Asthma and COVID-19: An early inpatient and outpatient experience at a US children's hospital

Sherry Farzan MD1,3,4,5 | Shipra Rai MD, MPH3 | Jane Cerise PhD6 | Shari Bernstein RN, MSN, AE-C3 | Gina Coscia MD1,3,4 | Jamie S. Hirsch MD, MA, MSB4,5,7 | Judith Jeanty RN, MSN, AE-C3 | Mary Makaryus MD3 | Stacy McGeechan MD3 | Alissa McInerney MD1,3,4 | Annabelle Quizon MD2,3 | Maria Teresa Santiago MD2,3

1Division of Allergy & Immunology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Great Neck, New York, USA
2Division of Pediatric Pulmonology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, New York, USA
3Department of Pediatrics, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, New Hyde Park, New York, USA
4Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health System, Manhasset, New York, USA
5Institute of Health System Science, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, New York, USA
6Biostatistics Unit, Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA
7Department of Information Services, Northwell Health, New Hyde Park, New York, USA

Abstract

Background: Initially, persistent asthma was deemed a risk factor for severe COVID-19 disease. However, data suggests that asthmatics do not have an increased risk of COVID-19 infection or disease. There is a paucity of data describing pediatric asthmatics with COVID-19.

Objective: The objectives of this study were to determine the prevalence of asthma among hospitalized children with acute symptomatic COVID-19, compare demographic and clinical outcomes between asthmatics and nonasthmatics, and characterize behaviors of our outpatient pediatric population.

Methods: We conducted a single-center retrospective study of pediatric patients admitted to the Cohen Children’s Medical Center at Northwell Health with symptomatic COVID-19 within 4 months of the surge beginning in March 2020 and a retrospective analysis of pediatric asthma outpatients seen in the previous 6 months. Baseline demographic variables and clinical outcomes for inpatients, and medication compliance, health behaviors, and asthma control for outpatients were collected.

Results: Thirty-eight inpatients and 95 outpatients were included. The inpatient prevalence of asthma was 34.2%. Asthmatics were less likely to have abnormal chest x-rays (CXRs), require oxygen support, and be treated with remdesivir. Among outpatients, 41% reported improved asthma control and decreased rescue medication use, with no COVID-19 hospitalizations, despite six suspected infections.

Conclusions: Among children hospitalized for acute symptomatic COVID-19 at our institution, 34.2% had a diagnosis of asthma. Asthmatics did not have a more severe course and required a lower level of care. Outpatients had improved medication compliance and control and a low risk of hospitalization. Biological and behavioral factors may have mitigated against severe disease.
1 | INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was discovered in Wuhan, China.¹ Now known as COVID-19, it was declared a pandemic on March 11, 2020, and a national emergency in the U.S. on March 13, 2020.² SARS-CoV2 is a beta coronavirus and a single strand positive-sense RNA virus that uses the ACE2 receptor to attach to the respiratory epithelial cells.³ The clinical picture of COVID-19 includes fever, fatigue, sore throat, cough, chest pain, dyspnea, headache, and diarrhea. The infection can lead to pneumonia and a cytokine storm.⁴ Patients with COVID-19 present with lymphopenia and elevated C reactive protein (CRP), procalcitonin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-Dimer.⁵ Although cases continue to rise, research is still forthcoming about the impacts of COVID-19 on both adults and children. Initially, the Centers for Disease Control and Prevention (CDC) listed asthma as significant comorbidity for COVID-19.⁶ However, in Wuhan, a retrospective analysis of the first 425 cases found that only 0.9% of the study population had asthma, which is lower than the adult asthma prevalence (4.5%).⁷ In the USA, hospitalized adult COVID-19 patients had a lower prevalence of asthma and COPD as compared to obesity, hypertension, and diabetes.⁸ A systematic review showed only 1.8% of patients had asthma in 18 studies that included 8690 patients.⁹ Among pediatrics, asthma was not considered significant comorbidity.⁹,¹⁰ Most children with asthma and COVID-19 did not require ICU admission and did not have a severe infection.¹¹,¹² Additionally, studies have shown decreased admission rates for asthmatics as compared to the same time period in previous years.¹³,¹⁴ A systematic review that evaluated 67 pediatric studies found no data on whether asthma constitutes an increased risk of COVID-19 infection or severity and called for more research.¹⁵

Professional societies recommend limiting in-person visits and having asthmatics continue their controller medications.¹² In a survey of 91 pediatric asthma specialists from 27 countries, about 39% stopped physical appointments and 47% stopped seeing new patients.¹⁴ Limiting in-person visits poses difficulties in management due to technological barriers and limited clinical information without spirometry.¹⁵ Providers are also concerned about the impact of corticosteroid use on patients infected with COVID-19. Adult patients with SARS or MERS had higher viral loads, longer duration of viremia, and worse clinical outcomes with systemic steroid use.¹⁶ However, specifically timed systemic steroid treatment in COVID-19 patients is now known to significantly decrease mortality and median hospital stay.¹⁷–¹⁹

Given the paucity of data regarding COVID-19 among pediatric asthmatics, the current study aims to describe the characteristics of hospitalized pediatric asthmatics compared to nonasthmatics, as well as the experience of outpatient pediatric asthmatics during the beginning of the pandemic. This data may provide clinicians with a basis for recommendations for pediatric asthmatics and their families during the COVID-19 pandemic. We examined if there was a difference in COVID-19 outcomes between asthmatic and nonasthmatics. We also hypothesize that among outpatient pediatric asthmatics, their asthma control improved during the pandemic.

2 | MATERIALS AND METHODS

A single-center retrospective chart review was conducted of pediatric patients who tested positive for SARS-CoV2 by PCR and were admitted to the Steven and Alexandra Cohen Children’s Medical Center (CCMC) at the Northwell Health System between March and July 2020. Using unique anonymized patient identifiers, reviews of the electronic health record (EHR) were performed by seven physician reviewers. Patients were excluded if they had a diagnosis of Multisystem Inflammatory Syndrome in Children (MIS-C), were less than two years old, or if they were asymptomatic for COVID-19. The charts were reviewed to confirm the diagnoses of symptomatic COVID-19 and asthma and to extract baseline variables or clinical endpoints that were not previously entered in the Northwell Consortium database. Asthmatic patients were defined as patients 2-18 years old with a diagnosis of asthma documented in the EHR. Baseline variables included patient’s age, gender, race, ethnicity, and body mass index percentile. COVID-19 related variables and endpoints included source of exposure, length of stay (LOS), days of illness before presentation, ICU admission, maximum ventilatory and oxygen requirement, days on a ventilator, medical management for COVID-19 (e.g., hydroxychloroquine, azithromycin, remdesivir), chest x-ray (CXR) findings, and discharge disposition. Laboratory markers included initial and peak measurements of white blood cell count (WBC), initial and nadir absolute lymphocyte count (ALC), absolute neutrophil count (ANC), CRP, erythrocyte sedimentation rate (ESR), ferritin, and D-dimer, if available. A primary outcome included the prevalence of asthma in the cohort of COVID-19 admissions. Secondary outcomes were differences between asthmatics and nonasthmatics admitted for COVID-19 with respect to baseline demographic and COVID-19 related endpoints. Data was entered into and managed by the Research Electronic Data Capture (REDCap) at Northwell Health.

Given the limits on in-person visits, parents of asthma patients seen in our pediatric asthma, pulmonary and allergy clinics were contacted for telephone interviews to assess asthma control and compliance during the initial phase of the pandemic (April–June 2020). A cross-sectional review of the families’ responses of 95 pediatric outpatients was performed. Responses regarding the patient’s level of asthma control, compliance with controller medication, use of rescue medication, exacerbations, and level of social distancing

**KEYWORDS**

asthma, COVID-19
during the pandemic and 6 months prior were assessed. Exposure to, symptoms of, and testing for COVID-19 were also collected. The inpatient portion of the study was approved by the Northwell Institutional Review Board under the umbrella of the Northwell COVID-19 Research consortium. The Northwell Institutional Review Board approved the outpatient portion of the study.

2.1 | Statistical analysis

Summary statistics were reported for demographics, laboratory variables, CXR results, and COVID-19 related endpoints by asthmatic/nonasthmatic status. Continuous variables were reported as medians, and interquartile ranges (IQR: 25th percentile to 75th percentile). Categorical variables were reported as frequencies and percentages. For continuous variables, Wilcoxon rank sum tests were used to test for differences in distribution between asthmatics and nonasthmatics. For categorical variables, chi-square tests or Fisher’s exact test were used, as appropriate, to compare asthmatics and nonasthmatics. For laboratory variables, only those assays that had 75% or more nonmissing values in both groups were presented and compared. The need for ventilatory support was analyzed as a binary variable with patients defined as needing ventilatory support if they were administered high flow oxygen, positive pressure ventilation, or mechanical ventilation. COVID-19 therapies were analyzed separately by treatment. Because one patient was still in the hospital at the last follow-up time available, length of stay was estimated using Kaplan-Meier treating the patient who was not discharged as censored, and asthmatics were compared to nonasthmatics, using Wilcoxon test.

A p-value < .05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Medical records of eighty-nine pediatric patients admitted to CCMC during the study period were reviewed. Eleven had MISC-C/PIMS, 12 were asymptomatic, and 28 patients were under 2 years of age. Of the remaining 38 patients, 13 (34.2%, 95% exact CI: 19.6% to 51.4%) had asthma. Demographic characteristics of asthmatics and nonasthmatics are summarized in Table 1. The nonasthmatics had significantly more women (18, 72.0%) compared to asthmatics (4, 30.8%) (p = .02). No significant differences were found between nonasthmatics and asthmatics with respect to race, ethnicity, age distribution, distribution of BMI percentiles, COVID-19 exposure, or days of illness onset before ER presentation. Four asthmatics (30.8%) were on daily ICS, none were on ICS/LABA and one was on montelukast (7.7%).

Ventilatory support, medical management, and outcomes are summarized in Table 1. Significantly more nonasthmatics (n = 11, 44.0%) required oxygen support compared to asthmatics (n = 1, 7.7%) (p = .03).
Additionally, two (8.0%) nonasthmatics versus no asthmatics required oxygen at discharge.

Radiographic findings and laboratory values in nonasthmatics and asthmatics are summarized in Table 2. Significantly more nonasthmatics (n = 15, 75%) had abnormal CXRs compared to two (22.2%) asthmatics (p = .01). Radiologic abnormalities consisted primarily of patchy infiltrates while one nonasthmatic patient had a consolidation and a pleural effusion. There were no statistically significant differences in WBC, ANC, and ALC, initial AST, and ALT between asthmatics and nonasthmatics. Median peak AST (58 [IQR: 35–131] vs. 33 [IQR: 20–54] [p = .02]) and ALT (60 [IQR: 29–158] vs. 19 [IQR: 15–44] [p = .004]) were significantly higher among nonasthmatics compared to asthmatics. Although not consistently measured in all patients, the median values for serum CRP (measured in 7 [53.8%] asthmatics vs. 16 [64%] nonasthmatics), troponin (4 [30.7%] asthmatics vs. 9 [36%] asthmatics), ferritin (6 [46.1%] asthmatics vs. 15 [60%] nonasthmatics), IL-6 and IL-10 (both measured in 1 [7.7%] asthmatic vs. 5 [20%] nonasthmatics) were above normal levels for our laboratory in both patient groups.

Data for 95 asthmatics followed in the outpatient clinic are summarized in Table 3. Forty-six percent of patients had mild persistent asthma and 43.1% had moderate persistent asthma. Fourteen patients (14.7%) were on a combined ICS/LABA and 81 (85.2%) were on ICS. Forty-one percent of patients reported better control of asthma and less use of rescue inhalers during the pandemic compared to what they recalled as their compliance 6 months earlier. Almost 70% of patients surveyed reported observing more social distancing than their peers during the pandemic. Twelve patients had close contact with infected individuals; of these, six (50%) reported symptoms, but only one was tested due to limited testing capability. None of the patients with

| TABLE 2 Radiographic and laboratory findings in asthmatic versus nonasthmatic pediatric patients admitted for COVID-19 |
|-----------------------------------------------|----------------|------------|----------------|----------------|----------------|
| Abnormal chest radiographs                    | Number         | Asthmatics | Number         | Nonasthmatics | p value        |
| WBC (3.8–10.5 K/uL)                           | 10             | 6.2 (IQR: 4.4–9.9) | 25             | 6.9 (IQR: 5.2–14.3) | NS             |
| Absolute lymphocyte count (1.0–3.3 K/uL)      | 10             | 0.95 (0.79–1.23) | 25             | 1.2 (IQR: 0.82–2.4) | NS             |
| Absolute neutrophil count (1.8–7.4 K/uL)     | 10             | 4.3 (IQR: 3.4–7.4) | 25             | 5.6 (IQR: 2.8–7.9) | NS             |
| Initial AST (4–32 u/L)                        | 11             | 33.0 (IQR: 15.0–54.0) | 24             | 49.0 (IQR: 30.0–81.0) | NS             |
| Initial ALT (4–33 u/L)                        | 11             | 19.0 (IQR: 15.0–44.0) | 24             | 34.0 (IQR: 19.0–73.0) | NS             |
| Peak AST (4–32 u/L)                           | 11             | 33.0 (IQR: 20.0–54.0) | 23             | 58.0 (IQR: 35.0–131.0) | p = .02        |
| Peak ALT (4–33 u/L)                           | 11             | 19.0 (IQR: 15.0–44.0) | 23             | 60.0 (IQR: 29.0–158.0) | p = .004       |
COVID-19 symptoms sought a sick visit with their pediatrician, had an ER visit, or required hospitalization.

### DISCUSSION

While the global SARS-CoV2 pandemic continues worldwide, the pediatric population has not experienced the level of morbidity and mortality faced by adults. Nevertheless, it is important to better understand risk factors for morbidity and mortality from COVID-19, especially among children. Since asthma is the most common chronic disease of childhood and SARS-CoV-2 primarily impacts the respiratory system, it is a valid concern that asthmatics would be at higher risk for severe disease. The CDC does designate that moderate to severe persistent asthma may be a risk factor for severe COVID-19. However, several studies, have not demonstrated that children or adults with asthma have a more severe presentation or worse outcomes. Several recent meta-analyses have examined COVID-19 in adult asthmatics demonstrating no increased risk of severity or mortality, but data on children is still limited. Our small cohort adds to this growing body of literature and provides a more detailed clinical picture of pediatric asthmatics admitted for COVID-19, as well as the outpatient experience.

This retrospective analysis demonstrates that of the 38 patients reviewed, 13 had a documented diagnosis of asthma, providing a prevalence of 34.2%, which is consistent with other reports. This does differ from the asthma prevalence rate reported in an overlapping cohort from our own institution, likely due to differences in study design and the time course of the two studies. Due to the difficulty of ascertaining an asthma diagnosis in patients admitted for recurrent bronchiolitis, patients under age two were excluded. We did not include a diagnosis of "reactive airway disease" among our asthma cases since this may have reflected those with other pulmonary conditions who used bronchodilators but without a true diagnosis of asthma. We also did not include patients who were asymptomatic for COVID-19. The exclusion of these patients likely contributed to the different rates. Overall, there were no significant differences between the nonasthmatics and asthmatics with respect to age, BMI percentiles, severity of illness, length of stay, ICU admission, or need for respiratory support or discharge disposition. Nonasthmatics were more likely to have an abnormal CXR, treated with remdesivir, and have oxygen requirements. Lab values such as WBC, ALC, ANC, initial ALT, and AST were not significantly different between the two groups.

| TABLE 3 | Survey of pediatric out-patients during COVID-19 pandemic, n = 95 |
|---------|---------------------------------------------------------------|
| N       | Percentage                                                  |
| Asthma severity |                                                |
| Intermittent 8  8.4  |
| Mild persistent 44  46.3  |
| Moderate persistent 41  43.1  |
| Severe persistent 2  2.1  |
| Asthma control |                                      |
| Better 39  41.0  |
| Same 52  54.7  |
| Worse 4  4.2  |
| Use of rescue inhaler |                      |
| Less 39  41.0  |
| Same 50  52.6  |
| More 6  6.3  |
| Compliance |                                           |
| More 17  17.9  |
| Same 71  74.7  |
| Less 7  7.3  |
| Exacerbations |                                     |
| Less 22  23.1  |
| Same 71  74.7  |
| More 4  4.2  |
| Close contact with COVID-19 |                         |
| Yes 12  12.6  |
| No 83  87.4  |
| Symptoms of COVID-19 |                                      |
| Yes 6  6.3  |
| No 89  93.7  |
| Social distancing |                            |
| More 66  69.5  |
| Same 15  15.8  |
| Less 0  |
| Don’t know 4  4.2  |

COVID-19 symptoms sought a sick visit with their pediatrician, had an ER visit, or required hospitalization.

The outpatient portion of this study demonstrated that pediatric asthmatics had the same or improved asthma control and compliance and that the majority had the same or less, level of exacerbations and rescue medication use during that time. There is only one other study examining behaviors of pediatric outpatient asthmatics, and it found that early in the pandemic, in-person asthma encounters and systemic steroid prescriptions decreased, consistent with our findings of improved control. These findings suggest that patient behaviors agree with the recommendations from professional bodies regarding the management of asthma during this pandemic.

In our cohort, we did not find evidence that asthma elevates a child's risk for more severe disease or outcomes with COVID-19, and adds to the existing literature demonstrating the same. This contrasts with the MMWR report in which the most common underlying condition was chronic lung disease,
including asthma. Nevertheless, our findings are reassuring given the fact that COVID-19 infects primarily through the respiratory epithelium. Allergic sensitization and atopic asthma are inversely associated with the expression of the ACE2 receptor, which is required for the entry of SARS-CoV2 into respiratory epithelial cells. Most childhood asthma is atopic in nature and 80% of asthmatics have co-morbid allergic rhinitis. IL-13 modulates the expression of ACE2 and transmembrane protease serine 2 (TMPRSS2) in airway epithelial cells, both of which are critical to infection by SARS-CoV2.

Our findings are unique in that they suggest that asthmatics in our cohort may have had their clinical course mitigated compared to other hospitalized children, since a statistically significantly higher number of nonasthmatics received remdesivir, had higher oxygen requirements and more severe CXR findings, suggesting that nonasthmatics hospitalized for COVID-19 had more severe disease. This may have been due to biological factors contributing to a less severe course among asthmatics. Nonasthmatics, who were medically complex children, had predictably worse outcomes. Additionally, although only four asthmatics were on ICS, their use may have provided protection against severe disease, as in vitro studies have shown that ICS may suppress common cold coronavirus, MERS-CoV, and SARS-CoV2 replication and cytokine production, although we were not able to analyze this question due to our limited sample size. Although our outpatient asthmatics had no control group for comparison, their benign experience suggests that asthmatics may be protected by ICS.

While this study is reassuring in that it does not demonstrate a higher risk for asthmatics, it has several limitations. Our study sample is small, therefore only large differences between asthmatics and nonasthmatics would have been detectible due to the sample size. It is a retrospective chart review, therefore, bias may be introduced during the extraction and recording of the data. Control of asthma is multi-factorial, and an assessment of other factors such as tobacco exposure and exacerbation history would have been helpful in risk stratifying these patients. We were not able to determine medication compliance with controller medications due to the retrospective nature of the study. Furthermore, there was incomplete data in that all patients did not have all endpoints, especially regarding laboratory values and CXRs performed. Sicker patients were more likely to have more extensive testing, therefore introducing selection bias into the analysis. Furthermore, as a retrospective study, there is implicit bias because management and treatment of COVID-19 patients evolved over time such that an early patient may not have had access to the medical options available later, such as remdesivir. For the outpatient analysis, although families are instructed to contact our office with loss of asthma control, they were contacted only once during the 4-month period to assess their clinical status. Given this limited interaction, the true extent of asthma control, or lack thereof, may not have been ascertained. In addition, control and compliance were reported subjectively by parents rather than using objective criteria such as the asthma control test or pharmacy refill records, respectively.

Despite these limitations, this study is one of the largest pediatric cohorts examining COVID-19 and asthma in both inpatient and outpatient settings. The study also examines variables and cofactors that have not been studied in other similar cohorts. Furthermore, although asthma is a chronic condition and every effort should be made to keep asthma well controlled, especially during a pandemic, we did not find that children with asthma had worse outcomes than children without. While further study is needed, this can be reassuring to families since children with other chronic illnesses such as diabetes, malignancy, or other chronic lung diseases, have been demonstrated to have more severe disease.

As the pandemic is surging in all areas of our country, it is reasonable to continue the management of asthmatics as much as possible via telemedicine. In-person visits should be accommodated when necessary, and the use of spirometry will need to be done with proper safety precautions in preventing the further spread and exposure of COVID-19. To fully understand the risk, or possible protection, provided by a diagnosis of asthma, large-scale cohorts studying outpatients and inpatients prospectively, both with and without asthma and chronic diseases must be undertaken. Given the role of systemic steroids in treating severe COVID-19 and in vitro studies demonstrating a negative effect of inhaled corticosteroids on the viability of coronaviruses, asthmatics with COVID-19 on ICS, and those under the care of a subspecialist should be studied. A more thorough analysis studying inpatient and outpatient pediatric cases may demonstrate different findings when comparing asthmatics to the general pediatric population.

5 CONCLUSION

In this combined inpatient and outpatient study of pediatric asthmatics, there was no observed difference in COVID19 outcomes in children with asthma compared to their hospitalized nonasthmatic counterparts and there was improved asthma control and compliance with medications in the outpatient setting during the pandemic. Asthma prevalence among inpatients was 34.2%, consistent with other studies. Biological and behavioral factors may have contributed to this risk mitigation. Further research examining the clinical course of asthmatics both inpatient and outpatient, should be undertaken, to better define the role of asthma in modifying a patient’s course with COVID-19.

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CONFLICT OF INTERESTS

The authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Sherry Farzan helped with conceptualization (lead); investigation (lead); methodology (lead); project administration (lead); supervision
(lead); writing original draft (lead); writing review and editing (lead). Shipra Rai helped with conceptualization (equal); data curation (lead); investigation (equal); methodology (equal); writing original draft (lead); writing review and editing (lead). Jane Cerise helped with formal analysis (lead); validation (equal); writing review & editing (equal). Shari Bernstein helped with data curation (supporting). Gina Coscia helped with conceptualization (supporting); data curation (equal); investigation (equal); writing review and editing (supporting). Jamie Hirsch helped with data curation (lead); software (lead). Judith Jeanty helped with data curation (equal). Alissa McInerney helped (lead). Judith Jeanty helped with data curation (equal). Mary Makaryus helped with data curation (equal). Alissa McInerney helped with data curation (equal). Annabelle Quizon helped with conceptualization (equal); data curation (equal); investigation (equal); writing review and editing (equal). Maria Santiago helped with conceptualization (lead); data curation (lead); investigation (lead); writing original draft (lead); writing review and editing (lead).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Sherry Farzan http://orcid.org/0000-0003-4790-8916
Maria Teresa Santiago http://orcid.org/0000-0002-2853-0615

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