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THE IMPACT OF COMORBIDITIES ON COVID-19 SEVERITY IN PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW

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Abstract

Background: *Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused over 6 million deaths worldwide. Comorbidities like obesity, asthma, and neurological disorders are risk factors for severe illness in pediatric patients. The direct impact of COVID-19 on child mortality is limited, with only 0.4% of deaths occurring in children under 20.*

Objective: *To identify risk factors and potential interventions to reduce severe illness and mortality in pediatric patients.*

Methods:*A systematic review of COVID-19, sars-cov-2, and novel coronavirus in children was conducted using PubMed and Google Scholar. Severe COVID-19 prevalence in children assessed using Strengthening the Reporting of Observational Studies in Epidemiology (STROME) and the Joanna Briggs Institute (JBI) checklists, assessing quality and bias.*

Results:*A review of 41 studies found a significant difference in severe COVID-19 infection risk among children with and without comorbidities, including hematologic, immune, respiratory, cardiovascular, neurological, obesity, and genetic syndromes.*

Conclusion:*Comorbidities in pediatric COVID-19 patients enhance the risk; vaccinations and increased vigilance should take priority.*

Keywords: *comorbidity; COVID-19; novel coronavirus; pediatric; SARS-CoV-2*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an extremely contagious viral illness brought on by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has resulted in more than 6 million fatalities worldwide.[1] Although the majority of pediatric patients affected by COVID-19 experience mild or asymptomatic cases, a subset of individuals may exhibit more severe manifestations of the disease. Recent research has centered on analyzing the influence of comorbidities on the severity of COVID-19 in pediatric patients.[1] Comorbidities such as obesity, asthma, and neurological disorders have been identified as risk factors for severe COVID-19 in pediatric patients.[2]

Recent studies have demonstrated that COVID-19 can indirectly impact child mortality through overburdened health systems, financial loss, and disruptions in care-seeking and prevention efforts such as vaccination.[3] However, the direct impact of COVID-19 on infant mortality has been minimal, with only 0.4% of reported COVID-19 deaths affecting children and adolescents younger than 20 years old.[3]

According to the Indonesian Pediatric Society Data Registry, there were 37,706 verified instances of COVID-19 in pediatric patients, resulting in 175 fatalities (CFR 0.46). Children aged 10 to 18 accounted for 26% (42 out of 159 cases) of the confirmed COVID-19 cases with the highest mortality rate. [4]

The causative agent of COVID-19, SARS-CoV-2, is highly contagious and is primarily transmitted through contact with infected individuals via secretions, saliva, or droplets.[5] While data from China suggest that pediatric COVID-19 cases might be less severe than cases in adults, severe outcomes have been reported in children, including deaths.[6]

This systematic review will provide a comprehensive overview of the latest research on the impact of comorbidities on COVID-19 severity in pediatric patients, focusing on identifying risk factors and potential interventions to reduce the risk of severe illness and mortality.

Methods

This study is a qualitative systematic review per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar to search for relevant articles published up to 2021 with the keywords 'covid-19,' 'sars-cov-2,' 'novel coronavirus,' 'child,' 'Pediatr*,' 'severe illness', and 'comorbidity'.

This review was conducted exclusively on studies that fulfilled the following inclusion criteria: (1) observational studies that involved preferably pediatric patient with comorbidities and one pediatric patient without; (2) confirmation of the COVID-19 diagnosis with RT-PCR; (3) studies that were completely accessible; and (4) studies featuring people with severe COVID-19 symptoms. Conforming to the following circumstances, criteria for exclusion were applied: (1) lack of crucial information, (2) exclusion of children with comorbidities, (3) usage of languages besides English and Indonesian, and (4) lack of reporting of the magnitude of COVID-19. The primary aim of this investigation was to compare pediatric patients with and without medical histories to ascertain the occurrence of severe COVID-19.

Prior to inclusion, the quality and risk of bias of the articles chosen were evaluated by two independent evaluators using *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE)-standardized critical assessment,[7] and the *Joanna Briggs Institute* (JBI) critical assessment.[8] Any conflicts between reviewers were settled through discussion or with the assistance of a third reviewer.

Two authors analyzed data using Review Manager 5.4. The data were extracted from the dataset, and the odds ratio (OR) was subsequently computed. A systematic review was conducted utilizing the random effect model to estimate the aggregated odds ratio (OR) and 95% confidence interval (CI) for the risk of severe COVID-19. A P value below the threshold of 0.05 was considered to have statistical significance. The I2 statistic was employed to measure the degree of heterogeneity.

Results

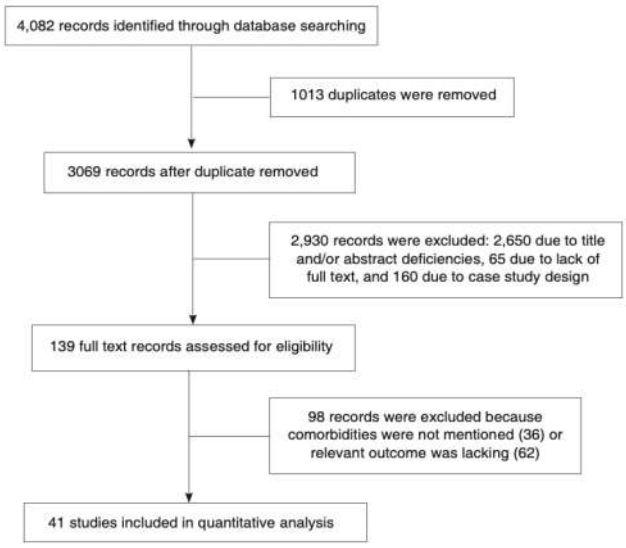

Figure 1. Flowchart of the study selection process

The preliminary literature searches conducted resulted in the identification of 4,082 studies. Following the removal of duplicate articles, we proceeded to assess the eligibility of each article, excluding studies that did not meet our predefined criteria. A total of forty-one studies were incorporated into the analysis, comprising two cross-sectional studies, thirty-three cohort studies, and six case series. The flowchart depicted in Figure 1 provides a visual representation of the process employed for selecting studies in this investigation.

The dataset comprises a total of seventeen articles originating from the United States, four articles from Italy, three articles from China, three articles from Spain, three articles from France, three articles from the United Kingdom, two articles from Iran, and one article each from Turkey, India, Brazil, Austria, Australia, and Kuwait. The quality of all the studies included in the analysis was assessed in terms of bias risk, and it was found that they exhibited a low bias risk. A comprehensive analysis was conducted on 41 observational studies that were published prior to 2021. These studies encompassed a total of 285,828 participants, with 140,404 (49.34%) identified as male and 144,160 (50.6%) identified as female. The entire cohort was affected by the COVID-19 infection and subsequently divided into two distinct groups: one consisting of 9,754 individuals with comorbidities and the other comprising 276,074 individuals without any underlying health conditions. Age group data was collected from a total of 706 children. Among these children, 207 (29.3%) were found to be 1 year old, 150 (21.2%) fell within the age range of one to five years, 153 (21.6%) were aged between six and ten years, and 196 (27.7%) were older than 10 years. Table 1 presents the key attributes of the investigations included in the analysis.

Table 1. Study design and initial features of the studies included
VSD=Ventricular Septal Defect, NAFLD=non-alcoholic fatty liver disease, MIS-C=multisystem inflammatory syndrome in children The systematic review of 41 studies demonstrated a significant association between comorbidities and the risk of severe COVID-19 infection in pediatric patients (odds ratio [OR] 4.07; 95% confidence interval [CI] 2.31 to 7.02; $p < 0.00001$). The prevalence of comorbidities in 29 studies indicated that hematologic and immune disorders, malignancies, respiratory, cardiovascular, neurological disease, obesity/overweight, and genetic syndromes were the most frequently observed. Additionally, the individuals exhibited a range of medical conditions, including chronic diseases including renal, atopic, dermatitis, respiratory, metabolic, liver, gastrointestinal, and psychiatric. Figure 2 presents a forest plot that compares comorbidities and the severity of COVID-19 in pediatric patients.

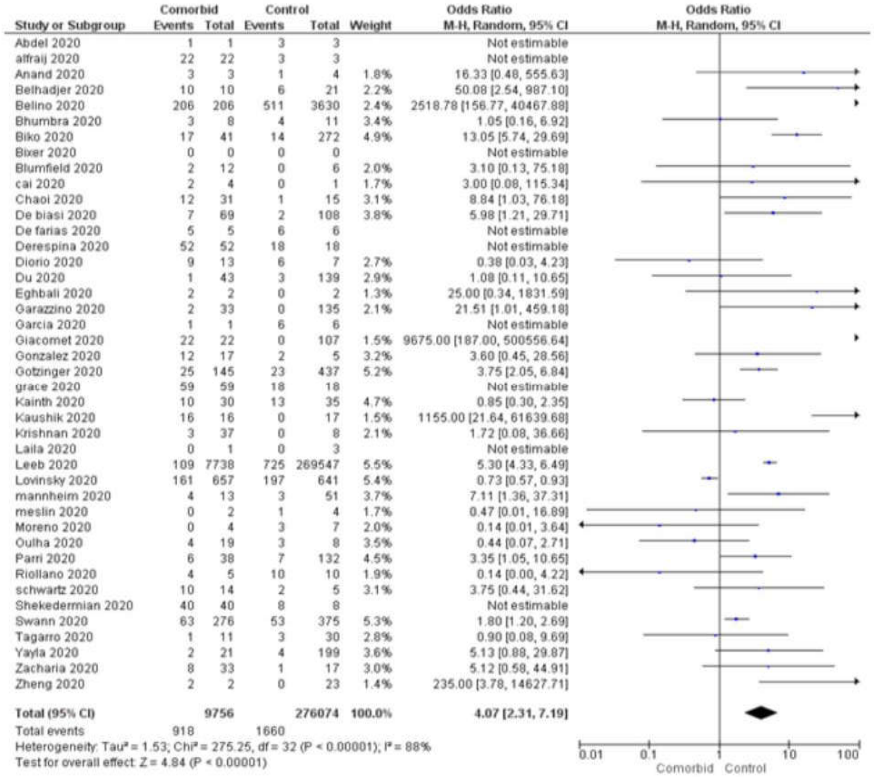

Figure 2. The forest plot is depicting the odds ratio of severe COVID-19 in pediatric patients with versus without comorbidities.

Discussion

According to multiple studies, the majority of children with COVID-19 have less severe symptoms than adults and a favorable prognosis. Moreover, adolescents are more likely to exhibit no symptoms.[47] Owing to the nascent stage of development of the angiotensin-converting enzyme (ACE) during the earlier stages of life, it is plausible that children may exhibit a reduced vulnerability to SARS-CoV-2. This is due to the virus's reliance on ACE as a means of infiltrating type

II pneumocytes.[48,49] A second hypothesis posits that repeated viral exposure could enhance the immune system's response to SARS-CoV-2 in young children susceptible to developing various viral infections.[50]

Individuals with comorbidities had greater severity of disease than those without. Even though the prevalence of comorbidities influences prognosis, the outcome for COVID-19-infected children is generally favorable. According to a prior systematic review, all pediatric age categories are at risk for COVID-19 infection. Severe illnesses and fatalities were extremely uncommon. Infants demand special attention for a greater risk of critical illness, despite the favorable prognosis.[51]

Nonetheless, comorbidities are not the sole variable influencing prognosis. The clinical symptoms of the patient additionally have a crucial role. The primary clinical manifestations observed in pediatric patients affected by COVID-19 include fever, cough, vomiting, diarrhea, hoarseness, and dyspnea, as well as notable laboratory findings such as a positive reverse transcription-polymerase chain reaction (RT-PCR) test, reduced oxygen saturation, and elevated D-dimer levels. Gastrointestinal symptoms exhibited a higher frequency among the teenage population. While it is true that children with COVID-19 generally exhibit lenient symptoms, experience better outcomes, and have fewer fatalities compared to adults, it is important to note that children can still serve as potential carriers of the infection, thereby contributing to the transmission of the disease within the population.[52]

Additionally, comorbidities like hematologic, immune, asthma, heart disease, hypertension, epilepsy, and obesity are more severely linked to a heightened manifestation of COVID-19. The appropriate triage of patients necessitates a comprehensive inquiry into each patient's medical history to ascertain individuals at a higher risk of experiencing severe adverse effects related to COVID-19.

In summary, the incidence of comorbidities among pediatric individuals affected by COVID-19 substantially augments the likelihood of experiencing severe symptoms. The prioritization of public health prevention and vaccine allocation efforts should be directed toward safeguarding children with comorbidities and chronic medical conditions from the risks posed by COVID-19. When medical professionals come across minors who are infected with COVID-19 and have comorbidities, it is important for them to recognize the potential necessity of increased vigilance.

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