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Research Article

The Impact of Asthma on Covid-19 Disease Severity in Children and Adolescents During the Delta Wave

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Abstract

Objectives: During the Alpha wave of the COVID-19 pandemic, asthmatic children initially appeared to have some protection but later exhibited more severe disease when presenting to the emergency department (ED). Given the Delta wave's higher transmissibility and viral loads, this study aims to examine whether similar trends persisted during the Delta wave.

Methods: A retrospective chart review across our health system was conducted to compare differences among asthmatics vs. non-asthmatic pediatric patients. We reviewed hospitalization rates and vaccination status of patients 6-18 years old who presented to the ED between June to December 2021 and tested COVID-19 positive. For hospitalized patients, we analyzed respiratory support rates and complications using order summaries, flowsheet data, and ICD10 codes.

Results: Based on 464 patients, asthmatics had a statistically higher hospitalization rates than non-asthmatics (24% vs 6%). Unvaccinated asthmatics were significantly more likely to be hospitalized than their non-asthmatic counterparts. Among the hospitalized patients, a higher proportion of asthmatics required respiratory support and developed complications compared to non-asthmatic patients. These differences however did not reach statistical significance, likely limited by a small sample size.

Conclusions: This study revealed that pediatric and adolescent asthmatics with COVID-19 during the Delta wave are a vulnerable group who may require increased monitoring.

Keywords: Pediatric COVID-19; Delta Variant; Hospitalization Rates; Respiratory Complications; Co-Morbidities; Vaccination

Introduction

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had profound implications for global health especially among individuals with chronic diseases. The impact of asthma, the most common chronic respiratory condition affecting millions of children worldwide, has been of significant concern during the pandemic. The Center for Disease Control and Prevention (CDC) highlighted the fact that individuals with moderate-to-severe or uncontrolled asthma faced higher rates of increased disease severity from COVID-19 [1]. This raised questions about the interplay between asthma and COVID-19 in the pediatric population.

Interestingly, in the initial phases of the pandemic when the Alpha variant of SARS-CoV-2 was the dominant viral strain, there was a notable decrease in asthma-related visits to emergency departments (ED) and hospital admissions [2,3]. This decline could have been influenced by factors such as reduced exposure to asthma triggers due to lockdown measures, changes in healthcare-seeking behavior, and the widespread adoption of telemedicine.

Our previous research demonstrated that during the alpha wave of the COVID-19 pandemic, asthmatic children and adolescents who presented to the ED, were more likely to be hospitalized and experienced more severe forms of COVID-19 compared to their non-asthmatic counterparts [4].

As the pandemic progressed, the virus underwent evolutionary changes, leading to the emergence of multiple variants. Among these, the Delta variant of SARS-CoV-2, also known as B.1.617.2, demonstrated increased transmissibility, higher viral loads, a 60 percent rise in hospitalization rates compared to the original strain, and diminished efficacy of existing vaccines at the time [5,6]. These factors and numerous subvariants exhibiting their own distinct characteristics, in May 2021, the World Health Organization classified the Delta variant as a Variant of Concern (VOC) [7-9].

Compared to adults, children had a reduced risk of experiencing severe illness, hospitalization, and mortality from COVID-19 [6,10].

There is a scarcity of information however regarding how different variants of the COVID-19 virus impact on pediatric populations with asthma.

Another consideration during the Delta wave was the strategic deployment of the COVID-19 vaccination campaign for children and adolescents by the United States Food and Drug Administration (FDA). The Pfizer-BioNTech vaccine received FDA emergency use authorization for those 16 and older on December 11, 2020, and this was extended to ages 12-15 on May 10, 2021. This authorization further included children aged 5-11 on October 29, 2021 [12,13]. The CDC's endorsement of these steps played a crucial role in boosting vaccination rates among these younger populations.

A retrospective cohort study design, was used to examine patient data from our electronic health records (EHR)to investigate whether asthma is a risk factor associated with increased COVID-19 disease severity among pediatric patients during the Delta variant phase of the COVID-19 pandemic. We aimed to (1) compare ED discharges and hospitalization rates between asthmatic and non-asthmatic children who tested positive during the Delta wave, (2) assess the need for ventilatory support and risk of complications in hospitalized asthmatic patients, and (3) explore the protective role of vaccination against hospitalization. We hypothesized an increase in hospital admissions for asthmatic patients during the Delta wave due to a greater severity of COVID-19 illness compared to their non-asthmatic counterparts, with vaccinations potentially mitigating hospitalization and severe disease risks.

Materials and Methods

A retrospective chart review was conducted from June 19, 2021, to December 18, 2021. This period corresponds to the Delta variant surge in New York City (NYC). Our inclusion criteria included patients aged 6-18 years who visited any ED within the Northwell Health hospital system and tested positive for COVID-19 via polymerase chain reaction (PCR) or antigen testing. We excluded patients less than 6 years of age, as younger children are often unable to perform spirometry and therefore, cannot conclusively be diagnosed to have asthma.

Our health system comprises 21 hospitals across New York State. Our study did not confirm the variant specifically but assumed that patients presenting with a positive result during this period were more likely to be the Delta variant. We excluded patients with positive COVID-19 antibody tests, as these could not be definitively attributed to prior infections or vaccinations during the concurrent vaccine rollout. Additionally, patients presenting with non-COVID-19-related complaints were not included to eliminate incidental COVID-19 positives.

Patients were classified according to their asthma status (with or without) as the primary independent variable. The study analyzed several dependent variables, including the patient's discharge status (ED discharge vs hospital admission, vaccination status, necessity for respiratory support, and the development of complications. International Classification of Diseases, Tenth Revision (ICD-10) codes found in Table 1 were utilized to classify patients.

Table 1: Collection methods for independent and dependent criteria.

Independent Variables	**ICD-10 Codes**
Asthma	J45
Allergic Asthma	J82
Dependent Variables	**ICD-10 Codes**
Respiratory Distress	R06.0
Respiratory Failure	J96.01, J96.91, OBH 17EZ
Pneumonia	J18, J12.82
MIS-C	M35.8
Stroke	I63
Myocarditis	151.4, I40
Acute Renal Failure	N17, N18, N19
Coagulopathy	D68.9
Septic Shock	R65.21, 785.52, 995.92
Multi organ Failure	R65.11
Death	R99

Vaccination status was determined by at least one dose of a COVID-19 vaccine prior to the ED visit, verified through the NYC Health Department's Citywide Immunization Registry (CIR).

Additionally, EHR data, including order summaries and flowsheet data, were analyzed to identify any respiratory support administered during the patient's hospital stay. Due to small sample size, respiratory support was defined as the patient requiring at least one of these four levels: nasal cannula, high-flow nasal cannula, non-invasive ventilation, and intubation.

Furthermore, the study assessed complications indicated by ICD10 codes listed in Table 1. These codes provided measures to establish the severity of the exacerbation.

Descriptive statistics were computed (e.g., frequency and proportions for categorical data). The Chi-square test or Fisher's Exact test was used to compare the association between asthma status and categorical factors such as age, gender, visit type, vaccination status, need for respiratory support, and development of complications, as appropriate. For all analyses, results yielding p-values <0.05 were considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

All patient information was de-identified. This study was submitted for approval to the Institutional Review Board of Northwell Health. An ethical review of the protocol was performed and deemed ethical (Protocol ID 20-1143).

Results

During the study period, 555 pediatric patients tested positive for COVID-19, as confirmed by PCR or antigen testing upon arrival to the ED. Of these, 91 patients who tested positive for COVID-19 after presenting with unrelated symptoms to COVID-19 were deemed as incidental positives and excluded from the study analysis, See Figure 1.

The analyzed cohort of 464 patients comprised of 37 (7.97%) patients with a diagnosis of asthma and 427 (92.03%) patients identified as non-asthmatic. In the comparative analysis of our patient cohort, the distribution of gender (p = 0.9187) and age (p =

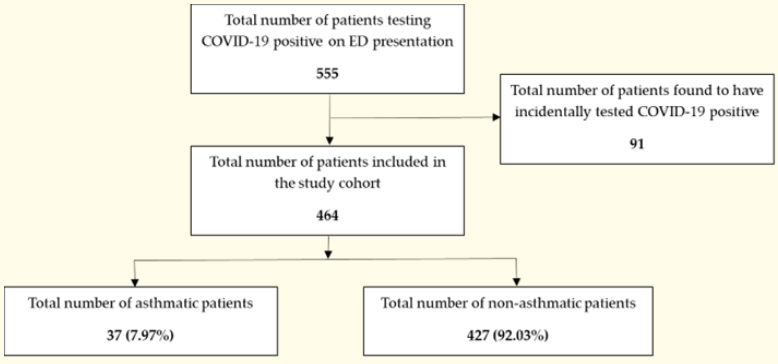

Figure 1: Flow diagram of study participants presenting to the Emergency Department (ED).

0.5906) demonstrated no statistically significant disparities between the asthmatic and non-asthmatic groups (See Table 2).

As shown in Table 3, our findings revealed that, of the 37 asthmatic patients, 28 (75.68%) were discharged from the ED, while 9 (24.32%) required hospitalization. In the non-asthmatic group, out

	Total Number of Patients N = 464	Asthmatic Patients N = 37	Non-Asthmatic Patients N = 427	P-Value
Age Range (In Years)				
6-11	195 (42.03%)	14 (37.84%)	181 (42.39%)	0.5906
12-18	269 (57.07%)	23 (62.16%)	246 (57.61%)	
Patient Gender				
Male	242 (52.16%)	19 (51.35%)	223 (52.22%)	0.9187
Female	222 (47.84%)	18 (48.65%)	204 (47.78)	

Table 2: Age and gender demographics of studied cohort.

	Total Number of Patients N = 464	Asthmatic Patients N = 37	Non-Asthmatic Patients N = 427	P-Value
Patient Disposition from ED				
ED Discharge	427 (92.03%)	28 (75.68%)	399 (93.44%)	0.0012
Hospital Admission	37 (7.97%)	9 (24.32%)	28 (6.56%)	

Table 3: Patient disposition from emergency department (ED) for asthmatics vs non-asthmatic patients.

of 427 patients, 399 (93.44%) were discharged, and 28 (6.56%) were admitted for inpatient management. A higher proportion of asthmatics were hospitalized compared to non-asthmatics (24.3% vs. 6.6% respectively), and this difference was statistically significant (p = 0.0012).

Additionally, of 37 inpatient admissions (9 asthmatic, 28 non-asthmatic), 17 (45.95%) required respiratory support, with a higher proportion in asthmatics (66.67%) compared to non-asthmatics (39.29%). However, a p-value of 0.25 suggests no significant link found between asthma and the need for respiratory support in the

setting of a COVID-19 infection. Complications occurred in 35.14% (13 out of 37) of the inpatients, distributed as 44.44% in asthmatics and 32.14% in non-asthmatics, with a p-value of 0.69 indicating no significant association identified with an asthma diagnosis and the development of complications from COVID-19. No fatalities were recorded in the study.

A total of 34 out of 464 patients (7.33%) were identified as having received at least one COVID-19 vaccination before ED arrival. Our study revealed that all vaccinated asthmatic patients were discharged from the ED, and none were hospitalized. Among the vaccinated non-asthmatic patients, 28 (90.32%) were discharged, with 3 (9.68%) patients requiring hospitalization. Although these results were not statistically significant, the trend was different for unvaccinated individuals. Of the unvaccinated asthmatics, 25 out of 34 (73.5%) were discharged and 9 out of 34 (26.5%) were hospitalized. In the unvaccinated non-asthmatic cohort, 371 out of 396 (93.7%) patients were discharged, and 25 out of 396 (6.3%) were admitted as inpatients. A p-value of 0.0005 indicates a statistically significant difference, suggesting that unvaccinated patients who were hospitalized were more likely to be asthmatic than non-asthmatic. Table 5 provides comparative data.

	Total Number of Patients N = 37	**Asthmatic Patients N = 9**	**Non-Asthmatic Patients N = 28**	**P-Value**
Respiratory Support Among Hospitalized Patients				
Required	17 (45.95%)	6 (66.67%)	11 (39.29%)	0.2505
Not Required	20 (54.05%)	3 (33.33%)	17 (60.71%)	
Development of Complications Among Hospitalized Patients				
Yes	13 (35.14%)	4 (44.44%)	9 (32.14%)	0.6906
No	24 (64.86%)	5 (55.56%)	19 (67.86%)	

Table 4: Respiratory support and complications for asthmatics vs non-asthmatic patients among hospitalized patients.

	Total Number of Patients N = 464	**Asthmatic Patients N = 37**	**Non-Asthmatic Patients N = 427**	**P-Value**
Vaccination Status				
Vaccinated	34 (7.33%)	3 (8.11%)	31 (7.26%)	0.7451
Non-Vaccinated	430 (92.67%)	34 (91.89%)	396 (92.74%)	
Patient Disposition in Vaccinated Patients	N = 34	N = 3	N = 31	
ED discharge	31 (91.18%)	3 (100.00%)	28 (90.32%)	1.0000
Hospital Admission	3 (8.82%)	0 (0.00%)	3 (9.68%)	
Patient Disposition in Non-Vaccinated Patients	N = 430	N = 34	N = 396	
ED discharge	396 (92.09%)	25 (73.53%)	371 (93.69%)	0.0005
Hospital Admission	34 (7.91%)	9 (26.47%)	25 (6.31%)	

Table 5: Comparison of vaccination status and patient outcomes among asthmatic vs. non-asthmatics.

Discussion

Our findings indicate that, during the Delta variant surge, asthmatic children and adolescents who presented to the ED with COVID-19 were significantly more likely to be hospitalized compared to their non-asthmatic peers. This disparity in hospitalization rates aligns with findings from a previous study, which demonstrated that the Delta variant caused a marked increase in hospital admissions among children compared to the Alpha variant [6]. Our study suggests that this rise in hospital admissions may be linked to the heightened severity of COVID-19 in asthmatic children compared to those without asthma.

In addition, our data indicates that asthmatic patients once hospitalized show a tendency to require more respiratory support and develop complications. Vaccination appeared to be protective against hospitalization for COVID-19 in children. However, these findings did not attain statistical significance, possibly because of the limited size of our hospitalized patient sample size, which constrained our ability to identify statistically significant outcomes.

According to the CDC in 2021, during the Delta wave, the national prevalence of pediatric asthma was 6.5%. Of the 464 patients in the study cohort, ages 6-18 years, presenting to the ED, 7.97 percent were asthmatics and 92.93% were non-asthmatic [14]. Our study results suggest that the observed higher percentage of asthmatics presenting to the ED, compared to the CDC's reported pediatric asthma prevalence, may indicate an increased risk of severe asthma exacerbations necessitating emergency care in this population [15]. During our retrospective chart review, we did not capture asthma severity, or the medications used to control asthma, such as biologicals.

Our results did not show statistical significance between age and gender in our analyzed cohort and align closely with national demographics [14].

Contrasting with our prior study that analyzed a cohort of 1,585 patients aged 6-20 during the Alpha wave of the COVID-19 pandemic, our health system witnessed a decrease in admissions during the Delta wave, with a cohort of 464 patients observed in this study [4]. This reduction can be partly attributed to the Delta wave's shorter duration in comparison to the Alpha wave. Additionally, 91 patients were excluded from the cohort as they tested positive for COVID-19 without displaying typical COVID-19 related symptoms. We intentionally excluded patients aged 18-20, who were noted to have a higher frequency of ED visits and hospitalizations, thus impacting the overall admission rates during the Delta wave. The availability of vaccines to adolescents during the surge of the Delta variant may also account for a decreased likelihood of infections severe enough to necessitate an ED visit.

During the Delta wave, pediatric populations experienced a significant increase in the severity of COVID-19 symptoms compared to earlier strains. A single-center retrospective study highlighted this trend, revealing that children infected with COVID-19 during the Delta wave exhibited persistent fever and pneumonia more frequently than those infected in the periods prior to Delta and during the Omicron wave. This period saw a notable rise in moderate cases of COVID-19 among children and a decrease in the incidence of mild cases, indicating a shift towards greater disease severity during the Delta variant's prevalence [16,17].

The data available points to the Delta variant's greater transmissibility and its capacity to lead to more severe outcomes of COVID-19, including a transmission rate approximately 60% higher than that of the Alpha variant, alongside an increased necessity for hospitalization and respiratory support. Yet, research by Molteni., *et al*. indicates that, although the symptom burden may be slightly higher with the Delta variant, the overall severity of the disease compared to the Alpha variant did not significantly differ [18]. These findings shed light on the nuanced and changing landscape of COVID-19 variants, underscoring the importance of ongoing monitoring and the adjustment of public health measures to effectively tackle the challenges presented by new variants.

During the Delta wave, the emergence of the Delta Plus variant in the United States marked a significant development, characterized by an increased number of mutations commonly found in highly transmissible variants. This variant exhibited enhanced transmissibility and a stronger binding affinity to lung mucosa, thereby increasing its capability to infect the respiratory system more efficiently [7]. The mechanism of SARS-CoV-2 infection involves targeting the angiotensin-converting enzyme 2 (ACE2) to facilitate entry into cells [19], with the level of ACE2 expression being directly associated with increased vulnerability to the virus in lab settings [20]. A study by Zhang., *et al*. underscored that the spike protein of the Delta variant demonstrated the highest binding affinity to the ACE2 receptor among the variants studied, indicating its superior transmissibility [21].

The process of viral transmission for SARS-CoV-2 involves a critical step known as proteolytic cleavage, which is facilitated by transmembrane protease serine 2 (TMPRSS2). TMPRSS2, located on the surface of endothelial cells, plays a vital role in the entry and

proliferation of coronaviruses, including SARS-CoV-2. Once the virus enters the body, it targets ACE2 receptors on both type I and II alveolar cells, where TMPRSS2 is present. The activity of TMPRSS2 can impede the immune system's ability to detect the virus. Research has shown that children possess fewer ACE2 and TMPRSS2 molecules on their alveolar cells compared to adults, and the occurrence of cells that express both ACE2 and TMPRSS2—critical for inducing severe immune responses—is significantly less common in children and increases with age. This is considered a protective factor against disease progression. Cells that are "double-positive" for ACE2 and TMPRSS2 can lead to an overproduction of interleukins IL-6 and IL-6R, which may trigger the cytokine storm observed in severe cases of COVID-19 in adults [22]. Interestingly, the Delta variant has been found to replicate more rapidly compared to the Omicron variant in laboratory cells that overexpress TMPRSS2 [23].

In children, asthma often involves type 2 inflammation, characterized by an increase in T helper 2 (TH2) cells, cytokines like IL-4, IL-5, and IL-13, and eosinophilia [24]. IL-13 has been shown to decrease the expression of ACE2, the primary receptor for SARS-CoV-2 on airway cells, potentially explaining the lower levels of ACE2 associated with allergies and high IgE levels. Eosinophilia has been linked to a lower risk of COVID-19, whereas eosinopenia promotes severe disease, suggesting a protective role of eosinophils in preventing severe COVID-19 outcomes. Furthermore, mast cells, which are involved in allergic responses, can produce substances that are antiviral [25]. Skevaki., *et al*. proposed that asthmatic patients infected with SARS-CoV-2 may initially experience protection due to the suppressive effect of TH2 inflammation on TH1 immunity, which reduces the production of pro-inflammatory cytokines essential for viral defense.

This protective effect is only seen in children with type 2 endotype. Asthma endotypes may be broadly categorized as type 2 (T2) high or T2-low [26]. In New York City, 90% of asthmatic children have the type 2 endotype [24,27-29].

During the Delta wave of the pandemic in New York City, the COVID vaccine was made available to adolescents, offering a potential shield against severe outcomes. Our study observed that unvaccinated asthmatic patients were significantly more likely to be hospitalized than unvaccinated non-asthmatic patients. The September 2021 MMWR report, highlighted a tenfold increase in hospitalization among unvaccinated adolescents during the Delta wave, underscoring the vaccine's protective effect against severe health outcomes [14,30-32].

As vaccination efforts progressed and COVID-19 cases started to fall, schools began reopening in the fall of 2020. However, this transition heightened exposure risks, with more children returning to crowded settings, complicating efforts to maintain social distancing. This concern was particularly acute given the Delta variant's increased transmissibility over previous strains.

Limitations of this Study

Although the study utilized multiple hospital centers across our health system, the numbers remained low, due to the short duration of the Delta wave and the fact that children and adolescents were less impacted than older patients. The specific SARS-CoV-2 variant was not confirmed; the analysis relied instead on the presumed prevalence of the Delta variant during the study period. This study is also susceptible to potential biases from inaccurate or missing documentation and coding, which could influence the observed associations.

Conclusion

We chose to look at the impact of the Delta COVID-19 wave on pediatric and adolescent asthmatic ED presentation and admissions, because the innate characteristics of the virus were different from the Alpha variant in that it was more transmissible and the likelihood of acquiring the virus increased as schools reopened; there was protection afforded by vaccine availability. Our results found that, as hypothesized, asthmatic children may be at higher risk of needing hospitalization, requiring respiratory support, and developing complications compared to non-asthmatic children. Vaccines appear to be protective against disease progression and severity for asthmatic patients.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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