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COMORBIDITIES AND COVID-19 SEVERITY IN PEDIATRIC PATIENTS: SYSTEMATIC REVIEW

Stevenie*

**Faculty of Medicine, Indonesia Prima University*

***Corresponding Author: -**
stevenie377@gmail.com

Abstract

There is inconsistency between the findings of the several research that have been conducted about the association between comorbidities and the severity of pediatric COVID-19. A fundamental disadvantage of the studies that are now available is that they do not provide sufficient information on the clinical presentation and results. The majority of research characterize the severity of COVID-19 merely by reporting admission or fatality rates from critical care units. Severe disease is uncommon in children as compared to adults, and the majority of studies reflect the severity of the disease (ICUs). Infections caused by SARS-CoV-1 and MERS-CoV, as well as adult corona virus disease 2019 (COVID-19), comorbidities that were already present at the time of infection are regarded to be a risk factor for more severe disease. The majority of studies point to a connection between obesity and the outcomes of COVID-19 patients, and this is true for both children and adults. Some experts have put forward a theory as to why children are not susceptible to COVID-19 is that because children are often exposed to the other four mild coronaviruses that circulate each year and cause the common cold. This provides a boost in immunity in children, but many dispute that argument because adults also get the common cold virus and children's immune systems especially children <5 years are still underdeveloped which should make them more vulnerable.

Keyword: *Comorbidities; COVID-19; Obesity; Pediatric; Severity*

INTRODUCTION

Pauline Vetter in an editorial in the British Medical Journal (BMJ) noted that deaths outside Hubei province were lower. Outbreaks in 2019-2020 have caused at least 119,120 confirmed infections and 4,284 deaths.[1] The incidence of COVID-19 in children is 2.4% with 0.2% of children experiencing critical illness.[2] There have been very few reports of clinical outcomes for children with COVID-19 to date. Limited reports from China suggest that children with confirmed COVID-19 attended hospital with mild symptoms. Certain populations of children may be at increased risk for severe infection, such as children with comorbid conditions.[3]

Comorbidities that were present at the time of infection are considered a risk factor for more severe disease in adult corona virus disease 2019 (COVID-19), as well as in infections caused by SARS-CoV-1 and MERS-CoV.[4] Patients who have pre-existing underlying comorbidities, such as chronic obstructive pulmonary disease, cardiovascular disease, diabetes, and obesity, are more likely to have severe disease in adult SARS-CoV-2 infections compared to healthy adults. This is because these patients are more likely to have compromised immune systems.[5]

The existing studies about the association between comorbidities and the severity of pediatric COVID-19 are inconsistent with one another. The lack of detailed data on clinical presentation and outcomes is a significant limitation of the studies that are currently available. Severe disease is uncommon in children when compared to adults, and the majority of studies describe the severity of COVID-19 simply by reporting admission or mortality rates from intensive care units (ICUs).[6] Multi inflammatory syndrome in children (MIS-C) is a severe manifestation of SARS-CoV-2 infection that typically occurs weeks after SARS-CoV-2 infection.[7]

Multi inflammatory syndrome in children characterized by gastrointestinal symptoms, mucocutaneous signs, and cardiovascular involvement. This severe manifestation of SARS-CoV-2 infection typically occurs in children. The connection between comorbidities and the incidence or mortality of MIS-C has been the subject of several investigations.[7] To the best of our knowledge, there is no data examining the connection between pre-existing comorbidities and the degree to which MIS-C symptoms are manifested.

The comorbidities and severity of COVID-19 in pediatric patients were investigated in this study, which was conducted on a pediatric population.

METHODS

Protocol

This investigation followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 standards in its methodology. These reasons affected the passage of the legislation.

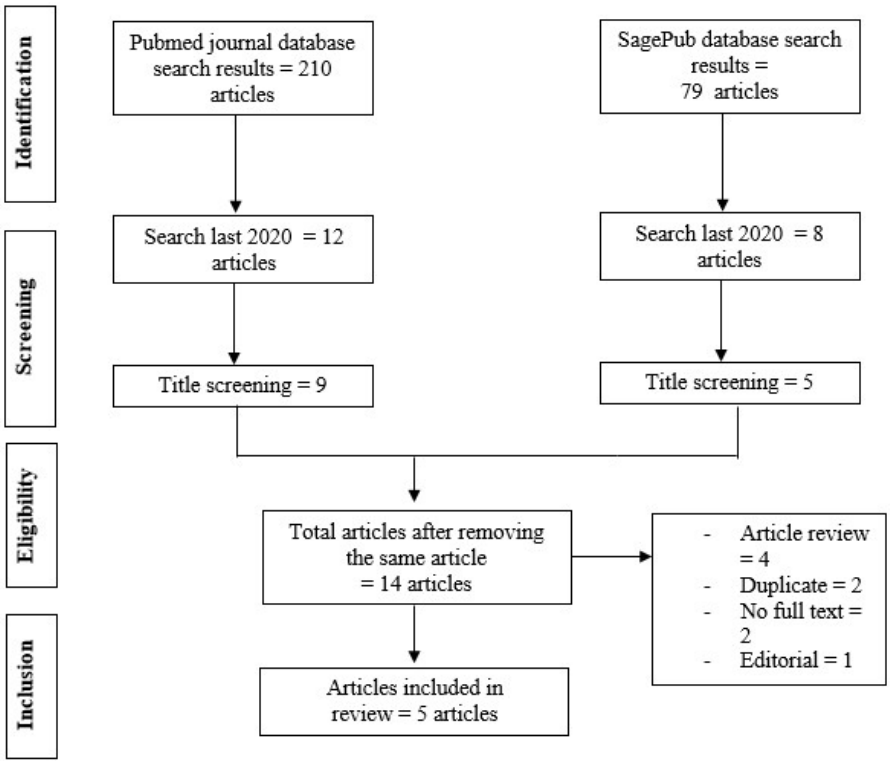

Figure 1. Article search flowchart

Criteria for Eligibility

By assessing or analyzing previous research on the subject, this review of the literature aims to demonstrate the comorbidities and COVID-19 severity in pediatric patients. This is a major concern raised in the current study. Researchers take part in studies that meet the following criteria: 1) To be considered for publication, articles must be written in English and highlight or focus on the comorbidities and COVID-19 severity in pediatric patients. 2) This evaluation included articles published after 2020 but before the period covered by this systematic review. Editorials, submissions without a DOI, previously published review articles, or entries that are very similar to those previously published in a journal, for example, will not be considered for publication.

Search Strategy

The search for studies to be included in the systematic review was carried out from January, 20th 2023 using the PubMed and SagePub databases by inputting the words: "comorbidities", "COVID-19 severity", and "pediatric population". Where ("comorbid"[All Fields] OR "comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "comorbidities"[All Fields] OR "comorbids"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields]) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("populate"[All Fields] OR "populated"[All Fields] OR "populates"[All Fields] OR "populating"[All Fields] OR "population"[MeSH Terms] OR "population"[All Fields] OR "population groups"[MeSH Terms] OR ("population"[All Fields] AND "groups"[All Fields]) OR "population groups"[All Fields] OR "populations"[All Fields] OR "population s"[All Fields] OR "populational"[All Fields] OR "populous"[All Fields]) is used as search keywords.

Data retrieval

After performing a literature study that included an analysis of the titles and abstracts of prior research, the author updated the inclusion and exclusion criteria. The new criteria are presented in the study's supplemental materials. This revealed the problem's breadth and emphasized the elements that require additional investigation. The author reached this result after performing research on numerous studies employing a similar structure. Only studies meeting all inclusion criteria were considered during the systematic review procedure.

This ensured that only pertinent data was uncovered. We did not evaluate any research proposals that did not match all of our criteria. This insured that a comprehensive assessment would be conducted. This endeavor yielded data pertinent to the studies, including their titles, authors, publication dates, locations, sorts of research investigations, and parameters. These are the accessible product categories. These are skills that can be developed. These data may be presented in a variety of formats, depending on the information source.

Quality Assessment and Data Synthesis

Each author conducted an independent investigation of a piece of research mentioned in the titles and abstracts of the papers before deciding which articles to investigate. The full texts of publications that meet the inclusion criteria for the systematic review will then be reviewed to determine which papers will be included in the review. This is done to determine which articles will be reviewed. To make the selection of articles for the review easier. Which studies have high enough quality to be included in the review?

RESULT

First study from Netherland showed obesity (21,7%), respiratory illnesses (19.6%), and neurological disorders (17%) were the most prevalent pre-existing comorbidities. For a comprehensive description of preexisting comorbidities within each comorbidity group. In the patient group without comorbidities (80.0%) and the patient group with comorbidities (63.2%), the majority of patients exhibited mild COVID-19 disease. All eight patients (13.8%) with severe or serious illness had coexisting conditions. One of these patients passed away as a result of COVID-19. Patients with comorbidities had a more severe acute COVID-19 infection than those without comorbidities (P = 0.041, OR 11.42, 95% CI 1.29–1507.49). Patients with a pre-existing comorbidity were more likely to be admitted to the ICU than those without comorbidities (P = 0.032, OR = 11.72, 95% CI 1.31–1547.79).[8]

Other study with 9-month trial period showed 150 (56.8%) of 264 hospital admissions involving children with SARS-CoV-2 infection were associated to COVID-19 and 100 (37.8%) were accidental infections (admissions for other reasons and found to be positive for SARS-CoV-2 on screening). Infants (37.3%) and adolescents (29.6%) accounted for the majority of cases. 52 (34.7%) of COVID-19-related hospital admissions were for patients with critical illness, 42 (28%) of whom required any type of respiratory or hemodynamic support, and 59 (39.3%) had at least one underlying

comorbidity. COVID-19 was more likely to be severe or life-threatening in children with obesity, chronic neurologic disorders, or chronic lung disease other than asthma.[9]

Bellino, et al (2020)[10] conducted a study with 3,836 pediatric patients. They median age was 11 years; 51.4% were male; 13.3% were hospitalized; and 5.4% had underlying medical problems. The condition was mild in 32.4% of cases and severe in 4.3%, especially in children 6 years old (10.8%); among 511 hospitalized patients, 3.5% were admitted to the intensive care unit, and four patients died. Increasing age and calendar time were related with a decreased risk of disease severity, whereas preexisting underlying medical disorders were associated with an increased risk (odds ratio [OR] = 2.80, 95% confidence interval [CI]= 1.74-4.44). Hospitalization rate, ICU admission, disease severity, and days from beginning of symptoms to recovery increased significantly with age in children, adults, and the elderly.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Period	Age	Result
Biharie, 2022[8]	Netherlands	Retrospective, observational cohort study	83 children with SARS-CoV-2 infection	March 2020 and April 2021	4-16 years old	Obesity (21,7%), respiratory illnesses (19.6%), and neurological disorders (17%) were the most prevalent pre-existing comorbidities. Patients with comorbidities had a more severe acute COVID-19 infection than those without comorbidities (P = 0.041, OR 11.42, 95% CI 1.29–1507.49). Patients with a pre-existing comorbidity were more likely to be admitted to the ICU than those without comorbidities (P = 0.032, OR = 11.72, 95% CI 1.31–1547.79).
Drouin, 2021[9]	United State	National prospective study	264 children with SARS-CoV-2 infection	Until Dec. 31, 2020	0-17 years old	During the 9-month trial period, 150 (56.8%) of 264 hospital admissions involving children with SARS-CoV-2 infection were associated to COVID-19 and 100 (37.8%) were accidental infections. Infants (37.3%) and adolescents (29.6%) accounted for the majority of cases. 52 (34.7%) of COVID-19-related hospital admissions were for patients with critical illness, 42 (28%) of whom required any type of respiratory or hemodynamic support, and 59 (39.3%) had at least one underlying comorbidity. COVID-19 was more likely to be severe or life-threatening in children with obesity, chronic neurologic disorders, or chronic lung disease other than asthma.
Bellino, 2020[10]	Italy	Cross sectional study	3,836 children with SARS-CoV-2 infection	No date	0-18 years old	The condition was mild in 32.4% of cases and severe in 4.3%, especially in children 6 years old (10.8%); among 511 hospitalized patients, 3.5% were admitted to the intensive care unit, and four patients died. Preexisting underlying medical disorders were associated with an increased risk (odds ratio = 2.80, 95% CI = 1.74-4.44). Hospitalization rate, ICU admission, disease severity, and days from beginning of symptoms to recovery increased significantly with age in children, adults, and the elderly.
Swann, 2020[11]	United Kingdom	Prospective observational cohort study	651 children with SARS-CoV-2 infection	17 January and 3 July 2020	0-13 years old	Children meeting MIS-C criteria were older (median age 10.7 (8.3-14.1) v 1.6 (0.2-12.9) years; P<0.001) and more likely to be of non-white ethnicity (64% (29/45) v 42% (148/355); P=0.004). Children with MIS-C were five times more likely to be admitted to critical care (73% (38/52) v 15% (62/404); P<0.001). In addition to the WHO criteria, children with MIS-C were more likely to present with fatigue (51% (24/47) v 28% (86/302); P=0.004), headache (34% (16/47) v 10% (26/263); P<0.001), myalgia (34% (15/44) v 8% (21/270); P<0.001), sore throat (30% (14/47) v (12% (34/284); P=0.003), and lymphadenopathy (20% (9/46) v 3% (10/318); P<0.001) and to have a platelet count of less than 150 × 109/L (32% (16/50) v 11% (38/348); P<0.001) than children who did not have MIS-C.
Martin, 2022[12]	US	Prospective cohort study	167,262 children with SARS-CoV-2 infection	Before September 24, 2021	0-18 years old	Variables associated with increased odds for MIS-C vs acute COVID-19 included male sex (OR, 1.59; 95% CI, 1.33-1.90), Black/African American race (OR, 1.44; 95% CI, 1.17-1.77), younger than 12 years (OR, 1.81; 95% CI, 1.51-2.18), obesity (OR, 1.76; 95% CI, 1.40-2.22), and not having a pediatric complex chronic condition (OR, 0.72; 95% CI, 0.65-0.80). The children with MIS-C had a more inflammatory laboratory profile and severe clinical phenotype, with higher rates of invasive ventilation (117 of 707 [16.5%] vs 514 of 8241 [6.2%]; P < .001) and need for vasoactive-inotropic support (191 of 707 [27.0%] vs 426 of 8241 [5.2%]; P < .001) compared with those who had acute COVID-19.

Swann, et al (2020) showed that 18% (116/632) of children were admitted to critical care. On multivariable analysis, this was associated with age under 1 month (odds ratio 3.21, 95% confidence interval 1.36 to 7.66; P=0.008), age 10-14 years (3.23, 1.55 to 6.99; P=0.002), and black ethnicity (2.82, 1.41 to 5.57; P=0.003). Six (1%) of 627 patients died in hospital, all of whom had profound comorbidity. 11% (52/456) met the WHO MIS-C criteria, with the first patient developing symptoms in mid-March. Children meeting MIS-C criteria were older (median age 10.7 (8.3-14.1) v 1.6 (0.2-12.9) years; P<0.001) and more likely to be of non-white ethnicity (64% (29/45) v 42% (148/355); P=0.004).[11]

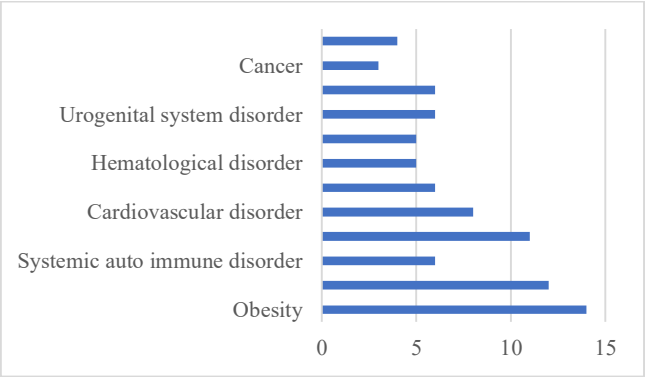

Figure 2. Comorbidites pediatrics patients with COVID-19

Children with MIS-C were five times more likely to be admitted to critical care (73% (38/52) v 15% (62/404); P<0.001). In addition to the WHO criteria, children with MIS-C were more likely to present with fatigue (51% (24/47) v 28% (86/302); P=0.004), headache (34% (16/47) v 10% (26/263); P<0.001), myalgia (34% (15/44) v 8% (21/270); P<0.001), sore throat (30% (14/47) v (12% (34/284); P=0.003), and lymphadenopathy (20% (9/46) v 3% (10/318); P<0.001) and to have a platelet count of less than 150 × 109/L (32% (16/50) v 11% (38/348); P<0.001) than children who did not have MIS-C. No deaths occurred in the MIS-C group.[11]

DISCUSSION

Age was related with a decreased chance of disease severity, however the existence of underlying medical disorders was associated with an increased risk. In fact, the number of pediatric patients with severe or critical symptoms reduced modestly over time, from 5.4% in the first month of the outbreak to 3.5% in the final three weeks of the observation period, while the percentage of children with mild symptoms decreased from 43.4-28.2%.[10]

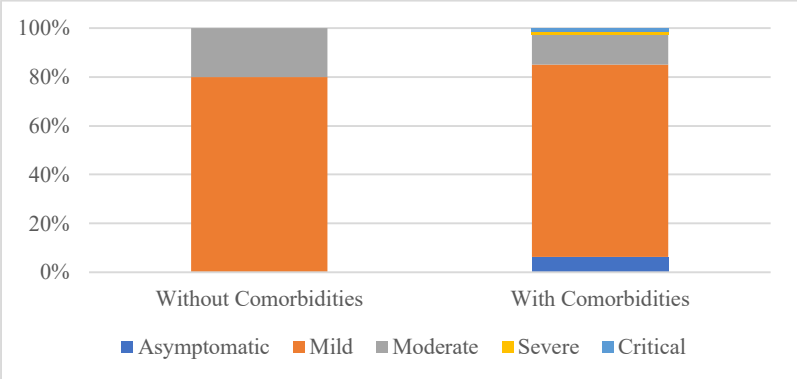

Figure 3. Comparison pediatric patients with and without comorbidites

However, this appears to be due more to the effect of the phase of the epidemic (during the height of the outbreak, only subjects with clear signs and symptoms of the disease were tested) and likely to a more efficient health care provision due to a decrease in the number of cases in the second phase than to a change in the pathogenicity of SARS-CoV-2. The clinical presentation and outcome variations of COVID-19 as it spread from China to Europe and the rest of the world are still under controversy; nonetheless, our results support the concept that the illness course and severity have not experienced significant modifications.[13]

The evolution of the virus during the pandemic is proceeding at a rate comparable to that of other viruses during an outbreak. Studies have demonstrated that children of all ages are susceptible to SARS-CoV-2 infection, although they appear to be less sensitive than adults and to exhibit milder symptoms.[10,13] They study matched with a Chinese study, who conducted with 2135 children (728 laboratory-confirmed cases), which found that 5% were severe (presenting hypoxemia, dyspnea, central cyanosis) and <1% were critical (with respiratory failure, acute respiratory distress syndrome, shock).[14] Some experts have put forward a theory as to why children are not susceptible to COVID-19 is that because children are often exposed to the other four mild coronaviruses that circulate each year and cause the common cold. This provides a boost in immunity in children, but many dispute that argument because adults also get the common cold virus and children's immune systems especially children <5 years are still underdeveloped which should make them more vulnerable.[2]

The South Thames Retrieval Service in London, England has published a report describing eight critically ill pediatric patients with features of hyperinflammatory shock with multiorgan involvement in early May 2020. In particular, children manifested with high fever, rash, conjunctivitis, peripheral edema, and gastrointestinal symptoms. The Royal College of

Paediatrics and Child Health (RCPCH) refers to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS).[15]

Children who already have one or more comorbid conditions had an increased risk of developing severe COVID-19, and this was found in a larger cohort of 3,837 pediatric patients. An link between more severe COVID-19 and neurological diseases was also discovered by another investigation. These neurological illnesses mostly consisted of epilepsy or severe neuro-disability and were observed in patients who were comparable to those in our study.[9,10]

Another multicenter observational study carried out in the United Kingdom came to the same conclusion. It indicated that neurological problems, such as neurodisability, were one of the most common comorbidities among patients who required critical care as a result of COVID-19. It is possible that neurological conditions such as cerebral palsy, which have an effect on motor functions, could lead to difficulties in spontaneous breathing and clearing respiratory secretions.[11]
This could make respiratory infections worse, which would explain this association with more severe acute COVID-19. In addition, the SARS-CoV-2 virus can have an effect on the nervous system by causing damage to neuronal cells, muscular tissues, and vascular cells; these are the types of cells that are likely to be more susceptible to harm in children who have other medical conditions.[16]

It is not apparent why children exhibited less severe COVID-19 symptoms than adults. Because a cytokine storm was found to be important in the pathogenesis of severe forms of the disease in adults, one of the possible explanations could be that children have a lower immune response to SARS-CoV-2 than adults do. Other possibilities consider the possibility of a "competition" between different viruses in the respiratory tracts of young children and the expression of the angiotensin-converting enzyme 2 receptor.[17,18]

Inside the first potential outcome, viral interference may result in a decreased viral load within youngsters. When it comes to the angiotensin-converting enzyme 2 receptor, this protein serves as the receptor for the SARS-CoV-2 virus, and it's possible that children's respiratory tracts produce this protein in a different way than adult respiratory tracts do.[18,19] A recent study found that the viral load of symptomatic and asymptomatic patients were comparable, suggesting that asymptomatic people are still capable of infecting others even after their symptoms have resolved.[20]
Children who had already been hospitalized for longer than five days prior to the beginning of symptoms had an increased risk of being transferred to the intensive care unit. This category necessarily contains children who have comorbidities, the presence of which was found to be related with admission to the intensive care unit. Nosocomial SARS-CoV-2 infections in children are not well recorded, and this field requires more investigation, preferably with the utilization of viral sequence data.[11]

Children who met the requirements for MIS-C in both the acute phase of infection (as determined by a positive polymerase chain reaction) and the post-acute or convalescent phase of infection (as determined by a positive antibody response). The post-acute group was more strongly associated with non-white ethnicity and muco-enteric symptom presentation (abdominal pain and conjunctivitis), whereas the acute group presented more commonly with respiratory symptoms.[11]
Although the two groups shared many similarities, important differences included the post-acute group being more strongly associated with non-white ethnicity and muco-enteric symptom presentation. Cardiac issues occurred in all groups, although they were more prevalent in the post-acute patients. These patients were also more likely to get intravenous steroids and immunoglobulins, so they were better equipped to handle the side effects of their treatment.[11]
Existing data in the United States shows that the most complications are cardiac dysfunction (40.6%), shock (35.4%), myocarditis, coronary artery dilation, and acute kidney injury. All of the children in Belhajer's study even had heart problems (35/35) but eventually got better. The prognosis of MIS-C patients is relatively good, recovery occurs more quickly. Most patients with dilated coronary arteries also recover normally in a short time.[21]

Case death rates from various countries in children with MIS-C are relatively low. Only two of the 78 children treated in the UK's PICU died. One of them had an arrhythmia caused by a cerebral infarction. Two other reports came from New York. The death toll across the US is 10 cases. The group with higher mortality is those showing symptoms and signs. from the respiratory system.[21]

Most studies show an association between obesity and patient outcomes with COVID-19, both in children and adults. Obesity seemed to be the most important independent risk factor, even in the mildest instances, consistent with evidence from the adult population. Several changed mechanisms, both related to obesity and its comorbidities, are at work.[22] These include: (1) altered respiratory physiology as a result of the pressure exerted on the lungs by abdominal adiposity, and defective lung mesenchymal stem cells, which are responsible for ineffective tissue repair processes and immune response, with an overall increased risk of pulmonary infections, asthma, and obstructive apneas; and (2) insulin resistance and hyperinsulinemia, because of which, in situations of intense metabolic activity, like during the response to SARS-CoV-2 infection, beta cells, already working at their limit, were not able to increase insulin secretion and can also be damaged by the virus. Moreover, they contribute to the onset of other metabolic and cardiovascular alterations; including (3) dyslipidemia (low HDL- and increased LDL-cholesterol levels contribute to endothelial dysfunction and atherosclerosis); (4) hypertension with consequent left ventricular hypertrophy; (5) non-alcoholic steatohepatitis; and (6) hyperuricemia. Finally, insulin resistance increases the (7) oxidative stress and, together with visceral adiposity, endothelium damage and

micronutrients deficiencies (i.e., vitamin D, C, A, E and B12, iron and folate, with anti-oxidative action) lead to (8) chronic inflammation, excessive and dysregulated inflammatory response, and increased coagulation activity.[23]

CONCLUSION

Children generally have mild illness, but pediatric patients with comorbidities are a group that experiences severe cases of COVID-19. Most studies show an association between obesity and patient outcomes with COVID-19, both in children and adults.

REFERENCE

[1]. Gorbalenya AE. Severe acute respiratory syndrome-related coronavirus – The species and its viruses, a statement of the Coronavirus Study Group. BioRxiv. 2020;2(7):93–7.
[2]. Rivers C. Coronavirus is mysteriously sparing kids and killing the elderly. Understanding why may help defeat the virus [Internet]. Washingtnpost.com. 2020. Available from: https://www.washingtonpost.com/health/2020/03/10 /coronavirus-is-mysteriously-sparing-kids-killing-elderly-understanding-why-may-help-defeat-virus/
[3]. Centers for Disease Control and Prevention. 2019 Novel Coronavirus (2019-nCoV). Washington DC; 2020.
[4]. Zimmermann P; Curtis N. Coronavirus Infections in Children Including COVID-19. Pediatr Infect Dis J. 2020;39(5):355–69.
[5]. Rajapakse N, Dixit D. Human and novel coronavirus infections in children: a review. Paediatr Int Child Health. 2021;41(1):36–55.
[6]. Jain V, Yuan J-M. Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis. Int J Public Health. 2020 Jun;65(5):533–46.
[7]. Nakra NA, Blumberg DA, Guerra AH, et al. Multi-System Inflammatory Syndrome in Children (MIS-C) Following SARS-CoV-2 Infection: Review of Clinical Presentation, Hypothetical Pathogenesis, and Proposed Management. Child. 2020;7(7):69.
[8]. Biharie A, Keuning MW, Wolthers KC, Pajkrt D. Comorbidities, clinical characteristics and outcomes of COVID-19 in pediatric patients in a tertiary medical center in the Netherlands. Vol. 18, World journal of pediatrics : WJP. Switzerland; 2022. p. 558–63.
[9]. Drouin O, Hepburn CM, Farrar DS, Baerg K, Chan K, Cyr C, et al. Characteristics of children admitted to hospital with acute SARS-CoV-2 infection in Canada in 2020. C Can Med Assoc J = J l'Association medicale Can. 2021 Sep;193(38):E1483–93.
[10]. Bellino S, Punzo O, Rota MC, Del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020 Oct;146(4).
[11]. Swann O V, Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ. 2020 Aug;370:m3249.
[12]. Martin B, DeWitt PE, Russell S, Anand A, Bradwell KR, Bremer C, et al. Characteristics, Outcomes, and Severity Risk Factors Associated With SARS-CoV-2 Infection Among Children in the US National COVID Cohort Collaborative. JAMA Netw Open [Internet]. 2022 Feb 8;5(2):e2143151–e2143151. Available from: https://doi.org/10.1001/jamanetworkopen.2021.43151
[13]. Gorbalenya A, Baker S, Baric R, de Groot R, Drosten C, Gulyaeva A, et al. Severe acute respiratory syndrome-related coronavirus : The species and its viruses – a statement of the Coronavirus Study Group. Nat Microbiol. 2020 Feb;2020.02.07.937862.
[14]. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6).
[15]. Riphagen S, Gomez X, Gonzales-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;
[16]. Leven Y, Bösel J. Neurological manifestations of COVID-19 - an approach to categories of pathology. Neurol Res Pract. 2021 Jul;3(1):39.
[17]. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
[18]. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088–95.
[19]. Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021;27(1):28–33.
[20]. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. Vol. 382, The New England journal of medicine. United States; 2020. p. 1177–9.
[21]. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporarily associated with COVID- 19 [Internet]. Royal College of Paediatrics and Child Health. 2020. Available from: https://www.rcpch.ac.uk/resources/g uidance-paediatric-multisystem- inflammatory-syndrome-temporally-associated-covid-19-pims
[22]. Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev. 2021 Feb;37(2):e3377.
[23]. Nogueira-de-Almeida CA, Del Ciampo LA, Ferraz IS, Del Ciampo IRL, Contini AA, Ued F da V. COVID-19 and obesity in childhood and adolescence: a clinical review. J Pediatr (Rio J). 2020;96(5):546–58.