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Prevalence and risk associated with asthma in children hospitalized with SARS-CoV-2: a meta-analysis and systematic review

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Clinical Implications

There is controversy about the risk factors for severe by severe acute respiratory syndrome coronavirus 2 infection and hospitalization in adult patients, but data in children are even more controversial. Clarification regarding this knowledge can help improve care and surveillance in children with asthma who developing by severe acute respiratory syndrome coronavirus 2 infection and its complications.

Children appear to be less affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection than do adults. They present with milder symptoms and develop less severe complications. Asthma has been suggested as a risk factor for moderate to severe SARS-CoV-2 infection in adults by the Centers for Disease Control and Prevention despite heterogeneous results from many studies. It is unclear whether children with asthma are at risk for severe SARS-CoV-2 infection. Although morbidity and mortality from SARS-CoV-2 infection are less in children, identifying risk factors for severe SARS-CoV-2 infection in the pediatric population is important.

We performed a meta-analysis to evaluate the prevalence of asthma in pediatric patients hospitalized with SARS-CoV-2 infection and to examine the association between asthma and the risk for hospitalization. We comprehensively searched MEDLINE, Embase, and Cochrane Database from inception to March 2021. The systematic literature review was undertaken independently by two investigators (W.M. and N.T.), applying a search approach that incorporated the terms "COVID 19" OR "SARS-CoV-2" combined with "asthma" AND "children" OR "pediatric". Eligible studies were prospective or retrospective observational studies (cohort, case-control, or cross-sectional studies) and randomized studies of any sample size that reported pediatric patients hospitalized for SARS-CoV-2 infection with the diagnosis of asthma. Patients hospitalized in any inpatient pediatric unit (critical care, acute care, and wards) were included. Case reports were excluded.

A total of 267 eligible studies were identified using this search strategy. After we excluded duplicate articles, case reports, correspondences, review articles, *in vitro* studies, adult patients, and animal studies, 47 articles met inclusion criteria for full-length review. Of the 47 articles, 38 studies were excluded owing to a lack of interest outcome. The remaining nine studies included in the analysis were all observational. A total of 1,193 pediatric patients were included in these studies.[1-9] Details of each study included in the analysis are listed in Table I.

The pooled estimated prevalence of asthma in children hospitalized for SARS-CoV-2 infection was 19% (95% confidence interval [CI], 13-26; $I^2 = 86\%$) (Figure 1). The highest prevalence of asthma was 49%, reported by Moeller et al,7 and the lowest was 9%, reported by Floyd et al.[5] The total number of children hospitalized with SARS-CoV-2 infection was 805; of these, 145 had asthma (18%).

Only five of nine studies had available data to analyze the impact of asthma on hospitalization risk among children with SARS-CoV-2 infection. The pool estimated odds ratio was 0.79 (95% CI, 0.25-2.46; $I^2 = 83\%$; $P < .59$) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Four of nine studies contained data for critical care admission versus general ward admission in children with and without asthma hospitalized with SARS-CoV-2 infection. The pool estimated risk report odds ratio was 0.82 (95% CI, 0.13-5.08; $I^2 = 67\%$; $P = .74$) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Our study demonstrated that around 19% of children hospitalized for SARS-CoV-2 infection had asthma (calculated with a random-effects model). However, there was high heterogeneity across studies, with $I^2 = 86\%$. One explanation for the high heterogeneity could be the differing asthma prevalence rate in each study population. Second, the difference in admission criteria for hospitalization in children with SARS-CoV-2 infection between locations may also have led to high heterogeneity. The sensitivity analysis was conducted by omitting one study at a time. The heterogeneity decreased to $I^2 = 19.3\%$ and the prevalence of children with asthma who were hospitalized for SARS-CoV-2 infection decreased to 12.9% when we omitted the study by Moeller et al. This finding confirmed our hypothesis mentioned earlier.

We demonstrated that asthma is not a risk factor for hospitalization in children with SARS-CoV-2 infection. In our meta-analysis, children with asthma did not experience a higher severity of SARS-CoV-2 infection. Furthermore, children with asthma and SARS-CoV-2 infection were not at risk for critical care admission.

The findings of our analysis may be explained by an association between the COVID-19 viral particle and angiotensin converting enzyme-2 receptors to which the viral particles attach to enter human cells. Patients with asthma have been shown to have decreased angiotensin converting enzyme-2 receptor gene expression compared with healthy controls, which may be the protective factor for an individual with asthma.[1]

There were several limitations to our study. First, all studies in our meta-analysis were observational; therefore, residual biases were inevitable. Second, there were differences in the cutoff age of pediatric patients in each study. Furthermore, one of the studies (Beken et al[1]) was less reliable for analysis because 80% of included patients were female whereas most children with asthma are male. Third, most of the included studies did not mention how asthma was diagnosed. Finally, the lack of covariates adjustment of important factors, such as the severity of asthma,

TABLE I. Study characteristics

First author	Year	Location	Average age, y	Female sex (%)	Total children hospitalized	Total children with asthma (%)	Total intensive care unit admission (%)	Intensive care unit admission with asthma (%)	Total ward admission (%)	Ward admission with asthma (%)
Beken[1]	2021	Turkey	8.5	49 (80.3)	61	9 (14.8)	N/A	N/A	N/A	N/A
Chao[2]	2020	NY	13.1	15 (32.6)	46	11 (23.9)	13 (28.2)	3 (6.5)	33 (71.7)	8 (17.4)
DeBiasi[3]	2020	Washington, DC	9.6	22 (50)	44	7 (15.9)	9 (20.4)	2 (4.5)	35 (79.5)	5 (11.3)
Elghoudi[4]	2020	United Arab Emirates	6.5	140 (48.6)	288	37 (12.8)	N/A	N/A	N/A	N/A
Floyd[5]	2021	Pa	N/A	48 (39.6)	121	11 (9)	N/A	N/A	N/A	N/A
Graff[6]	2020	Colo	11	27 (40.9)	66	16 (24.2)	11 (16.6)	N/A	55 (83.3)	N/A
Moeller[7]	2020	Europe*	N/A	N/A	78	38 (48.7)	23 (29.4)	5 (6.4)	55 (70.5)	33 (42.3)
Thiabaud[8]	2020	Switzerland	N/A	N/A	19	4 (21)	N/A	N/A	N/A	N/A
Verma[9]	2021	NY	5	30 (36.5)	82	12 (14.6)	23 (28)	5 (6)	59 (71.9)	7 (8.5)

*Austria, Netherlands, Spain, Switzerland, and United Kingdom.

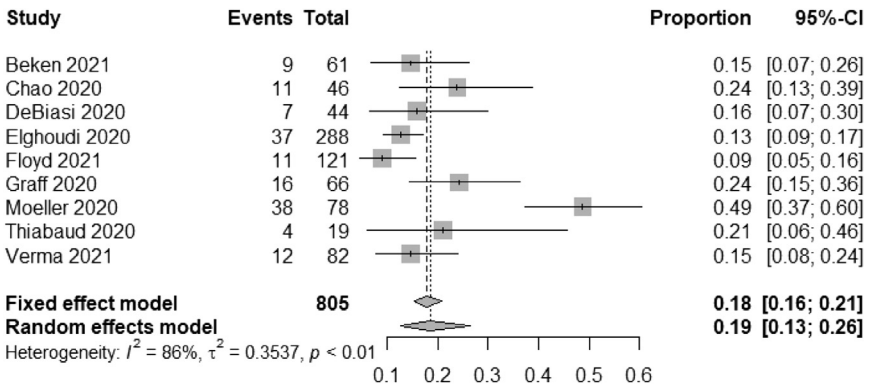

FIGURE 1. Prevalence of asthma in children hospitalized with SAR-CoV-2 infection. Square data markers represent the prevalence of asthma in each study. Horizontal lines represent 95% confidence interval (CI), with marker sizes reflecting statistical weights of each study. Diamond data markers represent overall prevalence and 95% CI.

treatment of asthma, asthma phenotypes, and comorbid diseases, and the lack of specific criteria for hospitalization and critical care admission may have led to the inclusion of a heterogeneous group of pediatric patients which might have affected the overall analysis.

Asthma does not appear to be a risk factor for hospitalization or critical care admission caused by SARS-CoV-2 infection in children. Further studies and detailed analyses should be performed to confirm this conclusion owing to the significant heterogeneity in our analysis.

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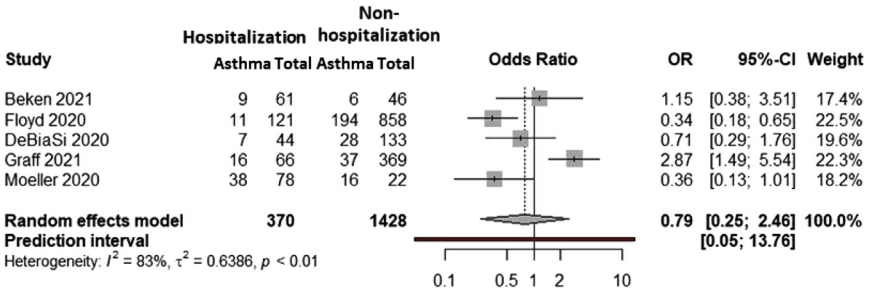

FIGURE E1. Forest plot representing association of asthma and risk for hospitalization in pediatric patients infected with SARS-CoV-2 infection. Square data markers represent odd ratio (OR) and horizontal lines represent 95% confidence interval (CI) with marker size reflecting the statistical weight of the study. Diamond data marker represents OR and 95% CI.

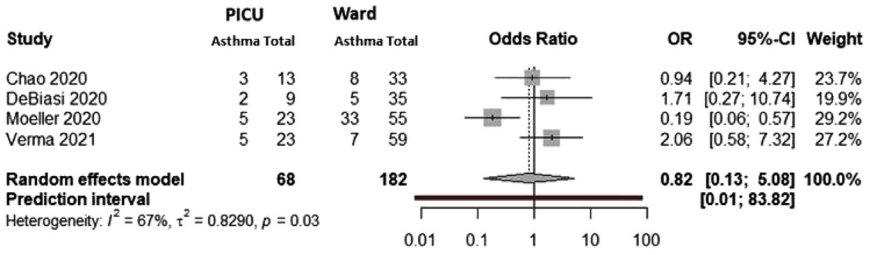

FIGURE E2. Forest plot representing association of asthma and risk for critical care admission in pediatric patients hospitalized with SARS-CoV-2 infection. Square data markers represent odd ratio (OR) and horizontal lines represent 95% confidence interval (CI) with marker size reflecting the statistical weight of the study. Diamond data marker represents OR and 95% CI.