Correlation between total IgE level and asthma symptom severity in hospitalized children

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Background: Status asthmaticus is a common reason for hospitalization and pediatric intensive care unit (PICU) admission among children. While previous studies have demonstrated a correlation between elevated IgE levels and asthma severity in outpatient settings, studies analyzing IgE levels in an inpatient cohort are limited.

Objective: We examined the relationship between baseline IgE levels and symptom severity, maximum respiratory support, and PICU and hospital length of stay in an inpatient pediatric cohort.

Methods: This was a single-center retrospective chart review of children admitted to the Children's Hospital at Montefiore with status asthmaticus as their primary diagnosis. The primary goal was to determine the relationship between baseline IgE levels and severity of illness at time of admission. Secondary outcomes included maximum respiratory support, and PICU and hospital length of stay.

Results: We identified a statistically significant difference ($P = .043$) in baseline IgE levels between the PICU (median, 608 U/mL) and floor groups (405 IU/mL). There was a positive correlation between IgE level and PICU length of stay ($P = .004$).

Conclusion: Elevated baseline IgE level is correlated with higher asthma symptom severity when hospitalized and with longer PICU length of stay. Our study adds to the growing body of evidence that those with high baseline IgE levels are at risk of having severe asthma symptomology. (J Allergy Clin Immunol Global 2025;4:100452.)

Key words: *Pediatric asthma, IgE, pulmonology, immunology, immunoglobulins, asthma exacerbation, status asthmaticus*

Abbreviations used
CHAM: Children's Hospital at Montefiore
GINA: Global Initiative for Asthma
HFNC: High-flow nasal cannula
HLOS: Hospital length of stay
PICU: Pediatric intensive care unit
PLOS: PICU length of stay
PPV: Positive pressure ventilation

Asthma is a common chronic respiratory disease in children. The 2024 Global Initiative for Asthma (GINA) states that asthma affects 1% to 29% of people worldwide.[1] In the United States, asthma prevalence is 6.5% in children younger than 18 years, and among those affected, 39.4% experience at least one asthma exacerbation yearly.[2] The reported emergency department visit and admission rate for children was 36.4 and 3.6 per 10,000 US census 2020 population, respectively.[2] Asthma exacerbations result in missed school days and high utilization of health care resources imposing an economic burden on the health system.[3,4] Furthermore, status asthmaticus is a common reason for pediatric intensive care unit (PICU) admission and is associated with significant morbidity and health care cost.[5]

Asthma is particularly important in the Bronx community, which our institution serves. According to a New York City Health Epidemiology Data Brief report, in 2017, 13% of children under 13 years residing in the Bronx were diagnosed with asthma.[6] This number is almost double the national average reported by the Centers for Disease Control and Prevention.[2] At the Children's Hospital at Montefiore (CHAM), over 6,000 children present to the emergency department yearly for treatment of asthma-related symptoms. Much of the geographic disparity in asthma prevalence has been attributed to environmental allergens, but research linking allergic asthma to severity of illness during asthma exacerbation is lacking.[4,7]

In this era of personalized medicine, asthma is being redefined as a heterogenous disease with subtypes based on distinct etiologies and associated clinical biomarkers.[8] Allergic asthma is the most common asthma phenotype and has a younger average age at onset than nonallergic asthma.[9] It is associated with elevated total IgE levels and sensitization to aeroallergens leading to airway inflammation and asthma symptoms.[10,11] For children aged 2 to 18 years, normal IgE levels vary by age, averaging between 3 IU/mL and 23.6 IU/mL; levels peak around age 9 to 10 years and trend down by adulthood.[12] Total IgE levels in individual patients have limited annual variability and do not undergo acute change during asthma exacerbations.[13] As such, a baseline IgE level can be considered an intrinsic characteristic of a patient. These attributes make total IgE an attractive biomarker to evaluate for correlation with asthma symptom severity in hospitalized children.

A large cohort study focusing on patients with severe or difficult-to-treat asthma reported that children with mild, moderate, and severe persistent asthma had mean IgE levels of 135 IU/mL, 146 IU/mL, and 280 IU/mL, respectively.[14] Higher IgE levels are also associated with more symptomatic asthma despite higher level of treatment in inner-city children.[7] A single-center

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retrospective study performed at Cincinnati Children's Hospital demonstrated that total IgE levels were higher in patients who required hospital admission for asthma compared to those who were treated as outpatients.[15] These studies suggest that severity of asthma may correlate with IgE level in children.

Although the above studies demonstrate a correlation between elevated total IgE levels and chronic asthma severity, limited studies explore the relationship between total IgE levels and acute asthma severity within an inpatient cohort. Examining this relationship may help to further identify asthma endotypes and phenotypes. This can potentially allow for identification of children at high risk for PICU admission and help prevent increased asthma morbidity and mortality.

We hypothesized that patients admitted to the PICU would have higher baseline IgE levels compared to those admitted to the floor, and that higher baseline IgE levels would correlate with the need for higher levels of respiratory support.

METHODS

Study population

This was a single-center retrospective cohort study of patients admitted to CHAM for status asthmaticus between January 1, 2015, and July 1, 2022. The Montefiore institutional review board granted approval and a waiver of informed consent. Subjects were identified using Looking Glass Clinical Analytics (Streamline Health, Atlanta, Ga) database by searching for the following inclusion criteria: patients aged 2 to 18 years admitted to CHAM during the study period with an ICD diagnosis of "asthma" during the target admission, and with documented IgE levels within 6 months of admission. Subsequent variables were collected via Epic (Epic, Verona, Wis) electronic health record review of identified subjects. Exclusion criteria included immunodeficiency, tracheostomy dependance, history of chronic lung disease such as bronchopulmonary dysplasia, home positive pressure requirement, and rapid response escalation from the general pediatric floor to the PICU.

Definition of variables

In this study, a hospital unit of admission—PICU or general pediatrics floor—was used as a marker of acute asthma symptom severity. Minimum criteria for PICU admission for status asthmaticus at our institution include the need for high-flow nasal cannula (HFNC), positive pressure ventilation (PPV), continuous albuterol, or continuous intravenous medications.

Secondary variables included highest level of respiratory support required during admission, PICU length of stay (PLOS) and hospital length of stay (HLOS) measured in days (with 24 hours considered 1 full day). PLOS and HLOS data were obtained from the electronic health record event log feature, which was not available before May 30, 2016. As such, those patients without PLOS/HLOS data were excluded from this subanalysis. HLOS was defined as total length of stay from admission to discharge including PLOS in the PICU cohort.

Asthma history indicates asthma severity classification at time of admission according to National Heart, Lung, and Blood Institute asthma severity classification guidelines. Controller history indicates if the patient received any form of daily asthma controller medication at the time of admission. Controller history category of "yes" indicates that the patient received one or more controller medications at time of admission, while "no" indicates the patient did not.

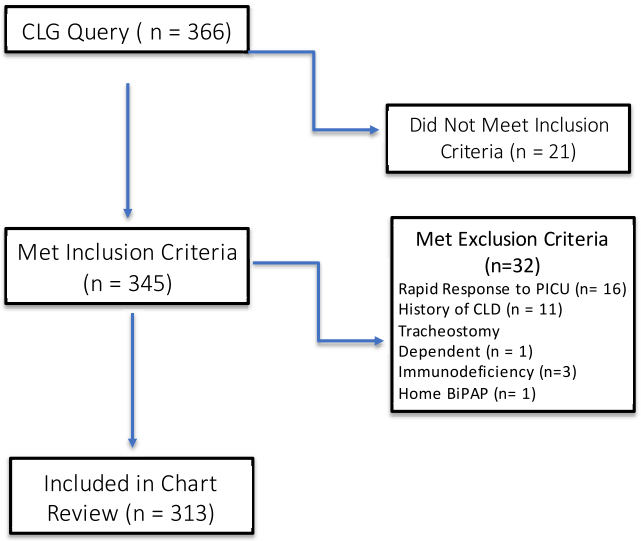


FIG 1. Patient selection for chart review.

Statistical and data analysis

Power analysis reference values for mean IgE levels of the US population aged 6 years and older and standard error were obtained from Gergen et al.[11] The standard error was used to calculate the standard deviation of mean IgE level, which was 137 kU/L (kU/L is equivalent to IU/mL). Sample size was calculated using the following parameters: $\alpha = 0.05$, $\beta = 0.2$, proportion of subjects in group 1 (PICU): 0.5, proportion of subjects in group 2 (floor): 0.5, with effect size of 60 and standard deviation of 137. The calculated sample size was 82 subjects per group, with a total of 164.

All statistical analyses were performed by GraphPad Prism 9.5.1 for Mac software (GraphPad Software, La Jolla, Calif). Categorical variables were analyzed by chi-square and Kruskal-Wallis tests, and continuous variables were analyzed by Mann-Whitney *U* test and unpaired *t* test. Correlation between baseline IgE level and HLOS and PLOS was evaluated by Spearman correlation analysis. $P < .05$ denoted significance.

RESULTS

The initial Looking Glass Clinical Analytics database query identified 366 unique medical record numbers. Twenty-one subjects did not meet the inclusion criteria: 8 had a primary diagnosis other than asthma, 10 never underwent hospital admission, and 3 did not have baseline IgE levels recorded. Of the remaining 345 patients, 32 met the exclusion criteria; 16 had rapid response escalation from floor to PICU, 11 had a history of chronic lung disease, 1 was tracheostomy dependent, 3 had immunodeficiencies, and 1 required home bilevel positive airway pressure. A total of 313 patients were included in the final analysis (Fig 1). The final PICU and floor groups consisted of 84 and 229 patients, respectively. There was no statistically significant difference in age, sex, weight, race, asthma history, or controller history (Table I). Omalizumab (Xolair) receipt was found in

TABLE I. Patient characteristics

Characteristic	PICU (n = 84)	Floor (n = 229)	*P* value*
Sex			.952
Male	47 (56)	129 (56)	
Female	37 (44)	100 (44)	
Race			.689
Asian	2 (2.4)	5 (2.2)	
Black	27 (32.1)	88 (38.4)	
White	7 (8.3)	13 (5.7)	
Other	44 (52.4)	117 (51.1)	
Unknown/declined	4 (4.8)	6 (2.6)	
Age (years)			.247
Mean (range)	7.8 (2.0-18)	7.2 (2.0-18)	
Difference in mean ± SEM	−0.7 ± 0.6		
Weight (kg)			.191
Mean	38.83	34.47	
Difference in mean ± SEM	−4.36 ± 3.33		
Asthma history			.401
No history	4 (4.8)	7 (3.1)	
Intermittent	12 (14.3)	31 (13.5)	
Mild persistent	19 (22.6)	76 (32.8)	
Moderate persistent	36 (42.9)	92 (40.2)	
Severe persistent	13 (15.5)	24 (10.5)	
Controller history	n = 83†	n = 227†	.593
Yes	66 (80)	174 (77)	
No	17 (20)	53 (23)	
Omalizumab receipt			.570
Yes	1 (1.2)	5 (2.2)	
No	83 (98.8)	224 (97.8)	

Data are presented as nos. (%) unless otherwise indicated. *SEM,* Standard error of mean.

**P* values by chi-square test for categorical variables (sex, race, asthma, controller history) and Mann-Whitney *U* test for continuous variables (age, weight). $P > .05$ for all, indicating no statistical difference in patient characteristics between PICU and floor cohort.

†Controller information not documented for 1 PICU patient and 2 floor patients.

1 PICU patient (1.2%) and 5 floor patients (2.2%), with no statistically significant difference between the two groups (Table I).

Baseline IgE levels in the study population had a nonparametric positively skewed distribution for both groups. Six floor patients with IgE levels reported as <2 IU/mL and >5000 IU/mL and one PICU patient with IgE level of 12686 IU/mL were excluded from all analysis involving IgE as a variable (223 for floor and 83 for PICU).

Baseline IgE levels were significantly higher in the PICU group ($P = .043$, median 608.0 IU/mL) compared to the floor group (405.0 IU/mL; Fig 2). There was no statistically significant difference in IgE levels when comparing different levels of maximum respiratory support required during admission ($P = .374$; Fig 3).

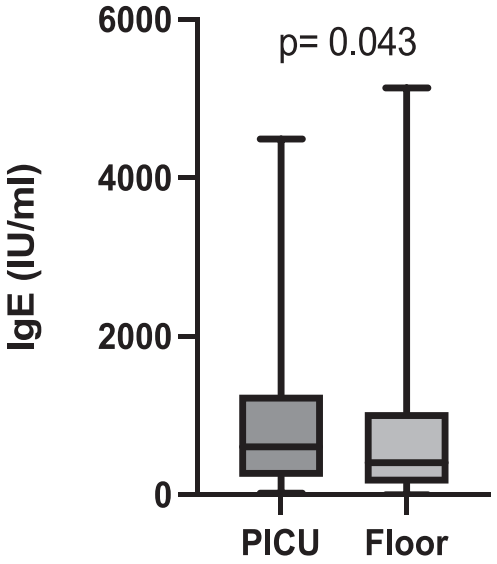
In further analysis of maximum level of respiratory support required during admission, all study patients were grouped on the basis of positive pressure requirement: group 1 included patients who received room air, nasal cannula, and HFNC, and group 2 included those who required PPV (either noninvasively or invasively). Of the 8 patients requiring HFNC, only one required maximum flow of 1.5 L/kg, and the rest had a maximum flow requirement of <1 L/kg. Given that these flows are unlikely to provide a physiologically significant amount of positive pressure, the HFNC group was included in the non–positive pressure group. Although the PPV group had a higher median (635.0 IU/mL, n = 60) compared to the non-PPV group (423.5 IU/mL, n = 246) the difference was not statistically significant ($P = .149$; Fig 4). There was a positive correlation between IgE levels and PLOS (Spearman correlation $r = 0.362$, $P = .004$; Fig 5); however, IgE levels did not correlate to total HLOS (Spearman correlation $r = 0.035$, $P = .507$; Fig 6).

DISCUSSION

The 2024 GINA Main Report defines asthma as a "heterogeneous disease, usually characterized by chronic airway inflammation [defined] by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity together with variable expiratory airflow limitations."[1] Traditional methods of stratifying asthma through clinical symptomology and symptom frequency fail to encompass all the pathophysiology that contributes to this complex disease. Therefore, it is crucial to determine how biomarkers such as IgE can be utilized to stratify asthma severity to help educate patients and potentially direct therapy. Previous studies demonstrated that higher IgE levels are found in patients with more severe disease and in those who required hospital admission for an exacerbation compared to those managed as outpatients.[7,14,15] Our analysis further indicates a correlation between higher IgE levels and increased symptom severity during hospitalization for acute asthma exacerbation. However, it is important to note this correlation does not imply that IgE levels alone should be used to determine PICU admission, as that determination should remain based on clinical findings.

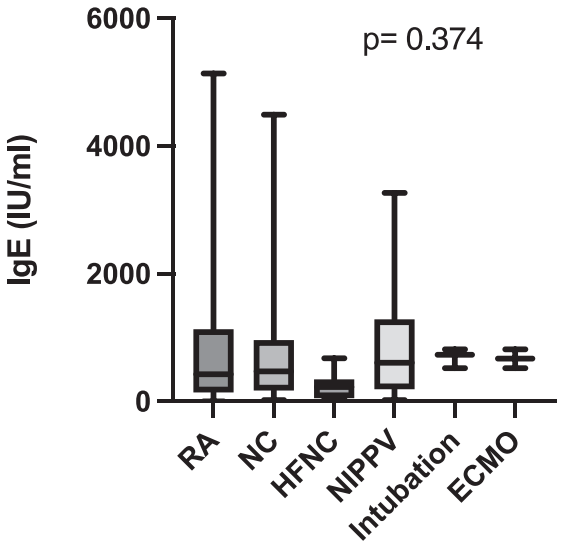
A focus of recent literature includes defining asthma subgroups through phenotypes and endotypes to better guide tailored clinical management.[8] Lötvall et al defined an *endotype* as a "subtype of a condition defined by a distinct pathophysiological mechanism."[16] In their practical allergy (PRACTALL) consensus report, asthma is categorized into 5 endotypes defined by clusters of phenotypes representing specific biological mechanisms and the corresponding pathophysiology. Three of these endotypes—allergic bronchopulmonary mycosis, allergic asthma, and asthma-predictive indices–positive preschool wheeze—have elevated IgE as part of their phenotypic characterization. Zoratti et al similarly categorized asthma into clusters of phenotypes.[7] In their study, the cluster of patients with the most symptoms despite receiving the highest level of asthma treatment had an elevated median total serum IgE of 616 kU/L. These studies imply a relationship between IgE levels and asthma symptom severity in the adult population. On the basis of these adult study findings, our study aimed to determine if a similar relationship between IgE levels and asthma symptom severity exists in the pediatric population, specifically in those with acute asthma exacerbation requiring hospitalization. Our study contributes additional evidence to support the importance of IgE as a biomarker in asthma by correlating it to need for PICU admission and longer PLOS.

While there has been a progressive reduction in asthma mortality since the late 1980s, there has been a stall in global asthma mortality reduction since 2006. Half of asthma deaths are considered preventable, which calls for novel strategies to identify high-risk patients to decrease asthma morbidity and mortality.[17] Current preventative medicine practices utilize the asthma control and childhood asthma control tests to assess the degree of asthma control obtained from a patient's treatment plan. These tests are age-adjusted questionnaires that focus on frequencies of symptoms and exacerbations, and they are used



	PICU (n=83)	Floor (n= 223)
Median	608.0	405.0
IQR	226.0 - 1267	140.0 - 1046
Minumim	21.2	2.1
Maximum	4491.0	5137.0
Mean (SEM)	903.8 (100.6)	812.2 (71.15)

FIG 2. Comparison of baseline IgE levels in patients admitted to PICU versus floor. *P* value for Mann-Whitney *U* test shown. *IQR,* Interquartile range; *SEM,* standard error of mean.

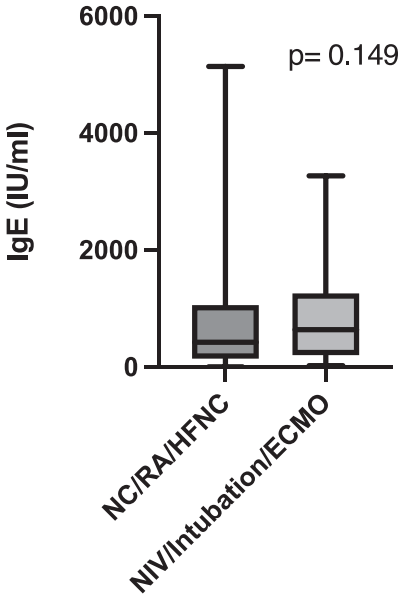


	RA (n= 191)	NC (n= 48)	HFNC (n = 7)
Median	427.0	470.5	226.0
IQR	144.0 - 1131	170.4 - 961.5	50.3 - 677.0
Minumim	2.1	23.0	41.2
Maximum	5137.0	4491.0	677.0
Mean (SEM)	884.1 (82.06)	689.0 (112.9)	252.5 (83.18)

	NIPPV (n=57)	Intubation (n= 3)	ECMO (n = 2)
Median	608.0	730.0	670.5
IQR	194.0 - 1288	522-819.0	522 - 819.0
Minumim	21.2	522.0	522.0
Maximum	3268.0	819.0	819.0
Mean (SEM)	672.8 (80.98)	690.3 (88.00)	670.5 (148.5)

FIG 3. Baseline IgE level across maximum required respiratory support. *P* value for Kruskal- Wallis test shown. *ECMO,* Extracorporeal membrane oxygenation; *IQR,* interquartile range; *NC,* nasal cannula; *NIPPV,* noninvasive PPV; *RA,* room air; *SEM,* standard error of mean.

to guide stepwise therapy. Notably, our results demonstrated a correlation between IgE levels and symptom severity during exacerbations that was independent of baseline disease control indicated by asthma symptom severity history and reported requirement for controller medication receipt. There was no statistically significant difference in asthma severity history or controller medication receipt between the PICU and floor cohorts, yet the PICU cohort had higher median IgE level. This suggests a potential preventative benefit of using IgE levels to identify children at risk of severe symptomology during exacerbations despite their overall disease control. These children might benefit from early specialist referral or from early addition of IgE-targeted therapy such as omalizumab, an anti-IgE monoclonal antibody that has been shown to reduce seasonal exacerbation among at-risk inner-city youth when added to a regimen of guideline-based therapy.[18,19] Parents could also receive additional anticipatory guidance that their child with higher IgE levels are at risk of severe exacerbation despite baseline disease severity level. Furthermore, IgE levels could potentially be used as a risk stratification tool to predict which patients may require escalation of care during hospitalization. As stated earlier, our study does not suggest using singular biomarker such as IgE as an admission criterion for PICU admission. This preliminary finding does not yet translate to direct clinical practice. However, our findings may be used as a starting point for further research to explore the relationship between elevated IgE levels and the need for PICU admission during an acute exacerbation that is independent of baseline disease control.



	RA/NC/HFNC (n=246)	NIPPV/Intubation/ECMO (n = 60)
Median	423.5	635.0
IQR	144.8 - 1057	204.8 - 1258
Minumim	2.1	21.2
Maximum	5137.0	3268.0
Mean (SEM)	828.1 (67.83)	873.7 (109.7)

FIG 4. Comparison of baseline IgE levels with and without positive pressure requirement. RA + NC + HFNC = no positive pressure; NIPPV + intubation = positive pressure. *NC,* Nasal cannula; *NIPPV,* noninvasive PPV; *RA,* room air.

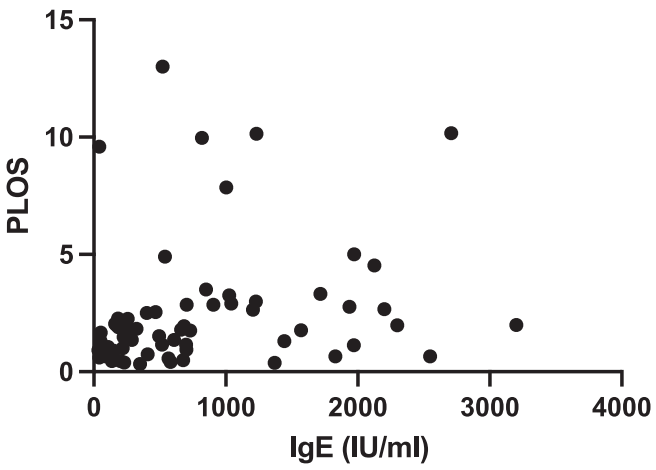


FIG 5. Baseline IgE level versus PLOS. Spearman correlation $r = 0.362$; $P = .004$.

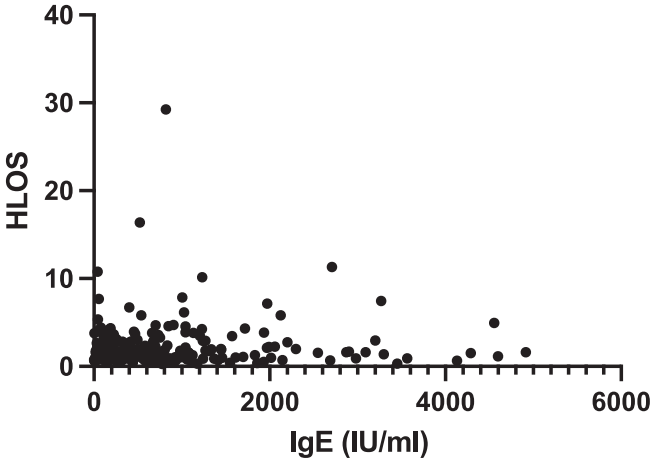


FIG 6. Baseline IgE level versus HLOS. Spearman correlation $r = 0.035$; $P = .597$.

This study has many limitations. First, it is a single-center retrospective chart review, so it is limited by inconsistencies in availability and documentation of certain variables, such as controller medication history or height for body mass index. Unfortunately, we were unable to effectively pull data such as pulmonary function test results and allergic comorbidities from outpatient encounters and found that inconsistent documentation limited our ability to use these data for the study population. These are potential confounding variables that could affect IgE levels at admission. Future studies should include detailed allergy and sensitization history that could contribute to building more comprehensive asthma phenotypes. The IgE levels used in this study were variable in temporal relationship to the hospitalization, as levels obtained within 6 months of admission were used. In order to draw clinically useful conclusions on the applicability of IgE levels in predicting symptom severity during an exacerbation, future studies should be designed to have IgE levels assessed at time of hospital admission. Additionally, this cohort's IgE levels represent an urban population and may have limited generalizability to different populations. A prospective multicenter study of a more diverse population in which IgE levels are obtained during admission for an asthma exacerbation may be useful to further evaluate the impact of IgE as a biomarker in predicting acute asthma exacerbation severity. Currently, status asthmaticus is managed using protocols that often do not address the heterogeneous nature of the disease by distinguishing management for allergic asthma versus nonallergic asthma. Further research is needed to evaluate if a different treatment approach may be warranted for those with allergic asthma.

In conclusion, in this urban single-center retrospective study, we found that higher IgE levels correlated with the need for PICU admission and longer PLOS in children admitted for an acute asthma exacerbation.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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