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Prevalence of Asthma in Hospitalized and Non-Hospitalized Children with COVID-19

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34 **Clinical Implications**

35 In our cohort of 979 children with PCR-confirmed COVID-19, 205 (21%) had asthma, a number
36 consistent with previously published asthma prevalence estimates within our network. Asthma
37 diagnosis was negatively associated with COVID-19–related hospitalization.

38 **Word Count:** 1000 words

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While initial reports of the novel coronavirus disease 2019 (COVID-19) showed limited and non-severe manifestations in children, more recent reports have begun to describe more serious illness in children, including patient characteristics associated with hospitalization and death.^{1,2} During the early stages of the pandemic, the United States' (US) Centers for Disease Control and Prevention listed moderate to severe asthma as a potential risk factor for severe COVID-19, yet there is little data to support this assertion in children and published data in adults are conflicting.³⁻⁵ The largest cohort of pediatric COVID-19 positive patients in the US included only descriptive statistics on underlying conditions and severity and did not delineate diagnosis-specific associations with hospitalization.⁶ To help address these gaps in knowledge, we completed a retrospective cohort study in a large pediatric cohort of patients with polymerase chain reaction (PCR) confirmed COVID-19 to determine the association between current asthma and hospitalization.

We extracted electronic health records (EHR), including demographics, clinical characteristics, and asthma medications for all children aged 21 years and under with a positive PCR test for SARS-CoV-2 at any Children's Hospital of Philadelphia setting (drive-through testing, outpatient, emergency department (ED), or inpatient) between 3/17/20-8/26/20. Presence of a current asthma diagnosis was determined using an existing EHR asthma registry definition, which required that they met either of the following criteria at the time of testing: (1) encounter diagnosis for asthma (International Classification of Disease, 10th Revision, code J45) within the past one year or an active problem list diagnosis for asthma AND a prescription for an asthma-specific medication in the last year; OR (2) an active persistent asthma diagnosis on the problem list. COVID-19 hospitalizations were defined as any hospitalization within 14 days of a first positive PCR for SARS-CoV-2. To account for potential confounding, multivariable logistic

regression was used to calculate adjusted odds ratios (ORs) for COVID-19 hospitalization. Since all hospitalized patients were screened for COVID-19 on admission regardless of symptoms or exposure risk, unlike other care settings, we performed a secondary analysis including only hospitalizations determined to be COVID-19-related on chart review by board-certified pediatricians (KM, SHE, DAH, CCK) to investigate for differential confounding by testing indication. For patients with a current asthma diagnosis, we classified asthma severity based upon asthma medications prescribed within the year before a first COVID-19 positive PCR, using tiers modeled from the Global INitiative for Asthma guidelines for asthma severity. The association between asthma controller prescriptions and COVID-19 hospitalization was examined using the Fisher's exact test.

From 3/17/20-8/26/20, 979 patients ages 0-21 years tested positive for COVID-19 within our health system. Of these patients, 205 (21%) had an active asthma diagnosis at the time of testing. One hundred twenty-one patients (12%) were hospitalized with COVID-19, 11 of whom had a current asthma diagnosis. (Table 1)

In bivariate modeling, asthma was associated with a lower odds of COVID-19 hospitalization (OR: 0.34; 95% CI: 0.16-0.65; $P = .001$). In the adjusted model (Table 2), asthma diagnosis remained associated with a lower odds of COVID-19 hospitalization compared to children without asthma (OR: 0.28; 95%CI: 0.14-0.55; $P < .001$).

The frequency of patients with an asthma controller medication prescription was higher in the subgroup of patients with COVID-19 hospitalizations compared to those who were not hospitalized (82% vs 41%, respectively, $P=0.01$). Of note, only two children were prescribed a biologic for asthma and neither of these children were hospitalized. (Figure E1)

In the sensitivity analysis, 74 of the 121 hospitalizations (61%) were determined to be COVID-related. In the multivariable sensitivity analysis regression, the association between asthma and lower odds of hospitalization remained (OR: 0.40; 95%CI: 0.19-0.84; P = 0.02) (Table 2)

In this study, we report data on asthma prevalence and odds of hospitalization among a cohort of children who tested positive for COVID-19 from a large pediatric health system. Despite an asthma prevalence (21%) in COVID positive children that is nearly identical to the asthma prevalence within the health system's primary care network, asthma was inversely associated with COVID-19 hospitalization, both in our main analysis and sensitivity analysis. Results from small cohorts of children with COVID-19 have demonstrated relatively high prevalence of asthma in hospitalized children (16-24%). However, in addition to smaller sample sizes, these studies either did not describe how they defined asthma¹ or used a less specific definition, such as asthma diagnosis in the last 5 years⁴, which might inflate the prevalence. In these studies, children with asthma did not have a higher risk of severe hospital outcomes, such as ICU admission or death.^{1,4} Our results add to these previous findings and suggest that asthma may actually be associated with lower hospitalization risk in children.

There are several suggested mechanisms for a potential protective effect of asthma against severe COVID-19. First, concern for COVID-19 causing severe asthma exacerbations may have led to increased adherence to protective behaviors like physical distancing, mask-wearing, and asthma controller medication adherence⁷, so children with asthma may have had a lower burden of COVID-19 symptoms when they presented. Second, early in the pandemic, inhaled steroids were hypothesized to protect against severe COVID-19 and thus lower the risk of hospitalization. This relationship, however, is still unclear and the majority of children in our cohort were not on

controller medications.⁸ Lastly, there is associative evidence that suggests underlying allergic inflammation may protect against SARS-COV-2 infection or severe COVID-19 outcomes.⁹

There are several limitations to this analysis. First, given our retrospective study design, we were not able to determine causality. Second, for children who only presented to the ED or inpatient setting, we could not ascertain past asthma encounters to primary care outside of our network and thus asthma in hospitalized children could be undercounted. However, our manual chart review of all hospitalized children did not identify missed asthma diagnoses in the hospitalized cohort. Lastly, our results reflect the experience of a single pediatric health system. Larger, multicenter studies are needed to confirm the observed negative association between asthma diagnosis and COVID-related hospitalization, as well as elucidate how asthma severity may affect COVID-19 outcomes.

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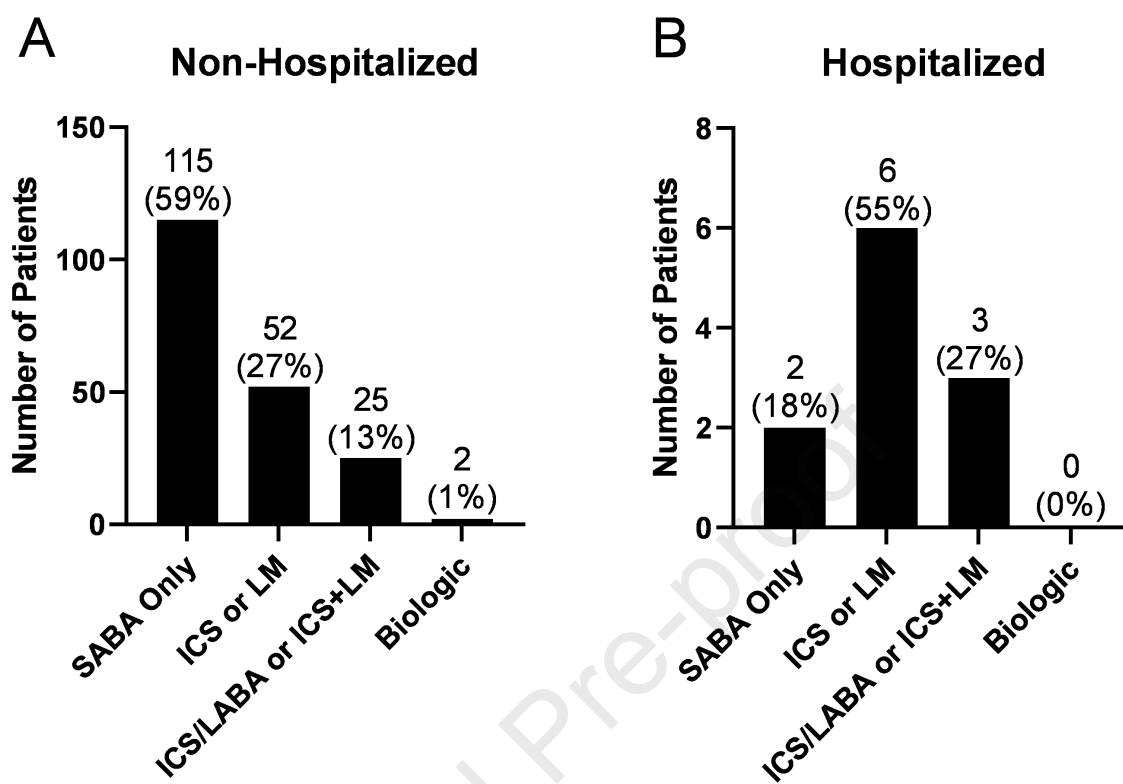
	All Patients (n=979)	Non-Hospitalized (n = 858)	Hospitalized (n=121)
Age (years)			
0-4	279 (28)	232 (27)	47 (39)
5-11	225 (23)	194 (23)	31 (26)
12-17	328 (34)	291 (34)	37 (31)
18-21	147 (15)	141 (16)	6 (5)
Sex			
Male	504 (51)	431 (50)	73 (60)
Race, n (%)			
Black	421 (43)	370 (43)	51 (42)
Non-Black	558 (57)	488 (57)	70 (58)
Ethnicity, n (%)			
Hispanic or Latino	145 (15)	121 (14)	24 (20)
Insurance Payer Status, n (%)			
Medicaid	477 (49)	399 (47)	78 (64)
Private/Unknown	502 (51)	459 (53)	43 (36)
Obesity Diagnosis, n (%)	101 (10)	91 (11)	10 (8)
Complex Chronic Conditions, n (%)			
0	615 (63)	575 (67)	40 (33)
1	175 (18)	746 (17)	29 (24)
2+	189 (19)	137 (16)	52 (43)
Asthma Diagnosis, n (%)	205 (21)	194 (23)	11 (9)
Asthma Treatment, n (%)*			
SABA Only	117 (57)	115 (59)	2 (18)
ICS or LM	58 (28)	52 (27)	6 (55)
ICS/LABA or ICS+LM	28 (14)	25 (13)	3 (27)
Biologic	2 (1)	2 (1)	0 (0)
Systemic corticosteroid	65 (32)	58 (30)	7 (64)

Table 1 – Demographic and clinical characteristics of COVID-19 patients stratified by hospitalization status

* Percentages represent the proportion of patients within the asthma cohort who were prescribed asthma medications in the year preceding positive SARS CoV-2 test. Categories are mutually exclusive with the exception of systemic corticosteroid; *SABA only*: short-acting-beta-agonist only; *ICS or LM*: inhaled corticosteroids or leukotriene modifier; *ICS/LABA or ICS + LM*: inhaled corticosteroid with long-acting-beta-agonist or inhaled corticosteroid and leukotriene modifier

158 **Table 2 – Multivariable model results demonstrating the odds of hospitalization by model**
 159 **covariate in (1) main model (all hospitalizations occurring within 14 days of a positive PCR**
 160 **for COVID-19) and (2) sensitivity analysis (COVID-19 related hospitalizations determined**
 161 **by chart review)**

	Main multivariable model		Sensitivity analysis model	
Covariate	Odds Ratio (95%CI)	P-Value	Odds Ratio (95%CI)	P-Value
Asthma	0.28 (0.14-0.55)	<0.001	0.40 (0.19-0.84)	0.02
Age				
0-4	1.65 (0.99-2.76)	.053	1.86 (0.99-3.50)	.055
5-11	1.47 (0.86-2.53)	.16	1.36 (0.68-2.71)	.39
12+ (Reference)	-	-	-	-
Sex				
Male	1.85 (1.21-2.82)	0.004	2.08 (1.22-3.52)	0.007
Race				
Black	1.07 (0.67-1.70)	0.79	1.06 (0.60-1.89)	0.83
Ethnicity				
Hispanic or Latino	1.11 (0.61-2.01)	0.73	0.98 (0.47-2.06)	0.96
Payer				
Medicaid	1.85 (1.17-2.93)	0.009	2.54 (1.40-4.62)	0.002
Obesity Diagnosis	0.76 (0.36-1.63)	0.49	0.66 (0.24-1.80)	0.42
Complex Chronic Conditions				
0 (Reference)	-	-	-	-
1	3.58 (2.10-6.12)	<0.001	3.51 (1.79-6.90)	<0.001
2+	6.54 (4.04-10.59)	<0.001	7.37 (4.05-13.41)	<0.001



Online Repository

Methods

Data Source and Identification of COVID-19

This retrospective cohort study was conducted at the Children's Hospital of Philadelphia (CHOP), a free-standing pediatric hospital with approximately 2500 asthma-related hospitalizations and 6000 ED visits annually. We extracted data for all children aged 21 and under with a positive polymerase chain reaction (PCR) test for SARS-CoV-2 at any CHOP setting (drive-through testing, outpatient, ED, or inpatient) between March 17th – August 26th. Mandatory pre-procedural testing was implemented on March 24th, and pre-admission testing for all hospitalized patients began on April 1st. We included children ages 18-21 since the transition to adult care often occurs late for children with chronic conditions at our institution and to allow for internal reliability and validity testing of our cohort definition with institutional data definitions of COVID-positive patients. Testing indications at drive through, outpatient, and ED sites included patients having symptoms of COVID-19 or having a recent high-risk exposure.

Determination of Asthma Severity

For those patients with a current asthma diagnosis, we classified asthma severity based upon asthma medications prescribed within the year prior to a first COVID-19 positive PCR. We broke down asthma severity into 4 tiers from low to high based on prescription for: (1) SABA only, (2) ICS or leukotriene modifier, (3) ICS and long-acting beta-agonist combination medication (ICS/LABA) OR ICS and leukotriene modifier, and (4) asthma biologic. These tiers were modeled from the Global INitiative for Asthma guidelines for asthma severity.

To account for whether patients with asthma had a recent asthma exacerbation, systemic corticosteroids prescribed within the year prior to a first SARS CoV-2 positive PCR were also included.

Demographics and Comorbidities

Demographic characteristics included age category, sex (female/male), race (Black/non-Black), ethnicity (Hispanic/non-Hispanic), and payer (Medicaid/non-Medicaid). Diagnoses for obesity were identified through ICD-10 codes. The number of complex chronic conditions (CCC) were quantified using a validated set of ICD-10 codes.

Statistical Analysis

We compared demographics and clinical characteristics between hospitalized and non-hospitalized children using Fisher's exact or Chi-square tests as appropriate for categorical variables. Multivariable logistic regression was used to calculate adjusted odds ratios (ORs) as well as the 95% confidence interval (CI) for COVID-19 hospitalization. The multivariable models included variables that have been shown to be associated with both severe COVID-19 and asthma in prior studies (i.e. sex, age, race, ethnicity, obesity, medical complexity), as well as additional covariates that were associated with hospitalization in bivariate analysis at a significance level of $P < 0.2$. The association between COVID-19 hospitalization and asthma controller prescription (inhaled corticosteroid (ICS), leukotriene modifier, inhaled corticosteroid/long acting beta-agonist combination (ICS/LABA), or a biologic in the preceding year) was examined using the Fisher's exact test rather than multivariable logistic regression, due to low prevalence of hospitalization in children with asthma.

We performed a secondary analysis including only hospitalizations determined to be COVID-19-related on chart review to investigate for differential confounding by testing indication. One of four board-certified pediatricians (KM, SEH, DAH, CCK) abstracted the charts of children with COVID-19 hospitalization using a standardized template. Hospitalizations were considered COVID-19-related based upon treating physician documentation. When relevant documentation was not present, this determination was made by the abstracting physician based upon recent symptoms consistent with COVID-19 and a plausible pathologic mechanism. Cases where this distinction was unclear were reviewed by the group and final consensus was consistent with initial determination in eight of the nine cases.

Statistical analyses were completed in STATA 16 (StataCorp LLC, College Station, Texas). The CHOP institutional review board reviewed the study and determined that it did not meet the criteria for human subjects research.

Figure Legends

Figure E1: Number of non-hospitalized (**Panel A**) and hospitalized patients (**Panel B**) grouped by four different asthma medication severity categories: *SABA only*, short-acting-beta-agonist only; *ICS or LM*, inhaled corticosteroids or leukotriene modifier; *ICS/LABA or ICS + LM*, inhaled corticosteroid with long-acting-beta-agonist or inhaled corticosteroid and leukotriene modifier; *Biologic*