Risk Factors Associated with Severe COVID-19 Among Pediatric Patients: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic continues to cause global havoc posing uncertainty to educational institutions worldwide. Understanding the risk factors of COVID-19 in children is important because of the potential impact on clinical management and public health decisions.
Methods: This systematic review and meta-analysis aim to determine the risk factors associated with severe COVID-19 in children. A comprehensive search on Medline through PubMed, Cochrane Library, WHO COVID-19 Database, Herdin Plus, and ACTA Medica Philippina from January 1, 2020 until January 31, 2022 was done. Included studies evaluated the risk factors associated with severe COVID-19 among pediatric patients. The authors determined the strength of this association using pooled Odds ratio with 95% confidence intervals.
Results: After retrieving 3,341 publications, full-text article review was done on 11 studies. Six studies were included in the final analysis and these studies were carried out in five countries. There were one cohort and five cross-sectional analytic studies. There were 47,486 pediatric patients with confirmed COVID-19 with 50.12% male population (n = 23,802). The patients' median age varied across all 6 studies from 16 months to 12 years. A total of 1,757 severe COVID-19 cases (3.62%) was reported across all 6 studies. Sensitivity analysis of studies with no serious risk of bias showed that the presence of underlying medical conditions increased the odds of having severe COVID-19 by almost three times (Odds Ratio (OR): 2.96; 95% CI: 2.27 – 3.87) compared to absence of underlying medical conditions (p-value = 0.22; I^2 = 31%; Chi^2 = 4.37). However, results showed that older age increased the odds of having severe COVID-19 by almost three times (OR: 2.77; 95% CI: 1.48 – 5.20) but the studies were heterogenous (p-value <0.00001; I^2 = 91%; Chi^2 = 64.34).
Conclusion: This systematic review and meta-analysis demonstrate that underlying asthma, diabetes, and cardiovascular diseases, and young age are risk factors for severe COVID-19 in children. Clinicians should pay close attention to these risk factors and provide timely and personalized treatment modalities to prevent progression to severe COVID-19 and reduce the risk of death.

Key words: coronavirus disease 2019 (Covid-19), meta-analysis

In late December 2019, an outbreak of pneumonia of unknown cause with clinical presentations greatly resembling viral pneumonia emerged in Wuhan, Hubei, China.[1] It was later confirmed by the World Health Organization (WHO) to be caused by a positive-sense single-stranded RNA virus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more commonly known as 2019 novel coronavirus, COVID-19. WHO then declared COVID-19 as a global pandemic in March 2020.

The clinical spectrum of COVID-19 disease ranges from a common cold to more severe disease forms such as bronchitis, pneumonia, severe acute respiratory distress syndrome, multiorgan failure and even death. Epidemiologic evidence indicates that children are less likely to develop severe COVID-19 than adults, and infected children typically have

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a good prognosis, with "trained immunity" as a potential explanation.[2] However, this contradicts the study from China in which they reported that infants and younger children are more likely to develop severe clinical manifestations than older children, likely due to an immature immune system.[3] The novel presentation of multi systemic inflammatory syndrome in children (MIS-C) alerted the medical community about the pathogenesis of COVID-19 in pediatric patients.[4,5]

A substantial number of studies have already been published on adults with COVID- 19, but there is limited information on the risk factors associated with severe COVID -19 in pediatric patients. This systematic review and meta-analysis aimed to determine the risk factors associated with severe COVID-19 among pediatric patients.

Review of Literature

Most children with SARS-CoV-2 infection have been asymptomatic or had mild COVID -19 symptoms, however, some children have had severe illness.[6] Several risk factors for severe COVID-19 had been identified.

In a cohort study done by Fisler, et al. (2020)[7], factors associated with severe disease included older age, presence of existing comorbidities, increased BMI, initial elevated WBC, platelet count, C- reactive protein (CRP), and ferritin. Factors associated with Pediatric Intensive Care Unit (PICU) admission were age ≥12 years and presence of comorbidity.

Another study done by Kompaniyets L, et al.(2021)[8] of which they included 43,465 children with confirmed COVID-19 had underlying medical conditions. The strongest risk factors for hospitalization were type 1 diabetes (adjusted risk ratio [aRR], 4.60; 95% CI, 3.91- 5.42) and obesity (aRR, 3.07; 95% CI, 2.66-3.54), and the strongest risk factors for severe COVID-19 illness were type 1 diabetes (aRR, 2.38; 95% CI, 2.06-2.76) and cardiac and circulatory congenital anomalies (aRR, 1.72; 95% CI, 1.48-1.99). Prematurity was a risk factor for severe COVID-19 illness among children younger than 2 years (aRR, 1.83; 95% CI, 1.47- 2.29).[8]

Another study done by Lu, et al.(2020)[9] of which they included children with COVID-19 showed that among the 171 patients, 3 (1.75%) with coexisting conditions (hydronephrosis, leukemia, and intussusception) required intensive care support, including invasive mechanical ventilation.

MATERIALS AND METHODS

Study Design

Systematic review and meta-analysis were done. This study conformed to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA-P) checklist and the PRISMA guidelines for the development of this systematic review and meta-analysis.

Search Strategy and Data Sources

Literature search for published studies from January 1, 2020 until January 31, 2022 on Medline through PubMed, Cochrane Library, WHO COVID-19 Database, Herdin Plus, and ACTA Medica Philippina was done. The combination of the following keywords and Medical Subject Headings (MeSH) was used: Severe COVID-19, Critical COVID-19, Pediatrics, Children, Adolescent, Risk Factors, Comorbidities and Predictors. To combine terms, the Boolean operators (AND and OR) were used. The search in each database was adapted accordingly. Cross-sectional studies, case-control studies and cohort studies were included. The reference lists of relevant articles were hand-searched to retrieve potential additional records. No restrictions on the country and language were applied.

Eligibility Criteria

Studies with evidence reporting the risk factors associated with severe COVID-19 among pediatric patients were included in our analyses. Severe COVID-19 is defined as early respiratory symptoms such as fever and cough, accompanied by gastrointestinal symptoms, such as diarrhea. This usually progresses around 1 week, and dyspnea occurs associated with central cyanosis. Oxygen saturation is <92%, with other hypoxia manifestations. Case-control studies and cohort studies were included. Case reports and case series, conference abstracts, commentaries, editorials, review papers, pre-prints, and cohort and case-control studies with less than 20 patients were excluded. Unpublished articles were excluded due to data uncertainty.

Participant/Population and Exposure

Children and adolescents less than 19 years of age diagnosed with COVID-19 infection based on RT-PCR were the population of interest.

Study Selection and Data Extraction

Two independent reviewers (CT and EB) performed. Literature search, initial screening of titles and abstracts and review of full text articles for eligibility, and data extraction. The extracted data included: First author, country, year of publication, study design, the total number of reported cases, the total number of severe and non-severe RT-PCR-confirmed COVID-19, sex, age, coexisting medical conditions, COVID-19 vaccination, measures of severe COVID-19. The results of this analysis were presented based on the PRISMA-P checklist. Extraction of the data from the studies was also done using JBI Sumari Online Software.

Risk of Bias (Quality) Assessment

Two reviewers independently assessed the Risk of bias of selected papers using Johanna Briggs Institute (JBI) Sumari Tool for cross-sectional, case-control or cohort studies (https://jbi.global/critical-appraisal-tools) Any discrepancies were resolved through discussion or, if required, through discussion with a third reviewer. Biases were assessed based on the following domains: bias due to missing outcome data, bias not from accounting for confounding factors, bias in measurement of outcomes, and bias arising from selective reporting of results.

Data Analysis and Presentation

An MS Excel spreadsheet was used, formatted according to the extraction tool used to extract data. The characteristics of the included articles were described, which were previously discussed and agreed upon within the study team. Mean and standard deviation for continuous variables and frequency and percentages for categorical variables were used in the baseline characteristics presentation. Effect estimates were either Odds Ratio (OR) or Risk Ratio (RR), and its 95% confidence intervals (CI).

Evidence Synthesis

Data of the included studies were qualitatively described and presented. Meta-analysis was carried out using RevMan 5.4 following the random-effects model if found to have high heterogeneity. The pooled Odds Ratio (OR) or Risk Ratio, adjusted OR with 95% confidence interval (CI) was calculated for categorical variables. For examining between-study heterogeneity, chi-square test statistic (Q), and I^2 were used in this analysis. I^2 of greater than 50% and chi-square statistic with a p-value of < 0.10 were interpreted as high. Publication bias was determined using Egger Regression asymmetry test and the use of funnel plot if there were at least 10 studies per outcome meta-analyzed.

RESULTS

Systematic Review

Search Results

The details on the literature search and processes of screening are illustrated in Figure 1. Following the removal of duplicate search records and screening titles and abstracts of studies, we further screened 11 relevant studies and found five articles that did not meet our eligibility criteria. A total of 6 observational studies were included for systematic review and meta-analysis.

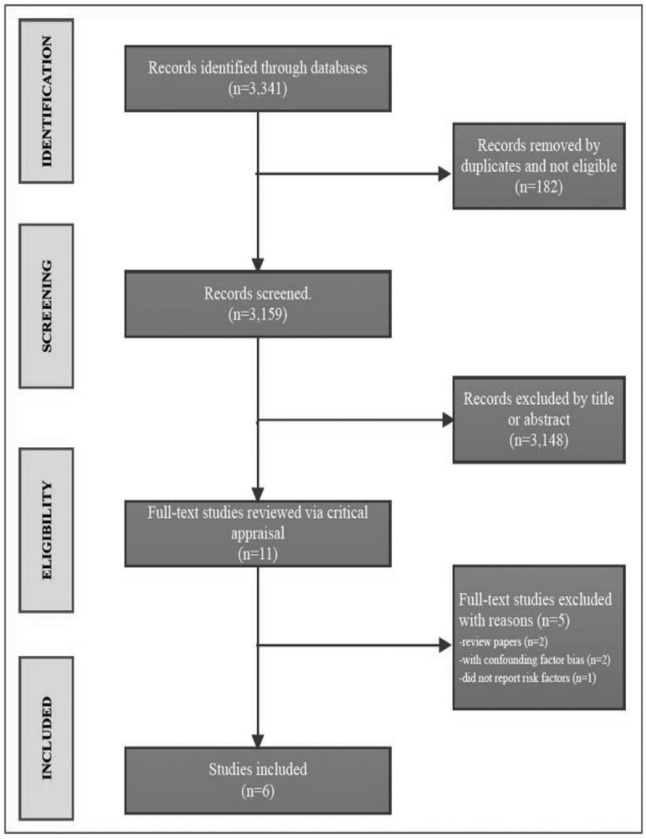

Figure 1. PRISMA flow diagram illustrating study selection.

Quality Assessment

The quality assessment JBI questionnaires from the JBI Sumari (https://sumari.jbi.global; Adelaide, Australia) for critical appraisal of the individual studies were used to evaluate the Risk of bias of the studies depending on the study design. All of the studies that had more than five 'yes' answers were rated low risk for bias (n=6). Upon critical appraisal, the included studies were heterogeneous in nature given that the primary estimates presented were different from each other. In addition, because of the differences in the main objectives, different clinical outcomes were measured, therefore significant heterogeneity was observed.

Characteristics of the Included Studies

The characteristics of the included studies are presented in Table 1. The included studies were published in various international peer-reviewed journals in 2020 to 2022. Six studies were carried out in five countries: USA (n = 2), Italy (n = 1), Spain (n = 1), France (n = 1), and Brazil (n = 1). Based on the study designs, five studies were analytical cross- sectional studies[8,10,11,12,13] while one was a cohort study.[14] Most of them were retrospective in nature (n=5). In the included studies, all articles described the risk factors of acquiring severe pediatric COVID-19 infection.

Table 1. Summary characteristic of included studies in systematic review (n=6).

Study	Study Design	Country	Setting/Context	Participant Characteristics	Outcomes Measured
Bellino S, et al. 2020	Cross- Sectional Study	Italy	Data from the national case- based surveillance system of confirmed COVID-19 infections until May 8, 2020 were analyzed.	Children aged <18 years with laboratory- confirmed COVID-19, reported to the Italian integrated COVID-19 surveillance system	Epidemiological and clinical characteristics of COVID-19 pediatric patients, disease severity risk factors, and compare children and adolescents with adults and the elderly
Tagarro A, et al. 2022	Cross- Sectional Study	Spain	Multicentre study (76 hospitals) that collected data from the beginning of the epidemic in Spain (March 12th) until March 22nd, 2021.	Eligible participants were children aged from 0 to 18 years who attended in any of the hospitals of the network with a SARS- CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR), rapid antigen test or children fulfilling WHO criteria for multisystem inflammatory syndrome in children (MIS- C).	MIS-C," "bronchopulmonary disease" (including pneumonia, bronchiolitis, bronchitis and asthma flare), "gastrointestinal disease" (including gastroenteritis and abdominal pain), "fever without a source" and "mild disease" (URTI, flu- like syndrome, skin or mucosae problems and asymptomatic patients)
Ouldali N, et al. 2021	Cross- Sectional Study	France	Recruited prospectively 60 hospitals using the French pediatric bacterial meningitis network from February 15 to June 1, 2020	Included all pediatric patients with SARS-CoV-2 infection who were hospitalized in one of the centers	Proportion of severe disease evolution among all included children with a SARS-CoV-2 infection, defined by the need for either ventilatory or hemodynamic support during hospitalization, or death

Study	Study Design	Country	Setting/Context	Participant Characteristics	Outcomes Measured
Kompaniyets L, et al. 2021	Cross- Sectional Study	United States	Data were collected from the Premier Healthcare Database Special COVID-19 Release, which included data from more than 800 US hospitals from March 1, 2020, through January 31, 2021.	Patients aged 18 years or younger who had an inpatient or Emergency Department encounter with a primary or secondary COVID-19 discharge diagnosis.	Two outcomes were considered: 1) hospitalization and 2) severe illness when hospitalized, a single severity indicator for experiencing an intensive care unit (ICU) or stepdown unit admission, invasive mechanical ventilation (IMV), or death. Hospitalization was defined by having an inpatient encounter, death was defined using patient discharge status, and ICU admission and IMV were determined using patient billing records.
Hendler JV, et al. 2021	Cross- Sectional Study	Brazil	Retrospective analysis of all COVID-19 hospital admissions registered in the Influenza Epidemiological Surveillance Information System; a nationwide surveillance database used to monitor severe acute respiratory infections (SARI)	All children (0 to 18 years old) with a positive quantitative RT- PCR (RT-qPCR) test result for SARS-CoV-2 who had been admitted to hospital between March 9, 2020 (11th epidemiological week) and December 10, 2020 (50th epidemiological week).	COVID-19 severity: severe illness was characterized by the need for hospitalization, while critical illness was deemed when there was a need for PICU admission, invasive mechanical ventilation, or when the patient died during hospitalization
Graff K, et al. 2021.	Cohort Study	United States	Retrospective study among children with positive SARS- CoV-2 PCR from March to July 2020 at Children's Hospital Colorado.	All patients <21 years of age with a positive SARS- CoV-2 molecular test performed at CHCO were included. Patients ≥21 years were included only if they were followed by the hospital for a chronic medical condition.	Categorized patients as requiring critical care if they either 1) were admitted to the pediatric intensive care unit (ICU) for symptomatic COVID-19, or 2) were admitted to the neonatal ICU for symptomatic COVID-19 and required a higher level of respiratory support than low-flow nasal cannula

Demographics Data

Overall, there were 47,486 COVID-19 pediatric patients (Table 1). Of the 47,486 pediatric cases with available data on sex the male percentage was 50.12% (n = 23,802). The patients' median age varied across all 6 studies from 16 months to 12 years.

Risk Factors

Underlying/Pre-existing Medical Condition

The presence of pre-existing medical conditions among pediatric patients increased the odds of having severe COVID-19 infection by almost three times [Odds Ratio (OR) = 2.80, 95% Confidence Interval (CI) = 1.74–4.48] compared to those who did not have any underlying medical conditions.[3] On the other hand, the team of Graff, et al.[14] reported that the presence of other medical conditions increases the odds of having severe pediatric COVID-19 infection by three times (aOR: 3.47; 95% CI: 1.5–8.1; p-value = 0.0087) after adjusting for confounding variables relative to those patients who did not have any medical conditions. Moreover, their research specifically reported these medical conditions such as gastrointestinal condition which increased the odds of having a severe pediatric condition by almost three times (aOR: 2.71; 95% CI: 1.3–5.7; p-value = 0.009), however, the association was not significant. Diabetes, on the other hand, increases the odds of having severe pediatric COVID-19 infection by almost seven times (aOR, 6.6; 95% CI: 1.1–39.8; p-value = 0.04) while asthma increased the odds by two-folds (aOR: 2.17; 95% CI: 1.1–4.5; p-value = 0.04).

Hendler, et al.[11] reported that presence of one medical condition increased the odds of having severe pediatric COVID-19 infection (OR: 5.08; 95% CI: 2.78-9.33) compared to those who did not have any medical conditions. Moreover, their research team reported that having two or more medical conditions increased the odds of having severe pediatric COVID-19 infection by almost seven times (OR: 6.60; 95% CI 3.17-13.74) compared to those who did not have any medical conditions. In addition, Kompaniyets, et al.[8] reported that the strongest risk factor as an underlying medical condition for pediatric patients was Type 1 Diabetes in which having the disease increases the risk by two- folds (adjusted Risk Ratio (aRR): 2.38; 95% CI: 2.06-2.76). They also reported that having cardiac and circulator congenital anomalies as a medical condition. These anomalies were reported to increase the risk of having severe pediatric COVID-19 infection by 72% (aRR: 1.72; 95% CI: 1.48-1.99) compared to those patients without these anomalies. And lastly, the study team of Tagarro, et al.[13] reported that having underlying medical conditions increases the odds of having severe pediatric COVID-19 infection, specifically MIS-C, cardiac diseases and asthma. Having pediatric MIS-C increases the odds of having severe pediatric COVID-19 by 14 times (OR: 14.4; 95% CI: 8.9 - 23.8), having cardiac diseases increases the odds by almost five times (OR: 4.8; 95% CI: 1.8 - 13), and having asthma increases the odds by two- folds (OR: 2.5; 95% CI: 1.2 - 5.2) compared to those patients without these medical conditions.

Age

A total of five studies reported age as a risk factor of having severe pediatric COVID- 19 infection.[8,11,12,13,14] The study team of Graff, et al.[14] reported that age of 0–3 months increases the odds of having severe pediatric COVID-19 by almost eight times (aOR: 7.86; 95% CI: 3.0–20.4) compared to those who were 11-15 years old. This only shows that higher age has a protective effect against severe COVID-19 infection. The study of Hendler, et al.[11] reported that children who were less than a month old has higher odds of having severe COVID-19 infection by nine times (aOR: 9.52; 95% CI: 3.01 - 30.08; p-value < 0.001) relative to those who were 2 to 5 years of age. Similarly, the research team of Kompaniyets, et al.[8] reported that premature children who were less than one year old were at risk of having severe COVID-19 infections by 83% (aRR:1.83; 95% CI: 1.47-2.29). On the other hand, Ouldali, et al.[12] reported that children who were ≥10 years of age had higher odds of having severe COVID-19 infection (OR: 3.4; 95% CI: 1.1–10.3). Lastly, Tagarro, et al.[13] reported that children whose age were in months had higher odds of having severe COVID-19 infection by a low percentage of 0.7% (OR: 1.007; 95% CI 1.004 - 1.01) compared to those children whose age were more than 12 months.

Others Factors

Aside from underlying medical conditions and age as independent risk factors associated with

severe COVID-19 infection, other factors were also identified but not across most of the included studies. Elevated C-reactive protein levels were reported to increase the odds of having severe COVID-19 infection by 20%[14] and by six times.[12]

Meta-Analysis

Underlying Medical Condition

One study did not mention underlying medical conditions as significant risk factors.[14] All other the included articles discussed the association between the presence of underlying medical conditions and the severity due to COVID-19. The results are shown in Figure 2. Results showed that the presence of at least one underlying medical condition was significantly associated with severe illness of COVID-19. The presence of underlying medical conditions increased the odds of having severe COVID-19 by four times (OR: 4.51; 95% CI: 2.27 – 8.94). It can also be seen that there was high heterogeneity among the included studies which was significant (p-value <0.00001; I^2 = 94%; Chi^2 = 46.16).

Age

Results showed that age as a risk factor was significantly associated with severe illness of COVID-19 and it increased the odds of having severe COVID-19 by almost three times (OR: 2.77; 95% CI: 1.48 – 5.20). It can also be seen that there was high heterogeneity among the included studies which was significant (p-value <0.00001; I^2 = 91%; Chi^2 = 64.34). (Figure 3)

Publication Bias

As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry. Thus, publication was not assessed because lower than 10 studies were included in the final meta- analysis.

DISCUSSION

There is a global estimate of 2.02 to 4.8% of severe COVID-19 infection among the pediatric population. In the United States alone, it is estimated that around 1.7% of COVID-19 infection came from the pediatric demography.[2,9] There is an observed low prevalence of COVID-19 infection from the pediatric population making it hard to generate strong conclusion regarding the different aspects of COVID virus among this vulnerable population.[9] Therefore, the reported number of pediatric cases is

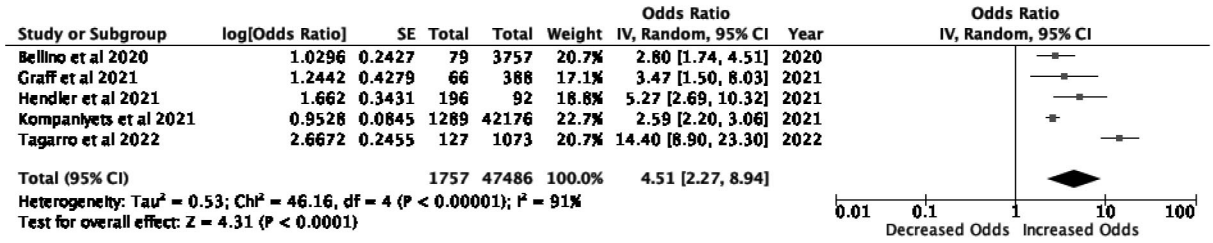

Figure 2. Meta-analysis results of the association between underlying medical condition and severe COVID-19 infection among the pediatric population.

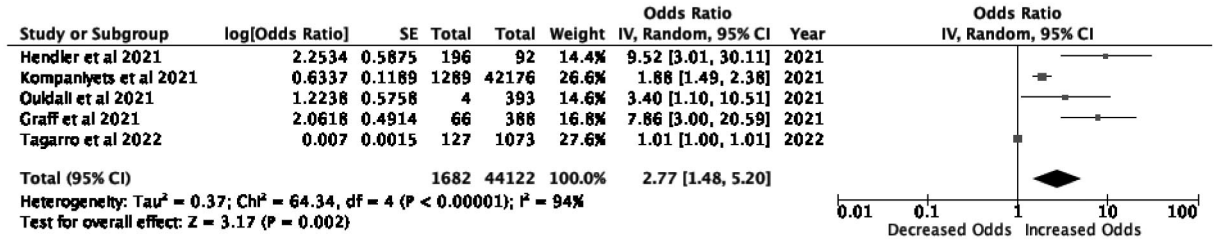

Figure 3. Meta-analysis results of the association between age and severe COVID-19 infection among the pediatric population.

more likely an underestimation of the true number of cases because as observed, most of the cases were either asymptomatic or mild. The clinical course as being continuously reported is generally milder and the clinical outcomes are better in the pediatric population compared with the adult.[3] These observations have underscored the gaps regarding the current information about pediatric COVID-19 and have raised many scientific inquiries about the risk factors associated with COVID-19, especially the severe ones.

This systematic review and meta-analysis showed that underlying medical condition and age are more likely to develop severe illness of COVID-19 among the pediatric population. The coronavirus that causes COVID-19 belongs to the genus β-coronavirus. The S-protein which is the spike protein coats of the coronavirus and plays an important role in the recognition of host cell receptors during the infection progression.[15] The S protein of SARS-CoV can bind to the angiotensin-converting enzyme 2 (ACE2) protein of alveolar epithelial cells and small intestinal epithelial cells, thereby mediating the virus to invade the cells to infect.[5] In addition to directly causing lung tissue damage, SARS-CoV-2 causes a cytokine storm that will further aggravate the inflammatory response. Abnormally elevated cytokines and overactivated immune cells are activated in the lung tissue, thereby causing diffuse damage to pulmonary capillary endothelial cells and alveolar epithelial cells. The accumulation of large amounts of exudate exacerbates the deterioration of lung function caused by airway obstruction, which aggravates ARDS and respiratory–circulatory failure. What is more serious is that it can develop into the uncontrolled systemic inflammatory response (SIRS), an essential factor leading to severe illness or death of COVID-19 patients.[16,17]

Underlying medical conditions such as lung diseases including asthma, diabetes, and cardiovascular disease, may be linked to the pathogenesis of COVID-19. Chronic diseases share several standard features with infectious disorders, such as the proinflammatory state, and the attenuation of the innate immune response.[18] COVID- 19 infection is caused by the binding of the virus surface spike protein to the ACE 2 receptor. ACE 2 is mainly present in the alveolar epithelium. Therefore, COVID-19 patients present with the most typical and significant lung involvement.[19] When a patient has a respiratory disease, such as asthma, the patient's lung function may be more severely damaged by the virus or even develop into ARDS.[20] Diabetes occurs in part because the accumulation of activated innate immune cells in metabolic tissues leads to the release of inflammatory mediators, especially IL-1β and TNFα, which promote systemic insulin resistance and β-cell damage.[21] SARS-CoV-2 may cause chronic inflammation, enhanced blood coagulation activity, and damage to the pancreas due to impaired immune response. This may be one of the potential mechanisms for the association between diabetes and COVID-19.[22] COVID-19 patients with cardiovascular diseases are more likely to have progressively weakened heart function due to other infectious diseases. When infected with SARS-CoV-2, these patients are more likely to have acute cardiovascular events and develop into severe infections. Acute heart injury and heart failure may be the main risk factors leading to death due to COVID-19.[17,23] Therefore, diseases such as respiratory diseases including asthma, diabetes, and cardiovascular disease are risk factors for severe illness of COVID-19 patients, which is consistent with the results of this meta-analysis.

Similar to adult patients, age has always been in the focus of analyses in pediatric population. On one hand, older age has been confirmed to be significantly associated with an increased risk of severity and mortality of COVID-19 in adults.[24] This is consistent between the published studies, and may be an adverse outcome of the decline in the immune function (e.g., T-cell and B-cell function).[6] In children, the majority of studies found that younger children had a worse clinical course. Children admitted to ICU and had severe COVID-19 tended to be older than those who were not[4,25], but children under one month of age were at highest risk.[1,7] The reasons for differences observed in disease severity among various age groups is yet to be determined.

The results of this systematic review and meta-analysis can provide precise and reliable evidence for the development of practice guidelines and management of COVID-19 in children. However, this study also has some limitations. First, we only included data reported in the studies, and did not contact the authors for unreported data. Moreover, geographical bias cannot be ruled out as a considerable part of the studies were conducted in the USA. Racial differences may also be present and may lead to bias in the results, and some studies had a small sample size, which may affect the reliability of the results. Therefore, it is suggested that future:

high-quality research should be carried out controlling for the factors that are most likely to influence the study results; and the definition of outcomes should be unified to enhance the homogeneity across studies.

SUMMARY AND CONCLUSION

The authors found that through this systematic review and meta-analysis, asthma, diabetes, and cardiovascular diseases, and age are risk factors for severe COVID-19 in pediatric patients. Clinicians should pay close attention to these risk factors and provide timely and personalized treatment modalities to reduce the risk of having severe COVID-19.

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