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Original Article

Comorbidities and COVID-19 severity in pediatric patients: systematic review and meta-analysis

Mas Wishnuwardhana, Mutiara Nindya, Glenn Fernandez, Axel Jovito

Abstract

Background COVID-19 has spread around the world. Although symptoms in children are often mild, children remain at risk of developing severe or critical forms of COVID-19, especially those with underlying or comorbid medical conditions.

Objective To evaluate the association between comorbidities and severity of COVID-19 in pediatric patients.

Methods A systematic review was performed in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) guidelines. We used *PubMed* and *Google Scholar* to locate observational studies that involved children with RT-PCR-confirmed COVID-19 with comorbidities and compared them with controls without comorbidities. Studies must also involve children with severe COVID-19 and provide the risk of severe COVID-19 in children with and without comorbidities as outcome. We performed a meta-analysis to estimate the pooled odds ratio (OR) of severe COVID-19 in children with vs. without comorbidities.

Results We included 41 observational studies with a total of 285,828 pediatric COVID-19 patients, comprising 9,754 patients with comorbidities and 276,074 controls. The comorbidities indentified included obesity, congenital malformations, neurological disease, and genetic syndromes. Children with comorbidities had a significantly higher risk of developing severe COVID-19 compared to those without (pooled OR 4.07; 95%CI 2.31 to 7.19; P<0.00001).

Conclusion The presence of comorbidities increases the risk of severe COVID-19 in children. **[Paediatr Indones. 2022;62:51-60 ; DOI: 10.14238/pi62.1.2022.51-60**].

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

In December 2019, the first cases of pneumonia with unknown cause were found in Wuhan, Hubei Province, China. On January 7, 2020, a new coronavirus, known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified in a throat swab sample from one patient. The *World Health Organization* (WHO) declared the disease caused by SARS-CoV-2 as coronavirus disease-2019 (COVID-19).[1] In the following months, COVID-19 has spread around the world. The WHO has documented a total of 28,276 confirmed cases with 565 deaths globally, involving at least 25 countries, as of February 2020. A *Public Health Emergency of International Concern* (PHEIC) alarm was issued by the WHO on January 30, 2020.[1] The cases continue to increase and reached 152,534,452 confirmed cases, and 3,198,528 confirmed deaths in May 3, 2021.[2] In Indonesia, the first confirmed SARS-CoV-2 case was identified in a throat swab sample from a female who had close contact with Japanese man; and the second case identified was her mother. The number of new

From the Pediatric Division, Chasbullah Abdulmadjid Hospital, Bekasi West Java, Indonesia.

Corresponding author: Mas Wishnuwardhana, Pediatric Division, Chasbullah Abdulmadjid Hospital, Jl. Pramuka, no. 55, Marga Jaya, South Bekasi, Bekasi city, Kota Bks, Jawa Barat 17141, Bekasi West Java, Indonesia. Telp.021-8841005 (Hunting) Fax.021-8853731. .Email: mas.wishnuwardhana@gmail.com.

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cases continued to increase, reaching 1.69 million confirmed cases with 46,137 deaths by May 3, 2021.[3,4]

The number of children diagnosed with COVID-19 was less than adults, and most of them had milder symptoms. Because widespread testing was prioritized for adults and seriously ill patients, the true incidence of SARS-CoV-2 infection in children is unknown. In China, most of the initial pediatric cases reported had a history of close contact with COVID-19 cases or were part of a family case group. Currently, experts suggest children may have less severe illness from COVID-19 compared to adults, due to the significantly lower hospitalization rates in children.[5]

The incubation period of COVID-19 ranges from 1 to 14 days, with an average of 3-7 days after contact with an infected person.[6,7] Symptoms of COVID-19 in children are often mild, including cough (48.5%), pharyngeal erythema (46.2%), fever (41.5%), diarrhea (8.8%), fatigue (7.6%), rhinorrhea (7.6%), vomiting (6.4%) and nasal congestion (5.4%). However, children remain at risk of developing severe forms of the disease. Evidence suggests that children with certain underlying or comorbid medical conditions are at higher risk of developing COVID-19 disease with a higher degree of severity; however, studies are still limited.[8-10] The aim of this study is to evaluate the association between comorbid conditions and severity of COVID-19 in pediatric patients in a systematic review and meta-analysis.

Methods

We performed a systematic review in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines. We used PubMed and Google Scholar to search for relevant articles published up to March 2021 with the keywords 'covid-19,' 'sars-cov-2,' 'novel coronavirus,' 'child,' 'pediatr*,' 'severe illness', and 'comorbidity'.

Our review was restricted to studies that met the inclusion criteria below: (1) involved pediatric patients with comorbid conditions infected with COVID-19 as subjects and patients without comorbidities as controls; (2) observational studies (cohort, case-control, cross-sectional, and case series) containing at least one pediatric patient with comorbidities and one pediatric patient without comorbidities; (3) confirmation of the COVID-19 diagnosis was done using RT-PCR; (4) available in full-text; (5) involved subjects with severe COVID-19 symptoms: hypoxia with oxygen saturation <90%, requiring supplemental help for normal breathing and/or PICU admission. Studies were excluded if they (1) did not provide the data required; (2) did not involve children with comorbidities; (3) used languages other than English or Indonesian; and (4) did not report the severity of COVID-19. The primary outcome was the prevalence of severe COVID-19 in pediatric patients with and without comorbidities.

Prior to inclusion, the studies selected were assessed for quality and risk of bias by two independent reviewers using standardized critical appraisal in accordance with *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) checklist for cohort, case-control, and cross-sectional studies,[11] and the *Joanna Briggs Institute* (JBI) critical appraisal checklist for case series.[12] Any disagreements that arose between the reviewers were resolved through discussion or with the help of a third reviewer.

The data were analyzed independently by two authors using *Review Manager version 5.4*. Data were extracted and assessed for odds ratio (OR). We performed a meta-analysis using the random effect model to estimate a pooled OR of the risk of severe COVID-19 with 95% confidence interval (95%CI). A P value of <0.05 was considered to be statistically significant. Heterogeneity was measured using I2. The review was registered with the *PROSPERO International Prospective Register of Systematic Reviews* (registration no. CRD42021242875).

Results

We identified 4,082 studies from our initial database literature searches. After removing duplicates, we evaluated the articles individually for eligibility at the level of title, abstract, full text, and study design, and excluded studies that did not meet our criteria. Forty-one studies were included, consisting of 2 cross-sectional studies, 33 cohort studies, and 6 case series. The flowchart of study selection is shown in **Figure 1**. Articles included originated from the USA (17), Italy (4), China (3), Spain (3), France (3), UK (3), Iran (2), as well as one study each from Turkey, India, Brazil,

Austria, Australia, and Kuwait. All included studies were assessed for quality (risk of bias) and were found to have a low risk of bias.

A total of 41 observational studies published before March 2021 were analyzed, with a total of 285,828 enrolled subjects, of whom 140,404 (49.34%) were male and 144,160 (50.6%) were female.[8,13-51] All subjects had COVID-19 and were divided into two groups: 9,754 subjects with comorbidities and 276,074 without. We were able to obtain age group data from 706 children, which consisted of 207 (29.3%) <1 year of age, 150 (21.2%) one to five years of age, 153 (21.6%) six to ten years of age, and 196 (27.7%) >10 years of age. The characteristics of included studies are shown in **Table 1**.

Pooled analysis of the 41 included studies revealed a statistically significant difference in the risk of severe COVID-19 between pediatric patients with and without comorbidities (OR 4.07; 95%CI 2.31 to 7.19; P<0.00001). The most common comorbidities were hematologic and immune disorders as well as malignancies in 29 studies, respiratory disease (e.g., asthma and chronic lung disease) in 27 studies, cardiovascular disease (e.g., congenital heart disease and hypertension) in 26 studies, neurological disease (e.g., epilepsy and cerebral palsy) in 19 studies, obesity/overweight in 17 studies, and genetic syndromes (e.g., autism and trisomy 21) in 12 studies. Other comorbidities included renal disease, atopic dermatitis, congenital respiratory malformation, sickle cell disease, metabolic and endocrine disease, liver disease, prematurity, rheumatologic disease, gastrointestinal tract disease, and psychiatric disease. **Figure 2** shows a forest plot of comparison between comorbidities and COVID-19 severity in pediatric patient.

Discussion

This meta-analysis demonstrates that pediatric COVID-19 patients with underlying diseases or comorbidities had a higher risk of developing severe COVID-19 than those without. As many studies have mentioned, most children with COVID-19 show

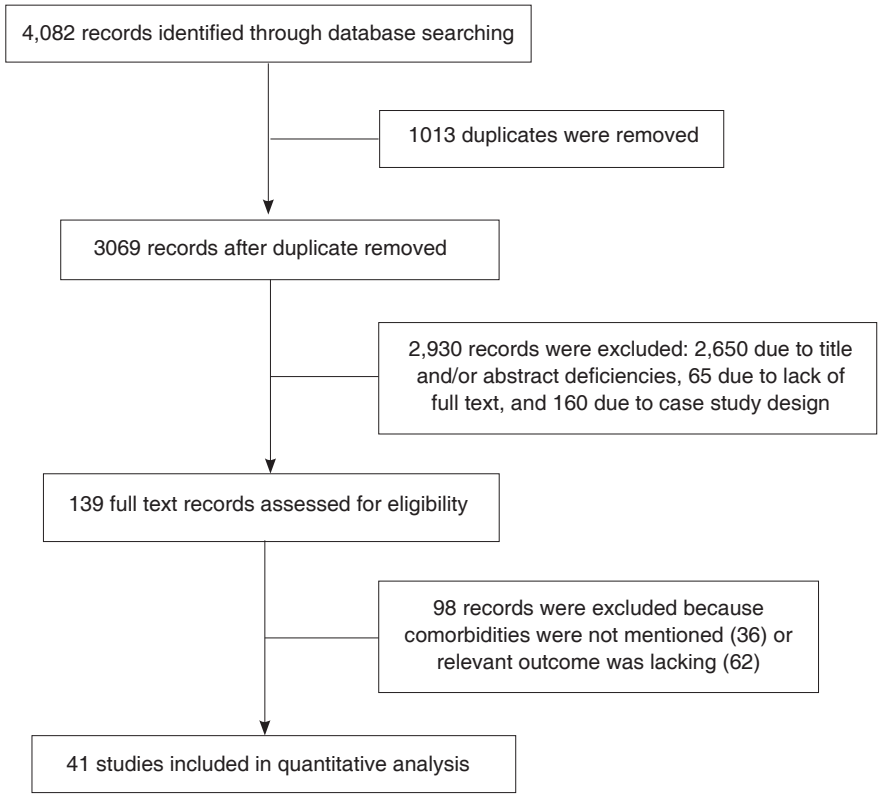

Figure 1. Quality of reporting of meta-analyses (QUOROM) flowchart of the study selection process

Table 1. Study design and baseline characteristics of included studies

Author	Year	Study design	Country	Population	Comorbidities included in study
Moreno	2020	Retrospective cohort	Spain	11 subjects, 4 in the comorbid group and 7 in the control group	Obesity, congenital respiratory malformation, congenital cardiac disease, Down syndrome, nephrotic syndrome
Oulha	2020	Retrospective cohort	France	27 subjects, 19 in the comorbid group and 8 in the control group	Neurological disease, respiratory disease, sickle cell, genetic syndrome, hematologic and immune disease, renal disease
Parri	2020	Retrospective cohort	Italy	170 subjects, 38 in the comorbid group and 132 in the control group	Epilepsy, autism, VSD, propionic acidemia, thrombocytopenia
Riollano	2020	Retrospective cohort	USA	15 subjects, with 5 in the comorbid group and 10 in the control group	Asthma, hypothyroidism, NAFLD
Shekedermian	2020	Cross sectional	USA	48 subjects, 40 in the comorbid group and 8 in the control group	Immunodeficiency, malignancy, obesity, DM, epilepsy, congenital heart disease, sickle cell, chronic lung disease
Swann	2020	Retrospective cohort	UK	651 subjects, 276 in the comorbid group and 375 in the control group	Neurologic disease, hematologic oncologic and immune disease, asthma, prematurity
Togarro	2020	Retrospective cohort	Spain	41 subjects, with 11 in the comorbid group and 30 in the control group	-
Yayla	2020	Retrospective cohort	Turkey	220 subjects, 199 in the comorbid group and 21 in the control group	Neurologic disease, chronic pulmonary disease, endocrine disease, metabolic disorder, rheumatologic disease, cardiovascular, gastrointestinal, hematologic disease, and malignancy
Zacharia	2020	Retrospective cohort	USA	50 subjects, 33 in the comorbid group and 17 in the control group	Obesity, asthma, immunosuppression, neurologic disease, sickle cell, cardiac disease, DM, genetic syndrome, chronic lung disease,
Zheng	2020	Retrospective cohort	China	25 subjects, 2 in the comorbid group and 23 in the control group	Congenital heart disease
Anand	2020	Retrospective cohort	India	7 subjects, 3 in the comorbid group and 4 in the control group	Immune and hematologic disease
Abdel	2020	Retrospective cohort	UK	4 subjects, 1 in the comorbid group and 3 in the control group	Obesity
Bellino	2020	Retrospective cohort	Italy	3836 subjects, 206 in the comorbid group and 3630 in the control group	Genetic syndrome, malignancy, cardiac disease
Belhadjer	2020	Retrospective cohort	France	31 subjects, 10 in the comorbid group and 21 in the control group	Asthma, malignancy, cardiac disease
Bhumbra	2019	Retrospective cohort	USA	19 subjects, 8 in the comorbid group and 11 in the control group	Cerebral palsy, restrictive lung disease, obesity, new onset diabetic ketoacidosis
Biko	2020	Retrospective cohort	USA	313 subjects, 41 in the comorbid group and 272 in the control group	Genetic syndrome, obesity, neurologic disease, chronic pulmonary disease, endocrine disease, metabolic disorder, rheumatologic disease, cardiovascular, gastrointestinal, immune, hematologic disease and malignancy
Blumfield E	2020	Retrospective cohort	USA	18 subjects, 12 in the comorbid group and 6 in the control group	Acute myocarditis, hypertension, obesity, MIS-C, neurologic disease

Table 1. Study design and baseline characteristics of included studies (continued)

Author	Year	Study design	Country	Population	Comorbidities included in study
Chaoi	2020	Retrospective cohort	USA	46 subjects, 31 in the comorbid group and 15 in the control group	Obesity, immunodeficiency, asthma, seizure disorder, malignancy, cardiac disease
De Farias	2020	Retrospective cohort	Brazil	11 subjects, 5 in the comorbid group and 6 in the control group	Asthma, diabetes, neurologic disease, obesity, cardiovascular, hematologic disease, and oncology
De Biasi	2020	Retrospective cohort	USA	177 subjects, 69 in the comorbid group and 108 in the control group	Asthma, diabetes, neurologic disorder, obesity, cardiovascular, hematologic disease, and oncology
Derespina	2020	Retrospective cohort	USA	70 subjects, 52 in the comorbid group and 18 in the control group	Obesity, respiratory and cardiovascular disease, immune, hematologic disease, and malignancy, diabetes/pre-diabetes, neurologic disease
Diorio	2020	Prospective Cohort	USA	20 subjects, with 13 in the comorbid group and 7 in the control group	Neurologic disorder, endocrine disorder, cardiovascular disorder, prematurity, respiratory disorder, malignancy, global developmental delay
Du	2020	Retrospective cohort	China	182 subjects, 59 in the comorbid group and 123 in the control group	Allergic rhinitis, atopic dermatitis, drug allergies
Eghbali	2020	case series	Iran	4 subjects, 2 in the comorbid group and 2 in the control group	Congenital heart disease, aplastic anemia
Garazzino	2020	Retrospective cohort	Italy	168 subjects, 33 in the comorbid group and 135 in the control group	Chronic lung disease, genetic syndrome, malignancy, epilepsy, gastrointestinal and metabolic disorder, immunodeficiency
Garcia Salido	2020	Prospective Cohort	Spain	7 subjects, 1 in the comorbid group and 6 in the control group	Allogenic hematopoietic stem cell transplant
Gonzalez	2020	Retrospective cohort	USA	17 subjects, 12 in the comorbid group and 5 in the control group	Respiratory disease, cardiovascular disease, malignancy, obesity
Gotzinger	2020	Cross-sectional	Austria	582 subjects, 145 in the comorbid group and 437 in the control group	Genetic syndrome, renal disease, respiratory disease, malignancy, neurological disorder
Kainth	2020	Retrospective cohort	USA	65 subjects, 30 in the comorbid group and 35 in the control group	Asthma, chronic lung disease, immunosuppression, neuromuscular disease, congenital heart disease, malignancy, hemoglobinopathy, DM
Kaushik	2020	Retrospective cohort	USA	33 subjects, with 16 in the comorbid group and 17 in the control group	Asthma, allergic rhinitis, obesity, cardiovascular disease, , immune and hematologic disease
Leeb	2020	Retrospective cohort	USA	277,285 subjects, 7738 in the comorbid group and 269,547 in the control group	Chronic lung disease, Impairment or disability, diabetes, psychiatric illness, current/former smoker, obesity, renal disease, cardiovascular disease, substance abuse
Lovinsky	2020	Retrospective cohort	USA	55 subjects, 24 in the comorbid group and 31 in the control group	Asthma, hypertension, hyperlipidemia, diabetes
Laila	2020	Retrospective cohort	Australia	4 subjects, 1 in the comorbid group and 3 in the control group	Asthma
Giacomet	2020	Retrospective cohort	Italy	127 subjects, 20 in the comorbid group and 107 in the control group	Chronic cardiac condition, gastrointestinal disease, obesity, chronic kidney disease, chronic neurologic disease, immune disease

Table 1. Study design and baseline characteristics of included studies (continued)

Author	Year	Study design	Country	Population	Comorbidities included in study
Alfraij	2020	Retrospective cohort	Kuwait	25 subjects, 22 in the comorbid group and 3 in the control group	Neurological disease, malignancy, congenital heart disease
Hari Krishnan	2020	Case series	UK	45 subjects, 37 in the comorbid group and 8 in the control group	Hematological disease, malignancy, genetic syndrome, respiratory, cardiovascular, neurologic, renal and inherited metabolic disease
Hari Krishnan	2020	Case series	UK	45 subjects, 37 in the comorbid group and 8 in the control group	Hematological disease, malignancy, genetic syndrome, respiratory, cardiovascular, neurologic, renal and inherited metabolic disease
Grace	2020	Retrospective cohort	USA	77 subjects, 59 in the comorbid group and 18 in the control group	Prematurity, respiratory disease, congenital heart disease, diabetes, immunosuppression, autoimmune disorder, bone narrow transplant, kidney disease, malignancy, genetic syndrome
Grace	2020	Retrospective cohort	USA	77 subjects, 59 in the comorbid group and 18 in the control group	Prematurity, respiratory disease, congenital heart disease, diabetes, immunosuppression, autoimmune disorder, bone narrow transplant, kidney disease, malignancy, genetic syndrome
Cai	2020	Case series	China	5 subjects, 4 in the comorbid group and 1 in the control group	Intussusception, perforated acute suppurative appendicitis, hydronephrosis and renal calculi
Mannheim	2020	Case series	USA	64 subjects, 13 in the comorbid group and 51 in the control group	Chronic lung disease, trisomy 21, immunocompromised, atopy, prematurity
Meslin	2020	Case series	France	6 subjects, 2 in the comorbid group and 4 in the control group	Jaundice, congenital heart disease
Schwatz	2020	Case series	Iran	19 subjects, 14 in the comorbid group and 5 in the control group	Prematurity, jaundice, congenital heart disease

VSD=Ventricular Septal Defect, NAFLD=non-alcoholic fatty liver disease, MIS-C=multisystem inflammatory syndrome in children

milder symptoms than their adult counterparts and have good prognosis. Children are also more likely to be asymptomatic.[52] This may be due to the relative immaturity of the angiotensin converting enzyme (ACE) at a younger age, rendering children more protected against SARS-CoV-2, since the virus utilizes ACE to enter type II pneumocytes in the lung. [53,54] Another theory postulates that since young children tend to experience many viral infections, the repeated viral exposure may strengthen the immune system's response to SARS-CoV-2.[55]

Our findings suggest that patients with comorbidities had greater disease severity compared to those without. Even though the presence of comorbidities affects prognosis, children with COVID-19 generally have a favorable prognosis. A previous meta-analysis showed that all pediatric age groups are prone to COVID-19 infection, but the disease usually has a mild clinical presentation and minimal sequelae; critical illness and death was extremely rare.[56] Despite the favorable prognosis, those under one year of age need special attention, as they have a higher incidence of critical illness.[57]

However, the presence of comorbidities is not the sole factor affecting prognosis. The clinical manifestations in a patient also play an important role. An earlier meta-analysis reported that the most frequent symptoms of COVID-19 in children are fever, cough, vomiting, diarrhea, sore throat, and dyspnea, and the common laboratory findings are a positive RT-PCR, low oxygen saturation, and elevated D-dimer levels. Gastrointestinal symptoms were more common among children. It should also be noted that although children with COVID-19 tend to have milder clinical manifestations, a more favorable prognosis, and lower mortality than adults with the disease, children are

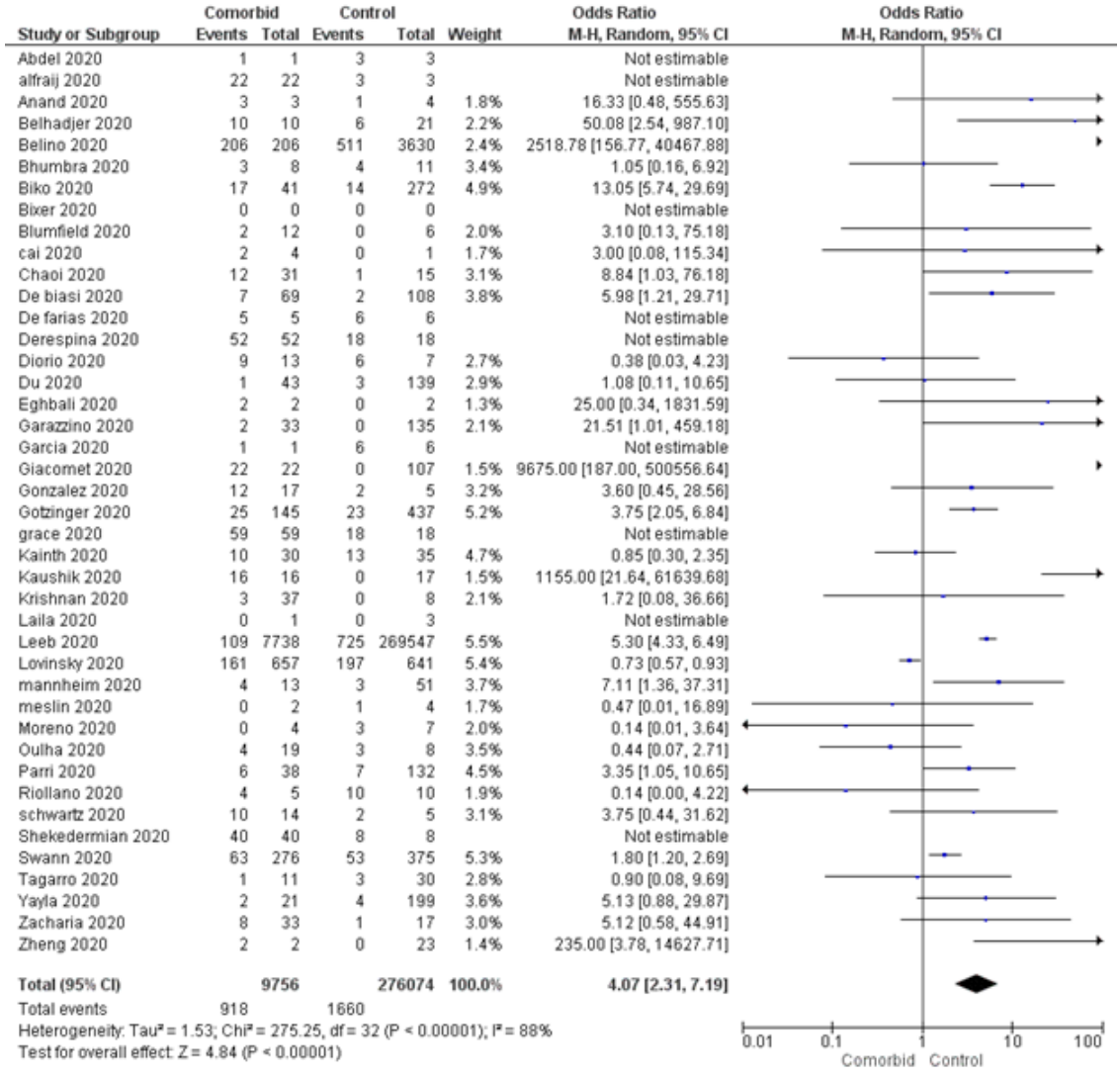

Figure 2. Forest plot of the odds ratio of severe COVID-19 in pediatric patients with *vs.* without comorbidities

potential carriers who can transmit the infection in the population.[58]

Furthermore, a the presence of comorbidities such as hematologic and immune disorders, asthma, chronic lung disease, congenital heart disease, hypertension, epilepsy, and obesity were found to be correlated with greater severity of COVID-19. Proper triage of patients should be implemented by carefully inquiring about patients' medical history in order to identify patients who would be more likely to develop serious adverse outcomes of COVID-19.

In conclusion, the presence of comorbidities in pediatric COVID-19 patients significantly increase the risk for developing severe symptoms. More attention should be given to protection against COVID-19 in children with comorbidities and chronic medical conditions, in the form of public health prevention and vaccine prioritization efforts. When encountering children with comorbidities infected with COVID-19, healthcare practitioners should consider the potential need for more vigilant management.

Conflict of interest

None declared.

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