It is unclear whether male gender and certain laboratory and imaging findings can also be considered as risk factors, because of insufficient data.

INTRODUCTION

Until recently, 6 different coronaviruses (CoVs) had been identified in humans (human CoVs [HCoVs]): HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1, severe acute respiratory syndrome (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 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

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(MERS)–CoV,[5] which is transmitted from dromedary camels to humans.[6] Collectively, these 2 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 recognized 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 CoV 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. This article analyzes 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 this 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 eventually selected, as shown in **Fig. 1**, and are discussed here. The factors that may introduce bias into the findings of this article are restriction to articles in English, together with database and citation bias.

Most of the studies originated in China, the United States, 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, 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 CORONAVIRUS DISEASE 2019

COVID-19 worldwide is 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.[8] In the United States, among 149,082 reported cases of COVID-19, 1.7% were in children aged less than 18 years.[9] From the currently available data, it seems that children tend to have asymptomatic or mild disease more commonly than adults,[8,10] 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 less than 20 years.[11]

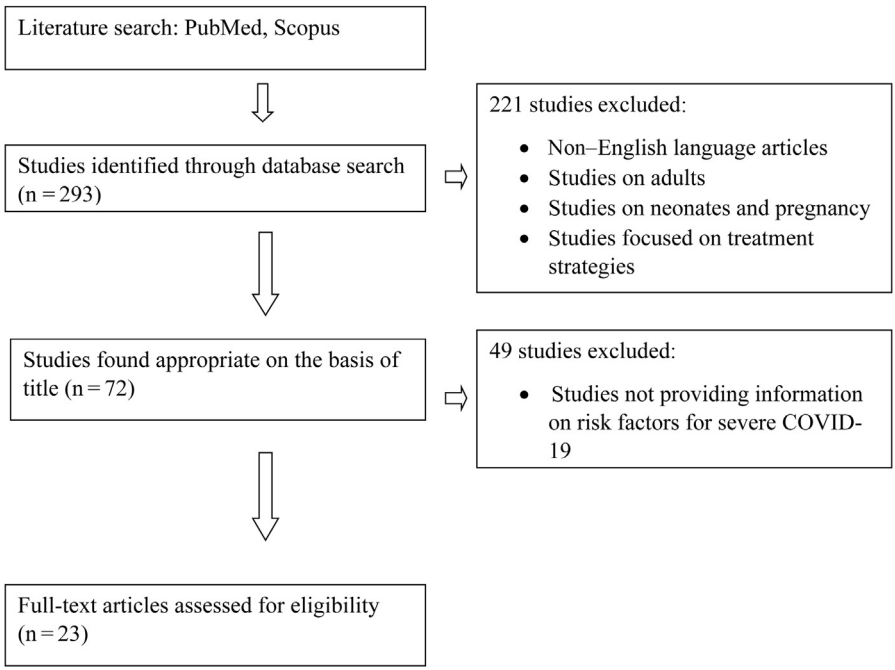

Fig. 1. The literature search on risk factors for severe COVID-19 in childhood (February 26 to June 10, 2020).

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, because their prevalence was 4.3%, and the highest prevalence was among infants aged 7 to 12 months.[12] Infection by these 4 strains usually causes acute respiratory disease, with severe manifestations in some children.[13] Regarding SARS-CoV, only 6 case series have been reported, including a total of 135 pediatric cases, from Canada, Hong Kong, Taiwan, and Singapore.[14] A milder form of the disease was observed in children compared with adults, and no child death was recorded.[15] In the MERS-CoV epidemic, pediatric cases were even fewer, because only 2 small case series of children were reported, both originating from Saudi Arabia, 1 of 31 children with a mean age of 10 years[16] and 1 of 7 children with a mean age of 8 years.[17] In both studies, 42% of the infected children were asymptomatic,[16,17] and in 1, 2 of the 7 had severe disease,[17] whereas in the other, 2 of the 31 children died (6%).[16]

RISK FACTORS FOR SEVERITY IN CORONAVIRUS DISEASE 2019 AND OTHER CORONAVIRUS INFECTIONS

The Impact of Age

Severe acute respiratory syndrome–coronavirus-2

In a series of 2135 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.[10] Severe and critical cases were reported in 10.6% of the children aged less than 1 year, 7.3% of those aged 1 to 5 years, 4.1%

Table 1
Studies on severity and risk factors of coronavirus disease 2019 in children (February 26 to June 10, 2020)

First Author	Region	Study Period	Number of Children	Mean Age (% of Young Children)	Underlying Diseases Present (Diseases)	Severity	Risk Factors
Bialek et al[9]	United States (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	2572	11 (<1 y, 15%)	23% (chronic lung disease, cardiovascular disease, immuno-suppression)	5.7%–20% hospitalized, 0.58%–2% admitted to ICU, aged <1 y: 15%–62% hospitalized, 3 deaths	Children aged <1 y, underlying condition
Dong et al,[10] 2020	Chinese CDC, cases from Hubei province and Anhui, Henan, Hunan, Jiangxi, Shanxi, and Chongqing	January 16 to February 8, 2020	2135 suspected and confirmed cases	7 (<1 y, 17.6%)	Not available	90% had asymptomatic to moderate disease Severe or critical disease in 10.6% <1 y, 7.3% 1–5 y, 4.1% 6–10 y, 3% >16 y; 1 14-year-old boy died	Young age
Lu et al,[30] 2020	Wuhan Children's Hospital, China	January 28 to February 26, 2020	171	6.7 (<1 y, 18%)	3 patients (hydronephrosis, leukemia, intussusception)	3 patients with invasive mechanical ventilation (all with underlying condition), 1 death	Underlying condition
DeBiasi et al,[22] 2020	Children's National Hospital Washington	March 15 to April 30, 2020	177	9.6	39% (asthma, neurologic condition, DM, obesity, cardiac problem, hematological disease, oncological condition)	9 critically ill patients	Adolescents and young adults

Parri & Leng,[32] 2020	Italy, 17 pediatric emergency departments, the CONFIDENCE study	March 3 to March 27, 2020	100	3.3 (40% <1 y, 14% <5 y)	27%, cystic fibrosis; neurologic, hematological, cardiac, immunologic, oncological conditions; metabolic disease; prematurity syndrome	1% had severe disease, 1% were in critical condition	Underlying medical condition, young age
Chao et al,[44] 2020	Single tertiary children's hospital, New York City	March 15 to April 13, 2020	67	13.1	Obesity and asthma	33 admitted to ICU	Higher levels of CRP, procalcitonin, and proBNP and platelet count
Whittaker et al,[24] 2020	8 hospitals in United Kingdom	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	Increased CRP and ferritin levels, older age, black or Asian race
Shekerdemian et al,[29] 2020	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	Underlying comorbidities
Tagarro et al,[35] 2020	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)	Perhaps young age, underlying condition

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Table 1
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First Author	Region	Study Period	Number of Children	Mean Age (% of Young Children)	Underlying Diseases Present (Diseases)	Severity	Risk Factors
Qiu et al,[43] 2020	3 hospitals, Zhejiang, China	January 17 to March 1, 2020	36	8.3 (<5 y, 28%)	Not available	All patients had mild or moderate type	Radiographic presentation, decreased lymphocyte counts, increased body temperature, high levels of procalcitonin, D-dimers, and creatine kinase-MB
Belhadjer et al,[49] 2020	14 ICUs in France and Switzerland	March 22 to April 30, 2020	35	10	28% had comorbidities (asthma, overweight)	Multisystem inflammatory syndrome–acute cardiac failure	Cytokine storm and macrophage activation
Bandi et al,[23] 2020	University COVID-19 clinic, Chicago, IL	12 March to 20 April, 2020	25	9.7 y	Not available (1 sickle cell acute pain crisis)	20% hospitalized, 12% admitted to ICU, 1 intubated	Older age African American race
Zheng et al,[33] 2020	10 hospitals, Hubei, China	February 1 to February 10, 2020	25	3 (<3 y 40%)	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 et al,[51] 2020	Columbia University Irving Medical Center/ New York-Presbyterian Morgan Stanley Children's Hospital in New York City	April 18 to May 5, 2020	17	8	3 mild asthma	Multisystem inflammatory syndrome	Inflammatory markers, troponin T, and NT-proBNP levels
Verdoni et al,[48] 2020	Bergamo province, Italy	February 18 to April 20, 2020	10	7.5	None	Multisystem inflammatory syndrome	Older age, features of macrophage activation
Riphagen et al,[47] 2020	ICU, United Kingdom	Mid-April, 2020	8	9	None	Multisystem inflammatory syndrome	Afro-Caribbean descent Male gender
Sun et al,[34] 2020	ICU of Wuhan Children's Hospital, China	January 24 to February 24, 2020	8	7 (3 children ≤1 y)	1 acute lymphoblastic leukemia	All admitted to ICU	Increased levels of CRP, LDH, procalcitonin, abnormal liver function, cytokine storm, abnormalities on chest CT
Liu & Zhang,[19] 2020	3 branches of Tongji Hospital, Wuhan, China)	January 7 to January 15, 2020	6	3 (4 children ≤3 y)	None	All 4 patients ≤3 y had pneumonia, 1 admitted to ICU	Uoung age
Cui et al,[18] 2020	Hubei Province, China	January 28, 2020	1	55 d	None	Pneumonia, myocardial injury, acute liver injury	Young age
Shi et al,[42] 2020	Hubei Province, China	February 3, 2020	1	2 mo	None	Severe pneumonia, need for noninvasive ventilation	Young age, coinfection with RSV

Abbreviations: CDC, Center for Disease Control and Prevention; CRP, C-reactive protein; CT, computed tomography; DM, diabetes mellitus; ICU, intensive care unit; LDH, lactate dehydrogenase; MB, myocardial band; NT-proBNP, N-terminal pro–b-type natriuretic peptide; proBNP, pro–b-type natriuretic peptide; RSV, respiratory syncytial virus.

of those aged 6 to 10 years, and 3% of the children aged greater than 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 2135 children, only 728 had laboratory confirmation, and the severe symptoms in the suspected cases may have been be caused by 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.[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.[20,21] In a study of 177 children from the Children's National Hospital in Washington, DC, the adolescents and young adults were more commonly critically ill than the younger children.[22] Another study from the United States 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% versus 1.7% of white children.[23] In a study in the United Kingdom, among 58 children, race (black or Asian) was described as a risk factor for COVID-19.[24]

Other coronaviruses

In the United States, in the case of other CoVs, specifically 229E, HKU1, NL63, and OC43, age less than 2 years has been reported as a risk factor for severe disease, defined as the need for respiratory support.[25] In contrast, in a series of 44 children in China with SARS-CoV, an age of greater than 12 years was associated with severe illness, requiring methylprednisolone therapy and oxygen supplementation.[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.[26,27]

The Impact of Male Gender

Male gender is a risk factor for severe CoV disease in adults.[28] A predominance of men was reported in all age subgroups among 2490 pediatric cases of COVID-19 in a series in the United States, but no details were given about the impact of gender on the severity of the disease.[9] Among 2143 Chinese children with COVID-19 in the study of Dong and colleagues,[10] 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. In a cross-sectional study of 48 children with COVID-19 admitted to US and Canadian intensive care units (ICUs), 52% were boys.[29] Severe disease has been reported in girls and the current data suggest that, in children, male gender is not an independent risk factor of severe COVID-19.

Underlying Medical Comorbidity

Severe acute respiratory syndrome–coronavirus-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 whom had underlying comorbidities. One was a 10-month-old male infant with intussusception who developed multiorgan failure and died 4 weeks after admission.[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.[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 The Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) study from Italy, which included 100 children, 27% had an underlying medical condition. Of the 9 children needing respiratory support, 5 were aged less than 1 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 whom had congenital heart disease. One of them also had malnutrition and a suspected hereditary metabolic disease, and the other had coinfection with *Enterobacter aerogenes*.[33]

The first report from the United States concerning children with COVID-19 is of 2572 pediatric cases. Among the children for whom hospitalization status was known, 20% were hospitalized. Because of 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 with 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 an 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[34] 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 less than 93%, and arterial partial pressure of oxygen less than or equal to 300 mm Hg, whereas critical cases were defined as the presence of septic shock or the need for mechanical ventilation or ICU admission. The age range of the patients in the 8 severe cases was from 2 months to 15 years, 6 were boys, and only 1 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 an ICU, and 4 needed respiratory support. Of these children, 1 had a previous condition (recurrent wheezing) and no patient died.[35] In a recent report from Paris, France, 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.[36]

It seems, therefore, that although 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 comorbidities are well documented as risk factors not only for admission to the ICU but also for mortality.[37]

Other coronaviruses

Severe pediatric disease from other CoVs reported in the United States, 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.[25] Ogimi and

colleagues[38] in the United States 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 found regarding the severity of illness among hospitalized children with different HCoV types.[25]

The 2 deaths reported in children with MERS-CoV in Saudi Arabia were in a 2-year-old child with cystic fibrosis[39] and a 9-month-old infant with infantile nephrotic syndrome,[40] whereas a 14-year-old girl with Down syndrome needed hospital admission but eventually recovered.[39]

Coinfection with Another Pathogen

Severe acute respiratory syndrome–coronavirus-2

Coinfection 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 coinfection with *E aerogenes*.[33] In a study of 20 pediatric cases from the same region, 40% had an underlying coinfection, but there was no report on their severity.[41] A severe case of COVID-19 has been reported in a Chinese 2-month-old infant who had coinfection with respiratory syncytial virus (RSV).[42]

Other coronaviruses

The presence of copathogens with more than 1 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 were more likely to present pulmonary rales than those infected by more than 1 HCoV strain or other respiratory pathogens.[12] The presence of RSV has been associated with lower respiratory tract disease or severe lower respiratory tract disease from HCoV.[38]

Laboratory Findings

This article reports 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.

Severe acute respiratory syndrome–coronavirus-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[43] 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 increased body temperature, a decrease in lymphocyte counts, higher levels of procalcitonin and creatine kinase-MB (myocardial band), and increased D-dimer levels.[43] Laboratory data from 8 severe pediatric cases in the same country showed normal or increased leukocyte count, and high levels of C-reactive protein (CRP), procalcitonin, and lactate dehydrogenase, whereas half had abnormal liver function tests.[34] In a study of 67 children in the United States, admission to an ICU was associated with higher levels of CRP, procalcitonin, and pro–B-type natriuretic peptide and an increased platelet count.[44]

Henry and colleagues[45] 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 investigators commented that the absence of lymphopenia in children may in part be explained by the milder disease. Another assumption was that increased procalcitonin level could be caused by a bacterial coinfection as a complication of COVID-19.[45] Procalcitonin level was increased in 80% of Chinese

pediatric patients in the study of Xia and Shao,[41] and, in that series, 40% of the children had a coinfection.

Other coronaviruses

Neutrophilia was a predictor of severe illness among 44 children with SARS.[15] Lymphopenia was detected in 10 children with SARS, of whom 4 needed oxygen therapy and 2 needed assisted ventilation.[46]

RISK FACTORS FOR PEDIATRIC MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH SEVERE ACUTE RESPIRATORY SYNDROME–CORONAVIRUS-2

A syndrome of fever and multisystem inflammatory syndrome (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.[47,48] These children presented with acute cardiac decompensation,[49] and some developed coronary artery aneurysms.[24] Among 44 children hospitalized in the United States with MIS, 84.1% had gastrointestinal symptoms as the presenting clinical complaint.[50]

Most studies to date have reported that MIS presents in children at an older age, with a median age of 8 to 10 years.[24,49,51] In a retrospective study of 35 children with MIS, admitted to ICUs in France and Switzerland, comorbidities were present in 28% of the children, including asthma and being overweight,[49] but most of the children in other studies reported from Europe, specifically Italy and the United Kingdom, were previously healthy.[24,48] In a study of 8 children from the United Kingdom with MIS, 6 were Afro-Caribbean and 5 were male.[47] It has been suggested that black and Asian races may be predisposed to this clinical complication.[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 increase in levels of inflammatory markers such as CRP and ferritin,[24] and a cytokine storm, with specific increase in the level of interleukin (IL)-6 and macrophage activation.[49,51] The patients often had a significant increase in B-type natriuretic peptide and troponin T.[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 polymerase chain reaction but positive viral serology.[52]

WHAT MECHANISMS PLAY A ROLE IN THE ATYPICAL PICTURE OF CORONAVIRUS DISEASE 2019 IN CHILDREN?

The SARS-CoV-2 is a β CoV of group 2B, with more than 70% similarities in genetic sequence to SARS-nCoV.[53] The established scientific evidence on SARS-novel coronavirus 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 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, because of 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.[54,55] CoVs are known to alter the epigenetic cellular mechanisms of the host associated with viral entry, replication, and innate immune control.[56]

Most children hospitalized with COVID-19, especially those in the ICU, were less than 3 years of age.[33,35] This finding may be explained by the immaturity of the immune system in this age period, the low likelihood of wearing face masks in this age group, and the subsequent high viral load.[57]

Another reason for the different clinical picture of COVID-19 in children is that they have fewer underlying disorders that may predispose to severe COVID-19 than adults.[58] The severity of COVID-19 is higher in children with preexisting conditions, such as asthma, malignancies, cardiovascular disorders, and immunosuppression.[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.[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 that counters the activity of the related angiotensin-converting enzyme (ACE) by reducing the amount of angiotensin-II.[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.[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 until puberty and progressive reduction after maturity.[63] In contrast, ACE2 expression in rat lung has been found to decrease dramatically with age.[64] Studies have provided evidence that ACE2 also protects against the severe acute lung injury that can be activated by sepsis, SARS, and avian influenza A H5N1 virus infection.[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.[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.[66]

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.[67] It has been shown that the number of viral copies is correlated with the severity of COVID-19.[68]

The immune system undergoes significant changes from birth to adulthood, especially in lymphocyte biology,[69] 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%)[70] but not in children

(3%).[30,45] However, in the 2003 SARS epidemic, lymphocytopenia was reported in 77% of infected children.[15] The changing level of T lymphocytes with age may also be a reason for the mild disease phenotype in childhood.[71]

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 proinflammatory cytokines, such as IL-2, IL-6, and tumor necrosis factor, in the lower respiratory tract and other tissues.[72] In some cases, the increase of cytokine levels is uncontrolled, leading to the detrimental cytokine syndrome, with a poor outcome.[73] The percentage of children with COVID-19 with increased levels of inflammatory markers is reported to be low, and this could be a cofactor for nonsevere disease.[45] In contrast, 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.[24]

Another immunologic aspect that could be related to the mild disease in children is trained innate immunity, because of the routine use of various vaccines, including bacillus Calmette-Guérin(BCG). BCG vaccination induces epigenetic changes in monocytes, and increased cytokine production in response to several different pathogens.[74] In mice, BCG also enhances nonspecific defense against influenza virus infection.[75]

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 reduce viral replication rates and the levels of proinflammatory cytokines.[76] 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.[77]

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 with 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 seems to be a risk factor for severe disease in children. Increased levels of the inflammatory markers procalcitonin and CRP could be caused by a bacterial coinfection as a complication of COVID-19. The recently described pediatric MIS seems 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 coinfection with RSV, responsiveness of the immune system, vaccination history, levels of vitamin D, and genetic polymorphisms, but the present paucity of data limits the 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

S. Tsabouri and A. Makis designed the study, and S. Tsabouri, A. Makis, and C. Kosmeri did the literature search. A. Makis, C. Kosmeri, and E. Siomou were responsible for the data collection. S. Tsabouri and C. Kosmeri collected and analyzed the data. S. Tsabouri, A. Makis, C. Kosmeri, and E. Siomou analyzed data and wrote the article.

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