REVIEW ARTICLE

WHO IS AT A HIGHER RISK? A BRIEF REVIEW OF RECENT EVIDENCE ON COMORBIDITIES IN CHILDREN INFECTED WITH COVID-19

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Background: COVID-19 has affected both adults and children with variable presentations and disease severity. Children can present with mild symptoms of fever, cough and shortness of breath, and rapidly progress to severe pneumonia, requiring mechanical ventilation. This population includes children who are younger than one year and older adolescents who have an underlying comorbidity-specifically immunosuppression or prior cardio-respiratory infections. In this review, we discuss the determinants of severe disease among the paediatric patients- primarily asthma, immune-status, obesity and multisystem inflammatory syndrome in children (MIS-C). Asthma and underlying lung pathologies can be a strong predictor (~20% prevalence) for development of severe COVID-19 infection, irrespective of age. However, as compared to asthma, a higher mortality rate was reported in immune-compromised patients. With a weakened immune system, immunosuppressed individuals were 1.55 times and immunocompromised patients 3.29 times more vulnerable to developing severer COVID-19 disease. Similarly, evidence suggests that a BMI of greater than 35 kg/m^2 renders individuals more susceptible to developing COVID-19-related complications. This observation is based on the negative impacts obesity has on pulmonary functions and in downplaying the immune system. Furthermore, a possible association of COVID-19 and MIS-C has been reported by multiple studies across the globe but it needs further studies to strengthen its stance due to the scarcity of data when compared with the other determinants discussed in this article. Authors recommend researchers directing attention on synthesizing the evolving evidence to fill the knowledge void in the paediatric population, which will better enable paediatricians to make informed decisions.

Keywords: COVID-19; Children; Asthma; Immunosuppression; Obesity; Comorbidities

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INTRODUCTION

The novel coronavirus outbreak erupted in the Wuhan City of China in December 2019, and presented as pneumonia of unknown aetiology. What seemed to start-off as a localized infection, soon developed into a global crisis and was declared as a Public Health Emergency of International Concern (PHEIC) on 30th January 2020 and given the status of a pandemic by The World Health Organization (WHO) in March 2020. At the time of writing, 24th Sept 2020, Worldometer reports >31.7 million cases and over 950,000 deaths worldwide (case fatality ratio: 3.06%).[1]

Regional distribution of COVID-19 shows a higher infectious burden in the West as compared to the East. The Americas reported approximately half (49.9%) of the globally reported cases, followed by the South-east Asia (20.2%), Europe (17.1%), Eastern Mediterranean (7.19%), and declining towards the Western Pacific region which reported 1.9% of the total infections.[2]

The pandemic has affected both adults and children with variable presentations and disease severity. This review is the first comprehensive narrative review on severe COVID-19 infections in the paediatric population with focus on determinants of severe disease among children.

Epidemiology & severity of COVID-19 in children

The incidence of COVID-19 in children aged less than nineteen years has varied from one to five percent, and is more prevalent in the younger children as compared to the older population.[3–6] Children can present with mild symptoms of fever, cough and shortness of breath, and rapidly progress to severe pneumonia- requiring mechanical ventilation.[4,7,8]

Albeit having a lower incidence than adults, children can develop acute respiratory distress syndrome (ARDS) and require hospital care for intensive care monitoring.[9] These include children who are younger than one year and older adolescents who have an underlying comorbidity-primarily immunosuppression or prior cardio-respiratory infections.[4,10]

A major determinant of severe COVID-19 infection in the paediatric population is the presentation of Multisystem Inflammatory Syndrome in Children (MIS-C). Patients who develop this syndrome are more predisposed to a severer inflammatory process, cardiac abnormalities and ICU admissions.[11] Table-1[3,4,7,10,12–17] summarizes important studies which address cases of severe COVID-19 in children, and includes co-morbidities (asthma, immunosuppression, obesity and MIS-C) which can determine the severity of the disease. The prevalence of the abovementioned determinants can be visualized in Figure-1.

Table-1: Summary of Published Reports on Severe Cases of Paediatric COVID-19

Authors	Number of COVID-19 Positive Children (n)	Number of Severe Cases Reported (n)	Findings
Chao *et al*.[12]	46	13	• Obesity and Asthma was highly prevalent in PICU patients • These patients had higher levels of inflammatory markers • Majority developed sepsis, shock, and acute respiratory distress syndrome (ARDS) • One mortality reported in child with underlying malignancy
Shekerdemian *et al*.[10]	48	19	• Two mortalities reported due to multisystem-organ failure (MOF)
Dong *et al*.[3]	728	21	• One mortality reported due to concurrent infection with Respiratory Syncytial Virus, resulting in ARDS and MOF
CDC and collaborators[4]	2572	3	• Most prevalent comorbidities reported were CLuD (1.6%), Cardiovascular Disease (0.97%), and Immunosuppression (0.39%)
Lu *et al*.[7]	171	3	• Three separate patients reported with leukaemia, lymphopenia, and hydronephrosis • One mortality reported due to MOF
Riphagen *et al*.[13]	8	1	• Hyper-inflammatory shock observed in all eight patients • One mortality reported due to cerebrovascular infarct
Sun *et al*.[14]	8	8	• Four separate patients developed septic shock and multi-organ dysfunction syndrome, hypoglobulinemia and gastroenteritis.
Tagarro *et al*.[15]	41	4	• Two patients had a concurrent Influenza B viral infection • One child reported recurrent wheezing
Gotzinger et *al*.[16]	582	48	• Most prevalent co-morbidities reported were CLuD (4.98%), underlying malignancy (4.64%), neurological disorders (4.47%), congenital heart disease (4.29%), chromosomal abnormalities (1.72%) and renal pathologies in 1.54% of the patient population
See *et al*.[17]	4	1	• One patient reported with asthma

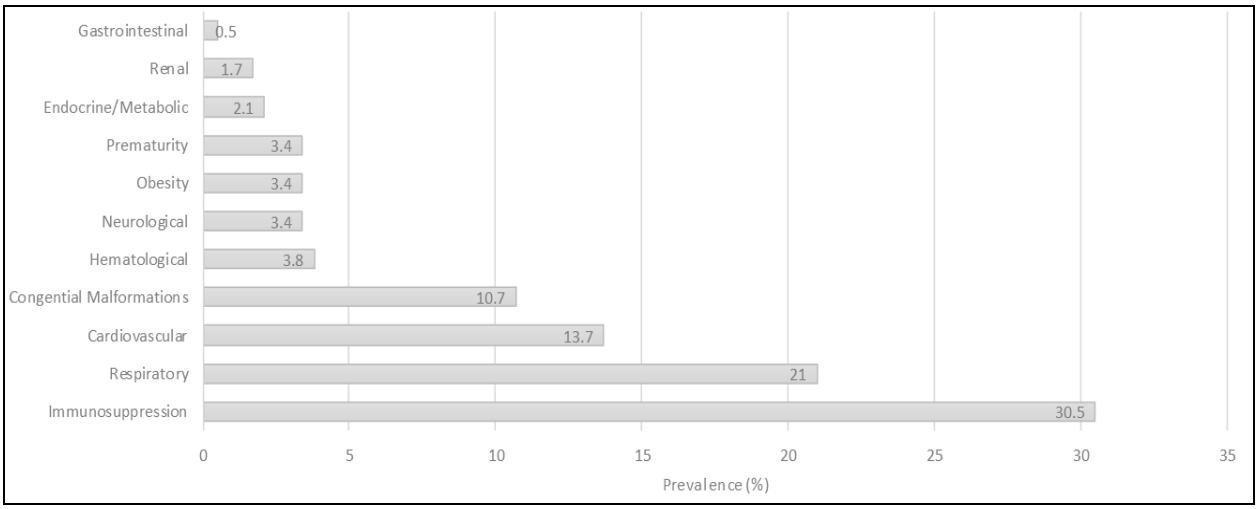

Figure-1: Prevalence of Reported Co-Morbidities in Severe COVID-19 Infection

Asthma & Lung Pathologies

Exploring Prevalence: Asthma and underlying lung pathologies can be a strong predictor for development of severe COVID-19 infection, irrespective of age. Table-2[4,8,18–20] summarizes the prevalence of such, as reported by surveillance agencies, e.g. WHO and CDC and published research.

A certain population of asthmatics may be considered at a higher risk for developing worse outcomes of COVID-19.[21] According to Asthma UK[22], these include people who are taking extra controller medicines as well as a preventer inhaler and continuous or frequent oral steroids; while British Thoracic Society[23] believes that patients taking biologic therapies for severe asthma are considered at very high risk.

The management of paediatric asthma during COVID-19 remained unchanged. Inhaled corticosteroid (IC) were continued in patients who required it, per their physician's assessment.[24] However, preference was given to inhalers, over nebulizers when administering IC's to decrease curb the spread of COVID-19.[25] Generally, patients with underlying lung pathology and mild symptoms were quarantined in non-hospital settings without any anti-viral therapy. Even asthmatic children who required hospitalization, did not warrant intensive care monitoring. In either settings, the prognosis remained encouraging- with patients fully recovering, with a slight few requiring an extended hospital stay for further monitoring.[12,17,25]

Table-2: Prevalence of Lung Disease in COVID-19 Cases

Reporting Institute/ Author	Population	Month (Year 2020)+	Lung Disease Prevalence
Williamson *et al*.[18] (NHS)	Adults MA: 63.8 years	January	RDeA*: 4.1% A (+) OC**: 1.7% A (-) OC***: 14.2%
CDC[4]	Children (<18y/o) MeA: 11 years 15–17y/o: 1/3rd cases 10–14 y/o: 27%	April	Asthma: 11.6%
Stokes *et al*.[19]	Children MA: 11.9 years	May	CLuD ♦: 17.5% CLuD <9y/o: 12.5%
WHO[20]	Mixed MeA: 55 years	May	CLuD: 23%
Hoang *et al*.[8]	Children MA: 8.9 years	Jun	CLuD: 21%

+ Arranged according to month of data release, *Respiratory Disease except Asthma, **Asthma *with* use of oral corticosteroids, *** Asthma *without* the use of oral corticosteroids, ♦Chronic Lung Disease, MA= Mean Age, MeA= Median Age

Cancer & Immune Suppression

Immunosuppression, secondary to transplant surgery, immunosuppressive medications, HIV, and cancer is a major factor in determining the prognosis of patients suffering from COVID-19 infection.[26,27] Table-3[8,19,20,28] summarizes the prevalence of such, as reported by surveillance agencies, e.g. WHO and CDC and published research.

In terms of management of immunocompromised and immune-suppressed patients, treatment regimens were modified to ensure a greater chance of fighting off the infection [29]. This included a withdrawal of drugs such as anti-metabolites and tacrolimus.[30] When considering chemotherapy in children, clinicians can consider reducing the intensity of the therapy with a prolongation between successive cycles. Since radiotherapy has lower potential of immune modulation, the therapy can continue per schedule.[31] When dealing with blood cancers such as acute lymphoblastic leukaemia, Sullivan and colleagues recommend COVID-19 positive children with hyperleukocytosis be shifted to treatment with supportive care and steroid prophase and resumption of disease-oriented therapy once RT-PCR is negative.[31,32]

The outcomes in COVID-19 children with immunosuppression has varied from full recovery to virus-related death. When comparing the severity of infection in both the cohorts, i.e., immunosuppressed vs immunocompetent, a higher prevalence of adverse outcomes were noted in the former population[30,33,34] ~mortality rate estimated at 28% at three weeks[35]. As compared to asthma, a higher mortality rate was reported in immune-compromised patients.[30]

To monitor the status of COVID-19 infection in immunosuppressed individuals, laboratory investigations such as C Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and plasma viscosity have shown to play a pivotal role. These reports can be correlated with patient's clinical status, D-Dimer results, lactate dehydrogenase and procalcitonin levels to modify treatment and predict outcomes.[36]

Table-3: Prevalence of Immunosuppression in COVID-19 Cases

Reporting Institute/ Author	Population	Month (Year 2020)+	Immunosuppression & Malignancy Prevalence
Gao *et al*.[28]	Mixed MA: 24.3 years	May	ImmuCo*: ↑ x3.29 ImmuSup**: ↑ x1.55
Stokes *et al*.[19]	Children MA: 11.9 years	May	ImmuCo: 5.3% ImmuCo <9y/o: 2.1%
WHO (Europe)[20]	Mixed MeA: 55 years	May	Malignancy: 25% ImmuCo: 3%
Hoang *et al*.[8]	Children MA: 8.9 years	Jun	ImmuSup: 30.5%

+ Arranged according to month of data release, *Immuno-compromised, **Immuno-suppressed, MA= Mean Age, MeA= Median Age

Obesity & Body Mass Index

WHO describes being overweight as having a BMI of greater than 25 kilograms/meter squared (kg/m^2).[37] Where obesity has been associated with non-communicable diseases such as cardiovascular thrombosis- secondary to atherosclerosis and adult-onset diabetes mellitus secondary to insulin resistance, it has also shown to result in adverse outcomes with COVID-19. Simonnet and colleagues identified patients with a BMI of greater than 35 kg/m^2, as being at a higher risk for developing severe COVID-19 infection- requiring intensive care monitoring and mechanical ventilation [38]. Other studies suggest otherwise. Table-4[10,12,39] summarizes the prevalence of obesity and COVID-19, as reported by published research from all over the world.

Possible explanations for the associations between obesity and severity of COVID-19 infection are as shown below:

1) Obesity has a negative impact on pulmonary functions in terms of decreased functional residual capacity and expiratory reserve volume.[40]
2) Abdominal obesity further decreases diaphragmatic excursion.[40]
3) Obesity has also been linked to increased production of inflammatory cytokines thereby adversely affecting the overall pulmonary function.[41]
4) Higher blood glucose levels can downplay the immune system.[42]

Table-4: Prevalence of Obesity and BMI in COVID-19 Cases

Reporting Institute/ Author	Population	Month (Year 2020)+	Obesity and BMI Prevalence
Chao *et al*.[12]	Children MeA: 13.1 years	May	Obesity: 30.43% ICU Support: 6.5%
Shekerdemian *et al*.[10]	Children MeA: 13 years	May	Obesity: 14.58% Mortality: 4.17%
Zachariah *et al*.[39]	Children 21 years and younger MeA/MA: NS	Jun	Obese: 22% OW*(of those 22): 72.73% MV**(of those 22): 54.54%

+ Arranged according to month of data release, *Overweight, **Mechanical Ventilation, MeA= Median Age, MA= Mean Age, NS= Not Specified

Multisystem inflammatory syndrome in children

COVID-19 has been suggested to have an association with Multi-System Inflammatory Syndrome in Children (MIS-C), which might lead to symptoms of shock and multi-organ failure. First cases of MIS-C were reported in the United Kingdom where children infected with COVID-19 presented with an inflammatory syndrome with clinical features similar to Kawasaki vasculitis.[43] With the increase in number of cases in United States, children started presenting with similar symptoms-suggesting correlations between MIS-C and COVID-19[43]; especially with raised inflammatory markers, e.g. Troponin T, NT-pro BNP, D-Dimer, and serum IL-6[44]. Studies, which have reported these observations, can be visualized in Table-5.[45,46]

Patients with MIS-C have reported ICU admission requiring invasive mechanical ventilation. Some of the debilitating sequelae include multi-organ failure, coronary artery aneurysm and cardiac dysfunction. To date, there are no definitive established protocols or published guidelines for the management of MIS-C associated with COVID-19. Similarly, a recent case series from Lahore, Pakistan comprising of eight paediatric patients reported elevated inflammatory markers; C-reactive protein, ferritin, and D-dimers, with a positive SARS-CoV-2 antibodies test in all patients and only one death was reported.[46]

Table-5: MIS-C in COVID-19 Cases

Author	Population	Location	Important Findings
Dufort *et al*.[45]	Children 21 years and younger MA: 8.8 years	New York, USA	• A total of 95 cases reported showing correlation of COVID-19 and MIS-C • Children presented with fever, tachycardia, rash, mucocutaneous changes, and gastrointestinal disturbances. • 10 patients received mechanical ventilation • Mortality: 2.10%
Toubiana *et al*.[46]	Children 18 years and younger MeA:7.9 years	Paris, France	• A total of 21 cases reported showing correlation of COVID-19 and MIS-C • 17 (80.95%) patients were admitted to PICU* • 16 (76.20%) patients developed myocarditis
*Paediatric Intensive Care Unit, MeA= Median Age, MA= Mean Age			

CONCLUSION

Our review highlights major themes which can determine the prognosis of COVID-19 in children. Factors such as underlying chronic lung disease, specifically asthma and immunosuppressive states, e.g. malignancy and organ transplantation, obesity and MIS-C render the individuals more susceptible to developing the severe form of the viral infection. Even though there is paucity of studies in children with comorbid conditions, available evidence suggests that children who have the aforementioned conditions are at a higher risk of ending up in a hospital; requiring intensive care monitoring and mechanical ventilation. The authors recommend that researchers explore this area and fill the information gap, to better assist paediatric physicians in making informed decisions.

DECLARATION

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