REVIEW

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Comorbidities as risk factors for clinical outcomes in pediatric patients with COVID-19: a comprehensive literature review

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ABSTRACT

Background: The population that in a high risk to have a svere COVID-19 infection is children. The difficulties can influence the risk of controlling their hygiene and be worsened by the immaturity immune system, especially in children with comorbidities. Moreover, this problem needs to be prioritized in children. Despite in worldwide spread of severe COVID-19 infection, there are limited data regarding severe COVID-19 disease in children. Thus, we investigated the effects of comorbidities as risk factors for clinical outcomes in paediatric patients with COVID-19.

Methods: This comprehensive literature review was from the PubMed, Google Scholar, and Science Direct databases through January 2021. The keywords used to obtain the literature include "COVID-19", "coronavirus", " pediatric", "children", "severity", "comorbidity", "mortality", "death," and "intensive". The article with the inclusion criteria was involved. The information about the COVID-19 severity and underlying comorbidities in children were the main criteria that were enrolled.

Results: The severe clinical risk factors in paediatric patients with COVID-19 that are reported most often are chronic lung disease (including asthma) (4312 critical patients), obesity (1007 critical patients), diabetes mellitus (815 patients), cardiovascular disorders (677 patients) and neurological disorders (542), prematurity (183 patients) and immunosuppression conditions including malignancy (143 patients). Other conditions in the form of hematological disorders, airway abnormalities, malnutrition and gastrointestinal disorders can also contribute to the clinical severity of paediatric COVID-19 patients.

Conclusion: Children with underlying diseases such as obesity, chronic lung disease, cardiovascular disease, and neurologic disease had a higher risk of severe COVID-19 than children without comorbidities.

Keywords: Comorbidities, risk factors, COVID-19, paediatric.
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INTRODUCTION

Coronavirus disease-2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and burdening healthcare globally.[1] COVID-19 morbidity and mortality varied significantly across age groups. Early research revealed that SARS-CoV-2 could cause various diseases in adults.[2] In comparison to adults, children and adolescents are less likely to develop serious illness, and critical condition from COVID-19 infection. However, it is still unclear why the epidemiology, clinical features, and outcomes of COVID-19 differ between children and adults.[3] According to previous research, children account for 18.2% of total COVID-19 infection cases in the general population. Most cases developed in mild illness with the main complaint of fever (46%) and cough (37%) while severe cases requiring oxygen supplementation occurred in 3% of cases.[4]

Despite the fact that the number of children infected with COVID-19 is far lower than that of adults, reports of confirmed childhood infection continue to raise public concern.[5] The paediatric population may play a significant role in the spread of SARS-CoV-2.[6] Children continue to be at risk of developing severe disease cases. Comorbidities such as lung disorders and asthma, obesity, diabetes, heart disease, and so on impair immune responses in children, worsening clinical outcomes. Other aggravating factors, such as impaired organ function in children with comorbidities, contribute to this condition. In several cases, the individualistic approach was used, and the administration of drug combinations based on the comorbidities of the infected children was also optimized.[7] In addition, the procurement of the COVID-19 vaccination which is being intensified so that it can be used for children with comorbidities, is also being further investigated.[8] However, the children with certain underlying diseases are still at higher risk of developing COVID-19 disease with a higher degree.[9] This study aimed to identify among children at high risk of severe COVID-19 and their comorbidities.

METHODS

The literature was searched from PubMed, Google Scholar, and Science Direct that

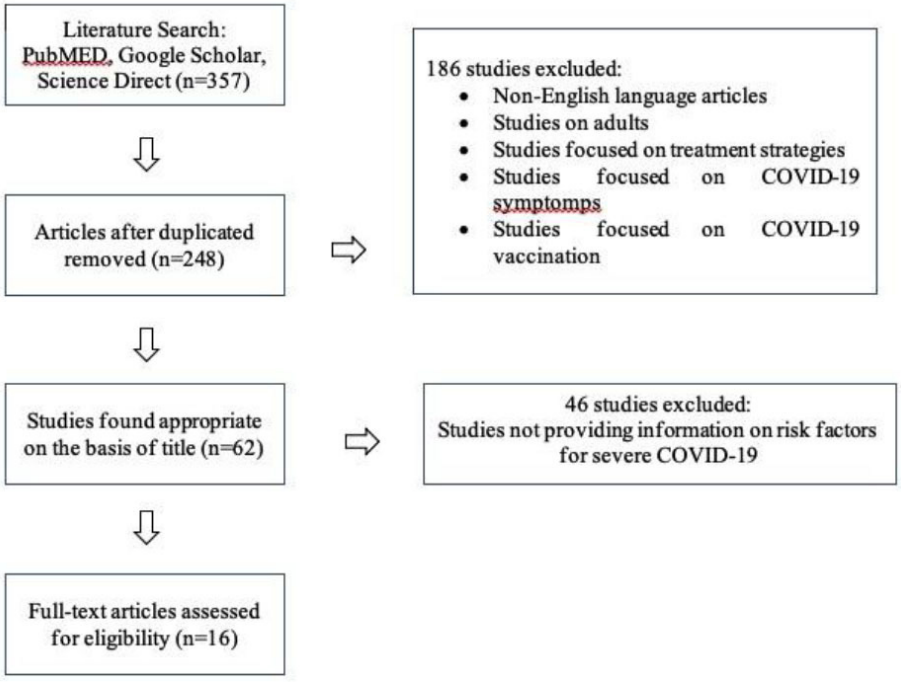

Figure 1. Flow Diagram of The Literature Search.

has been published among January 1st, 2020 until January 1st, 2021. To obtain articles, the entry terms "COVID-19", "coronavirus," "paediatric", "children", "severity", "comorbid", "mortality", "death", and "intensive" were combined. Only English-language articles were considered for inclusion. From the beginning procedure, the articles were screened from the abstract content, after that the full articles were selected by adjusting the content with the topic and variables needed. The inclusion criteria also has been considered, as follows 1) RT-PCR was used to confirm the COVID-19 diagnosis; 2) there were a clear statement of the severity and outcomes of COVID-19 infection among paediatric; 3) the variables identified was obesity, diabetes, chronic lung disease, heart disease, neurologic disease, prematurity in young infants, and immunocompromised status that described clearly in the article (Table 1).

The study authors, study design, year of publication, country of origin, study period, aims, paediatric sample size, the amount of COVID 19 patient, disease severity, number of patients with specific comorbidities, number of patients with ICU admission and/or death were collected for each included literature. The studies defined the extracted comorbidities. Obesity, diabetes, chronic lung disease (including asthma), heart disease (including congenital heart disease), neurologic disease (including epilepsy and neurodevelopmental disorders), prematurity, and immunocompromised status (including primary/secondary immune deficiency and hemato-oncologic disorders) were reclassified. Participants with COVID-19 under the age of 18 were considered paediatric patients. For the children with COVID-19 infection that required supporting tools for breathing in intensive care unit we defined as a severe COVID-19. The samples that has BMI ≥ 95th percentile among children according to the CDC provision was belong into obesity.

RESULTS

Literature Search And Study Characteristics

The initial search yielded 357 articles, of which 62 studies were deemed relevant to the goal of this review after screening their titles. Adult studies were excluded, 11 studies were excluded because data was not detailed, and 5 studies were excluded because they discussed the impact of COVID-19 on patients' comorbidities. As a result, 16 articles were ultimately chosen, as shown in Figure 1, and are discussed here. Table 1 summarizes the characteristics of the included studies and the associated risk factors.

Chronic Lung Diseases and Asthma

Three studies evaluated the chronic lung disease as comorbid of COVID-19 among children. Research conducted by Woodruf, et al. reported that among hospitalized children aged <2, the risk of severe COVID-19 was higher in comorbid chronic lung disease (aRR: 2.2; 95% CI: 1.1–4.3; P5.03).[10] Other studies stated that chronic lung disease lead to 28% of children passed away.[11] Asthma was also comorbid among children that infected corona virus. There were 6 studies discussed about asthma related COVID-19 among children. Asthma was reported to be the second common comorbid after obesity in children.[11] Other evaluation reported that, children with asthma were more likely to receive respiratory support (P =0.02), without a difference in critical care needs (P = 0.26).[12] In addition, research by Graff et al. showed the most commonly identified types of comorbidities in paediatric COVID-19 patients with severe illness were pulmonary diseases (16.7%), including Asthma (73%), sleep apnea (40%) and chronic lung disease (14%). From the research that conveyed that asthma and chronic lung disease as risk factors for severe COVID-19 obtained Odd Ratio (OR) values of 2.85 (1.6–5.2), p= 0.0006 for hospitalization and OR 3.67 (1.8-7.6), p= 0.0004 for breathing aids.[13] Based on the research of Swet et al, respiratory comorbidities were associated with critical care in univariable analysis (P=0.019). Whereas in the sub-analysis for patients without MIS-C, respiratory comorbidities remained significantly associated with critical care compared to patients without respiratory comorbidities (P= 0.004).[14]

Obesity

Obesity is one of the most common comorbidities of COVID-19, with clinically severe in children. In 11 studies critical patients were obese.[10,12–16,11,17–20,9] Research by Graff et al. suggests that obesity and severe obesity are significantly associated with admissions and ventilation

support. The Odds Ratio (OR) for admission in obesity is 2.48 (1.2-5.1), p= 0.01 and OR= 4.8 (1.9-12.1), p= 0.0009 in severe obesity. Ventilation support with OR=2.66 (1.1-6.3), p=0.03 in obesity and OR=3.25 (1.1-9.4), p=0.03 in severe obesity.[13] The research of Woodret al.t al, in a multivariable analysis, showed a higher risk of severe COVID-19 among children with obesity (aRR: 1.2; 95% CI: 1.0–1.4; P=5 .0003.[10] Similar results were shown by Verma's study, where obesity was the most common risk factor for critical care with P-value was 0.02.[12] Research by Kompaniyets et al with a population of inpatients aged 12-18 years showed that the adjusted Risk Ratio (aRR)of obesity-relatedd to severe disease during hospital admission was 1.57(1.32-1.85) (95% CI).[20] Research by Kara et al in 2 patient groups, namely group 1 (mild) and group 2 (moderate, severe, and critical diseases,) showed that the ratio of obese patients was 1.0% in group 1 (mild) and 13.8% in group 2 and significantly higher in group 2 (p <0.001).[11]

Diabetes

Ten studies showed comorbidities of diabetes with severe or critical COVID-19. Graff et al. in a multivariable analysis, found that diabetes (aOR=6,6; P = 0.04), and was a predictor for hospital admissions in paediatric COVID-19 patients.[13] Research by Woodruff et al. showed that children aged 2 to 17 years old were hospitalised, diabetes mellitus (aRR: 1.9; 95% CI: 1.6–2.3) was associated with severe COVID-19.[10] Meanwhile, in the study Kompaniyets et al. showed that chihdren with type 1 diabetic had a high risk of severe COVID-19 (aRR, 2.38; 95% CI, 2.06-2.76).[20] The study of Zachariah et al showed a significant difference between COVID-19 with (22%) or without (2%) diabetes (p= 0.79).[18] Debiasi et al also showed similar results (p= 0.37)[17] and in the study by Verma (4%) diabetic patients were treated in critical care p=0.28.[12]

Heart Diseases

Another comorbiditiy that related with COVID-19 severity was congenital hearth disease. In this article, 15 researches with severe and rcriticalCOVID-19 patients showed that congenital heart disease increased the clinical severity of paediatric COVID-19 patients.[9,15,16,21,10–13,17–20,22,23,24] Research by Kompaniyets et al. showed that the risk of severe COVID-19 was highest among children with congenital and vascular abnormalities (aRR: 1.72; 95% CI = 1.48-1.99). Research by Debiasi et al showed cardiac comorbidities more commerce only hospitalized compared to non-hospital cohorts, but there was no difference in critical care (p=0.18).[17] In addition by Woodruff et al. that cardiovascular disease was associated with an increased risk of severe COVID-19 (aRR: 1.1; 95% CI: 1.1-1.1; P <.0001).[10] In contrast, study the of Zachaet al.et al where heart diseases including restrictive cardiomyopathy and congenital heart disease were found in paediatric COVID-19 patients with severe clinical, but did not differ statistically significantly (p=0.56).[18] Similar results were shown by the research of Graff et al. were OR 1.42, p= 0.60.[13]

Neurologic Diseases

Nine studies on this systematic review showed that neurological disorders and neurodevelopmental conditions such as epilepsy and cerebral palsy became comorbid in patients with severe clinical COVID-19. Graff et al. showed that comorbid neurological diseases (10.6%) convulsive disorders 19 (45%), structural brain defects/malformations 12 (29%), significant Cerebral palsy were found in patients requiring critical care (p= 0.04, OR 2.18) and respiratory support (OR: 2.51, p=0.04).[13] The research of Woodruff et al., in a multivariable analysis, showed a higher risk of severe COVID-19 among children with neurological disorders (aRR: 2.0; 95% CI: 1.5–2.6; P <0.0001). Among the 12 (0.5%) with severe COVID who died during hospitalization, neurological disorders (58%) were the most common underlying conditions found.[10] Research by Kompaniyets et al. showed comorbidities associated with a higher risk of developing inpatient admission were patients with neurodevelopmental disorders (aRR: 1.64; 95%CI, 1.47-1.83); other condition that contribute in the severe COVID-19 infection among children until needed a intensive treatment was epilepsy and seizures (aRR: 1.71; 95% CI, 1.41-2.08).[20] Götzinger et et al. their study in COVID-19 patients with comorbid neurological disorder reported that there were a significant differences in clinically severe patients with neurological comorbidities compared to patients without neurological comorbidities (p= 0.037).[9] Other study has been published the similar research and found that in more than half of the 12 child mortality in hospitals and were associated with an increased risk of severe COVID-19 in several subgroups of the child population.[10]

Prematurity

Four studies related prematurity as a risk factor for COVID-19 in paediatric. Research by Woodruff et et al., showed a higher risk of severe COVID-19 among children with prematurity (aRR: 1.6; 95% CI: 1.3–2.1; P .0001).[10] The research of Kompaniyets et al. Showed results where prematurity is a risk factor for severe COVID-19 disease in children < 2 years old (aRR, 1.83; 95% CI, 1.47-2.29).[20] In contrast, Grafet al.al in their study showed no significant results (OR 1.3 (0.1–12.6), p= 0.84).[13]

Cancer and Immunocompromised Status

Five studies inoculated in this systematic review showed cancer patients risk of hospital admission and COVID-19-related critical care admissions. The study of Götzinger et al showed the presence of significant vs non-ICU treatment in cancer patients (p= 0.047, OR 2.7).[9] Research by Verma et al showed cancer patients underwent significantly higher critical care (5 (22) vs. 4 (7) p=0.10).[12] DeBiasi shows the significance of admission in cancer patients (p=0.013) for admissions, but for critical care it is not significant.[17] The existence of a significantly underlying oncology diagnosis is more common in pediatric COVID-19 patients who are hospitalized compared to those who do not require hospitalization, but there is no significant difference in critical care.[17] These results are in line with a number of previous reports where some children with underlying or immunosuppressive malignancies tolerate SARS-CoV-2 infection very well.[25]

For immunocompromised

patients, there were 8 studies involving immunocompromised paediatric COVID-19 patients. In the study Graff et al showed immunocompromised is a predictor for hospital admission (P = 0.004), but not for ICU treatment (p = 0.34).[13] Meanwhile, the research of Zachariah et al showed no significant differences in immunocompromised patients who experienced severe disease compared to without immunocompromised (p= 0.66). Patients with immunosuppression mostly remain stable during treatment.[18] Swann et al., research shows no link between previous immunosuppressant use and critical care.[14] In research Woodruff et al. showed that immunocompromised conditions and blood disorders, were not associated with an increased risk of severe COVID-19.[10] Kara Immunodeficiency and the use of immunosuppressive drugs were not associated with severe clinical covid (p>0.05).[11]

DISCUSSION

There were several comorbid have been identified related to the COVID-19 such as chronic lung disease, asthma, obesity, diabetes, heart disease, neurological disease, prematurity, cancer and immunocompromised. Those comorbid leads to a certain condition, such as a patient with asthma or chronic lung disease were more likely to need a rescue breathing apparatus rather than other comorbid, and obesity become the most comorbid among children with COVID-19.[10,12–16,11,17–20]

Children with asthma are 4.1 times more likely to develop moderate-severe COVID-19 infection.[11] Severe symptoms can affect children with COVID-19 and coexisting respiratory illnesses. Meanwhile, her severe COVID-19-infected child's asthma remains controversial. In contrast, the results of this systematic review found that asthma was associated with the risk or severity of her COVID-19 in children. Only two reports describe bronchial asthma or recurrent wheeze as risk factors for COVID-19.[26] It might due to the double burden of respirator tract due to COVID-19 infection and history of respiratory tract disease in the patient. The controversy might due to the plasmin mechanism that increase the ability of virus to bind with ACE2 receptors. In the other hand, patient with COPD had higher activity of plasminogen activator inhibitor-I (PAI-I) that inhibit plasmin activation. Thus, it will reduced the affinity of receptor to bind with the virus. Meanwhile, further investigation is needed to test the validity of this theory.[27]

Among the children with COVID-19 infection closely related with the multisystem inflammatory syndrome in children (MIS-C), research by DeBiasi et al, in obese patients undergoing critical care compared to non-critical treatment showed statistically insignificant results (p= 0.21).[17] Obesity results in more than double the likelihood of hospital admissions related to COVID-19 in children, where severe obesity increases almost 5 times this possibility. In addition obesity is associated with the need for critical care, respiratory assistance, associated with the use of mechanical ventilation in children 2 years or older.[14] It might happen due to obesity can induces the chronic inflammation. Therefore, obese people with reduced dyspnea may delay treatment or develop more serious illness.[11]

Diabetes is another possible comorbidity in children infected with COVID-19. It is due to changes in immunity in diabetic patients. Studies performed in humans and his type 2 diabetic laboratory mice show a shift in the immune profile from regulatory T cells to proinflammatory CD4 + Th1 and Th17 T cells. This mechanism and its effects are thought to make diabetics susceptible to infections. In addition, diabetes is also known as a maladaptive inflammatory response that exacerbates the course of viral infections and leads to possible bacterial complications.[27] In diabetic conditions, high blood glucose levels increase direct replication of SARS-CoV-2 in monocytes, and glycolysis supports SARS-CoV-2 replication through the production of mitochondrial reactive oxygen species (ROS). Therefore, high blood sugar may favor viral growth. Therefore, it is an independent predictor of morbidity and mortality in SARS patients. Patients with diabetes tend to fall into the category of more severe SARS-CoV-2 infections than those without, and poor glycemic control leads to increased need for medication and hospitalization, and higher mortality. is expected to become.[28]

Paediatric patients with heart defects are more likely to experience inpatient admission than paediatric COVID-19 patients without comorbid heart defects.[17] Research by Swann et al in patients without MIS-C, cardiac comorbidities remain significantly associated with admission to critical care.[14] The results of this review are consistent with other studies. In her case series of nine pediatric patients with both COVID-19 and CAD, two patients died. One of them, she is a 14-year-old girl with severe aortic stenosis, and one of her has CHD, hypoplastic left heart syndrome (HLHS), and a 10-month-old male. It is a combined form of patent ductus arteriosus (PDA).[29] Approximately 2.5% to 16% of adult COVID-19 patients have cardiovascular comorbidities. RAS is involved in the regulation of blood pressure and cardiovascular activity. Angiotensin 2 has properties such as vasoconstrictor and pro-inflammatory effects, whereas angiotensins 1-7 exhibit beneficial cardiovascular properties such as "antithrombotic and antiarrhythmic". A balance between ACE1 and ACE2 is essential for maintaining cardiovascular health. Any comorbidity with cardiovascular disease should be carefully monitored.[27] It is also important to note that many of the symptoms of COVID-19 can mimic the symptoms of a worsening heart condition in the CHD population. Symptoms such as shortness of breath, palpitations and fever are commonly seen in endocarditis which is a major concern in patients with CHD. The same symptoms can also be seen in decompensated heart failure due to viral diseases and these considerations should be remembered. during the COVID-19 pandemic.[30]

Among the neurological disorders found in severe COVID-19 patients in children is Cerebral Palsy (CP). Regardless of the severity of their musculoskeletal symptoms, CP patients have impaired respiratory function due to impaired diaphragmatic hypertension that persists into adulthood. There are fewer diaphragm motor neurons in animal models of CP, which consist of the motor units of the diaphragm muscle, are prone to fatigue, and are required for airway clearance such

as coughing and sneezing. In addition, neuromuscular transmission is disrupted in these more fatigued motor units, further limiting diaphragm muscle movement.[31]

Prematurity anomalies are the most frequent and associated with the highest risk of COVID-19 disease among patients under 2 years of age. Premature is a risk factor for adverse long-term sequelae, including those affecting the system.[20] In patients without MIS-C, prematurity is also significantly associated with critical care admissions.[14] Premature birth can have lifelong adverse effects on various physiological systems, but can primarily affect the respiratory system. Accumulating new evidence suggests that respiratory drive/control can be severely impaired in conditions of hypoxemia. well known to decrease. Decreased ventilatory response to hypoxia can exacerbate systemic hypoxemia. This can be a problem in clinical populations suffering from hypoxemia. Accumulating other evidence suggests that premature infants may be associated with higher ACE2 activity and/or expression.[32] Thus, for several condition in children with COVID-19 infection, any comorbidity could make the condition worse.

CONCLUSION

Although children are less susceptible to COVID-19 and their clinical presentation is often different from that of adults, underlying chronic conditions may predispose to severe illness in both age groups. Her COVID-19 as a child presents with unique symptoms and risk factors of different severity than adult patients. In some reports, the most commonly reported serious clinical risk factors in pediatric patients with COVID-19 are asthma, obesity, diabetes mellitus, chronic lung disease such as cardiovascular disease, as well as neurological disease, immaturity It is an immunosuppressive disease that includes infantile and malignant tumors. Other conditions such as blood disorders, airway abnormalities, malnutrition, and gastrointestinal disturbances may also contribute to the clinical severity of pediatric COVID-19 patients. It is important to further investigate potential risk factors for serious illness in children and uncover underlying mechanisms to improve management of children with COVID-19 and support the development of new treatments.

DISCLOSURE

Conflict Of Interest

None.

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Author Contribution

All of the author are participated in selecting the topic until manuscript preparation for the publication

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Table 1. **Studies on risk factors of severe COVID-19 in children.**

Number	First Author and Year	Region	Types of Studies	Number of Children	Underlying Diseases	Clinical Outcomes	Journal Title	Conclusion
1	Graff et al., 2021	United States	Cohort Retrospective	454	Gastrointestinal disease, asthma, diabetes, obesity	Hospital admission, needed respiratory support, needed critical care	*Risk Factors for Severe COVID-19 in Children*	comorbidities [including immunocompromised disease (aOR, 3,5; P = 0.004), gastrointestinal conditions (aOR, 2.7; P = 0.009), diabetes (aOR, 6.6; P = 0.04), asthma (aOR, 2.2; P = 0.04)], and the specific symptoms on the presentation are predictors for admission. Ages 0–3 months or >20 years, asthma, gastrointestinal conditions, and similar symptoms in presentations are also predictors for respiratory support. Increased C-reactive proteins were associated with the need for critical care with a median of 17.7 mg/dL (IQR, 5.3-22.9) versus 1.95 mg/dL (IQR, 0.7-5.5) among patients requiring critical versus non-critical care (OR, 1.2; P = 0.02)
2	Zachariah et al., 2020	United States	Cohort Retrospective	50	Obesity	Needed respiratory support	*Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York*	Obesity (11 [22%]) is the most common comorbidity associated with the severity of the disease. Young and immunocompromised age does not increase the risk of severe disease.
3	DeBiasi et al., 2020	United States	Cohort Retrospective	177	Neurologic disease, Heart disease, Hematological disease, and cancer	Hospital admission	*Severe Coronavirus Disease-2019 in Children and Young Adults in the Washington, DC, Metropolitan Region*	neurological disorders are more common in hospitalized cohorts (8/44; 19%; P <,001) compared to non-hospitalized (3/133; 2%; P <.001). Cardiac comorbidities (P = 0.004), hematology (P = 0.004), and oncological (P = 0.013) are more common in inpatients compared to non-hospitalized cohorts. Although asthma is the most common underlying condition overall, it is no more common in hospitalized cohorts (7/44; 16%) compared to non-hospitalized cohorts (28/133; 21%; P = 0.46) and in critically ill (2/11; 22%) compared to noncritical cohorts (5/35; 14%; P = .62).

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4	Swann et al., 2020	United States	Cohort Retrospective	650	Prematurity, respiratory disease, cardiology, obesity	Critical care	*Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study*	The comorbidities most commonly associated with critical care on univariable analysis are prematurity (50% (15/30) of critical care v 18% (30/165) standard care; P = 0.001), respiratory comorbidity (10% (12/115) v 4% (21/491); P=0.019), comorbidities of the heart (13/115 (11%) v 25/493 (5%); P=0.018), and obesity (6% (7/115) v 2% (10/487); P=0.028) MIS-C was associated with obesity (10% (5/51) v 2% (6/385); P=0.005) but not with other comorbidities In patients without MIS-C, respiratory and cardiac prematurity and comorbidities remained significantly associated with critical care alongside neurological comorbidities (22% (17/77) v 10% (46/481); P = 0.003), neurodisability (13 % (9/71) v 5% (22/463); P=0.014), and gastrointestinal comorbidities (9% (7/77) v 2% (11/480); P=0.007)
5	Woodruff et al., 2022	United States	Cohort Retrospective	2293	Chronic pulmonary diseases, neurology, cardiology, prematurity, airway abnormalities	Death in hospital, respiratory assistance Death in the hospital, respiratory assistance, critical carean, critical care	*Risk Factors for Severe COVID-19 in Children*	Among hospitalized children aged <2, the risk of severe COVID-19 was higher in comorbid chronic lung disease (aRR: 2.2; 95% CI: 1.1–4.3; P5.03), neurological disorders (aRR: 2.0; 95% CI: 1.5 –2.6; P < .0001), cardiovascular disease (aRR: 1.7; 95% CI: 1.2–2.3; P 5 .004), prematurity (aRR: 1.6; 95% CI: 1.3–2.1; P ≤ .0001) or airway abnormalities (aRR: 1.6; 95% CI: 1.1-2.2; P 5 .02) Among hospitalized children aged 2 to 17, the risk of severe COVID-19 was higher among children with feeding tube dependencies (aRR: 2.0; 95% CI: 1.5–2.5; P <.0001), diabetes mellitus (aRR: 1.9; 95% CI: 1.6–2.3; P < .0001) and obesity (aRR: 1.2; 95% CI: 1.0–1.4; P 5 .0003

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6	Kompaniyets et al., 2021	United States	*Cross-sectional*	43465	Diabetes, obesity, neurological, cardiological, prematurity,	Hospital admission, respiratory support, critical care, death in the hospital	*Underlying medical conditions associated with severe COVID-19 illness among children*	Type 1 diabetes, obesity, and congenital and vascular heart defects are the strongest risk factors for hospitalization, with adjusted risk ratios (aRRs) of 4.60 (95% CI, 3.91-5.42), 3.07 (95% CI, 2.66-3.54), and 2.12 (95% CI, 1.83-2.45). In children aged ≤1 years and 2 to 5 years, heart and congenital anomalies are common (306 of 7904 [3.9%]; 84 of 5034 [1.7%]) and are associated with a higher risk of severe disease while hospitalized (aRR, 1.89; 95% CI, 1.48-2.41; aRR, 1.50; 95%CI, 1.05-2.16) Among inpatients aged 12 to 18 years, risk factors for severe COVID-19 disease are type 1 diabetes (aRR, 2.47; 95% CI, 2.12-2.87), epilepsy and/or seizures (aRR, 1.89; 95% CI, 1.53 -2.34), obesity (aRR, 1.57; 95% CI, 1.32-1.85), essential hypertension (aRR, 1.23; 95% CI, 1.01-1.51), and asthma (aRR, 1.17; 95% CI, 1.02-1.33)
7	Götzinger et al., 2020	25 Europe Country	Cohort retrospective	582	Chronic, neurological, cardiological, malignant pulmonary diseases	Critical care	*COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study*	Risk factors for ICU admission in multivariable analysis were age younger than 1 month (OR 5.06.95% CI 1.72–14.87; p=0.0035), male sex (2·12, 1· 06–4·21; p=0.033), comorbid medical conditions (3·27, 1·67–6·42; p=0.0015) factors associated with the initiation of drug treatment with antiviral or immunomodulatory activity consist of pre-existing malignancies (OR 6.3.95% CI 2.8–14.2), heart disease (4,2, 1.8-10.0) , or respiratory diseases (6·5, 3·0–14·2); immunosuppressive therapy (6·5, 3·0–14·2) or chemotherapy (6·1, 2·6–14·1)
8	Fernandes et al., 2021	United States	Cohort retrospective	281	Obesity	Critical care, respiratory support	*Severe Acute Respiratory Syndrome Coronavirus 2 Clinical Syndromes and Predictors of Disease Severity in Hospitalized Children and Youth*	In multivariable analysis, obesity (OR 3.39.95% CI 1.26-9.10, P = 0.02) and hypoxia during admission (OR 4.01; 95% CI 1.14-14.15; P = 0.03) is a predictor of severe respiratory disease

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9	Verma et al., 2021	United States	Cohort retrospective	82	Obesity, asthma	Critical care, respiratory support	*Characteristics of hospitalized children with SARS-CoV-2 in the New York City metropolitan area*	Children with comorbidities are more likely to require critical care (70% vs 37%, P 5 0.008), with obesity as the most common risk factor for critical care (63% vs 28%, P 5.02). Children with asthma are more likely to receive respiratory support (28% vs 8%, P 5 .02), without a difference in critical care needs (P 5 .26)
10	Kara et al., 2021	Turki	*Cross-sectional*	292	Obesity, asthma	Critical care, respiratory support	*Evaluation of predictors of severe-moderate COVID-19 infections at children: A review of 292 children*	The most common associated diseases are obesity (5.1%) and bronchial asthma (4.1%). Clinically severe associated with comorbidities, especially obesity and bronchial asthma (for patients with OR obesity [OR] 9.1, CI95% [CI] 1.92-43.28, p = 0.005 and for patients with bronchial asthma OR 4.1.95% CI 1.04-16.80, p = 0.044)
11	Harman et al., 2020	United Kingdom	Cohort retrospective	5	Cerebral palsy, prematurity, *Wilson disease*, and *dilated cardiomyopathy*	Hospital admission, respiratory support, mechanical ventilation, antibiotics, antiviral therapy, liver transplantation	*Ethnicity and COVID-19 in children with comorbidities*	Pre-existing comorbidities include cerebral palsy, prematurity, Wilson's disease, and dilated cardiomyopathy
12	Sun et al., 2020	China	Cohort retrospective	8	Leukemiia, acute limfoblastic, faringitis	Respiratory support, mechanical ventilation, antiviral treatment, symptomatic treatment	*Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study*	Acute lymphocytic comorbid leukemia, undergoing blood transfusions, patients with serious complications (septic shock, DIC, MODS) are shown by patients with severe clinical
13	Zheng et al., 2020	China	Cohort retrospective	25	Congenital heart disease, malnutrition, hereditary metabolic diseases	Hospital admissions, antiviral therapy, mechanical ventilation, systematic corticosteroids, and intravenous immunoglobulins	*Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China*	Children less than 3 years of age account for the majority of cases and critical cases. Critical illness-related comorbidities are Congenital heart disease and malnutrition
14	González-Dambrauskas et al., 2020	Chile, Colombia, Italia, Spain, and United States	Cohort retrospective	17	Respiration, cardiovascular, cancer and/or immunosuppression diseases, obesity	respiratory support, antiviral agents, vasoactive infusions	*Pediatric Critical Care and COVID-19*	Reported risk factors for severe illness include age, cardiorespiratory comorbidities, and obesity

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15	Leeb et al., 2020	United States	Cohort retrospective	277285	Chronic lung disease (including asthma), disability (including neurological or neurodevelopmental disorders, intellectual or physical, and visual or hearing impairments) immunosuppressive conditions of diabetes cardiovascular disease and severe obesity	Hospital admission, ICU admission	*COVID-19 Trends Among School-Aged Children — United States, March 1–September 19, 2020*	At least one comorbid condition was reported for 16% of school-age children hospitalized with COVID-19, 27% of those admitted to the ICU, and 28% of patients who died. comorbid chronic lung diseases, including asthma, were most commonly reported (55%), followed by disability (9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%).
16	Shekerdemian et al., 2020	United States	*Cross-sectional* .	48	Complex diagnosis, immunosuppression/ malignancy, Obesity, Diabetes, Seizures 6%, Congenital heart disease, Sickle cell disease, Chronic lung disease, Other congenital malformations	Respiratory support, mechanical ventilation, endotracheal ventilation or tracheostomy, additional ventilation interventions or extracorporeal therapy	*Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units*	Prehospital comorbidities are an important factor in severe COVID-19 in children. 50% had 1 comorbidity, 17% with 2, and 19% with 3 or more significant comorbidities obesity is an important comorbidity (20.5% of patients aged ≥6 years are obese)