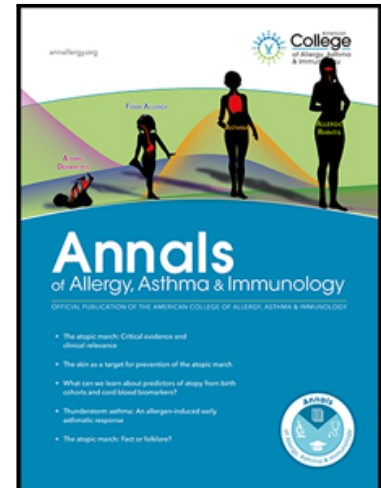


Race Specific Characteristics in Pediatric Eosinophilic Esophagitis in an Urban Inner-City Clinic

Mark Mahon MD , Noé D Romo MD , Gabriele de Vos MD , Daniela Levanon MD

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Title: Race Specific Characteristics in Pediatric Eosinophilic Esophagitis in an Urban Inner-City Clinic

Authors: Mark Mahon, MD¹; Noé D Romo, MD¹; Gabriele de Vos, MD¹; Daniela Levanon, MD¹

¹ Lewis M Fraad Department of Pediatrics, NYC Helath+Hospitals/Jacobi Medical Center, The Bronx, NY

Corresponding Author Information:

Mark Mahon, MD

Lewis M Fraad Department of Pediatrics, NYC Helath+Hospitals/Jacobi Medical Center, 1400 Pelham Parkway S. The Bronx, New York, NY 100461.

+1 646 288 0059

Mahonm3@nychhc.org

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Abbreviations/Acronyms:

EoE: Eosinophilic Esophagitis

BMI: Body Mass Index

AEC: Absolute Eosinophil Count

PPI: Proton Pump Inhibitor

HPF: High Power Field

SPT: Skin Prick Testing

EEE: Extra-esophageal eosinophilia

Word Count: 2319

Figures: One

Tables: Five

Abstract:

Background: Manifestations of pediatric Eosinophilic Esophagitis (EoE) are varied and dictated by multiple factors. The influence of race is limited to small observational cohorts of dichotomized data (Caucasians v. non-Caucasians) or single racial analysis.

Objectives:

Our analysis aims to better understand the phenotypic variability in the manifestation and atopic sensitization of pediatric EoE, from the perspective of race.

Methods:

Retrospective observational cohort study performed at a tertiary referral center. Subjects were included if <21 years old, with suggestive clinical features and histopathological (>15 eosinophils/hpf) confirmation of EoE. Statistical computation was performed using StataIC 11 on variables of interest.

Results:

Thirty-four subjects were included in analysis. The median [IQR] age for initial atopy was 2 [1,5] years. The median [IQR] age for EoE diagnosis was 5 [3,8] years. Age of EoE diagnosis was higher for Black/African-Americans compared to non-Black/African-Americans ($p = 0.012$). Between the racial groups there was no difference in the total number of food sensitizations ($0 = 0.139$), yet environmental allergy testing demonstrated that Black/African-Americans were more likely to be sensitized for weeds ($p = 0.037$), dog ($p = 0.009$) and mold ($p = 0.006$). On histopathological analysis, Black/African-American subjects were found to have more prominent mid-esophageal eosinophilia at median 50/hpf [20,80/hpf], while Hispanic/LatinXs have more prominent lower-esophageal eosinophilia at median 40/hpf [IQR 20,40/hpf], compared to other races; $p = 0.048$ and $p = 0.044$ respectively.

Conclusions:

Black/African-Americans are more likely to present at an older age, have aeroallergen sensitization and more prominent mid-esophageal eosinophilia.

INTRODUCTION:

Manifestations of pediatric Eosinophilic Esophagitis (EoE) are varied and dictated by multiple factors. Race may play an important role as suggested in preliminary studies.⁽¹⁻⁷⁾ It appears that cases of EoE manifest at an earlier age and with growth faltering in non-Whites compared to their White counterparts.⁽³⁻⁵⁾ The former are also more likely to have more allergic

sensitizations.⁽⁵⁾ Data on Asian and Hispanic/LatinX pediatric cohorts are otherwise limited to small proportions of studies.^(2-4,6-8)

In our study, we analyzed the demographics, clinical presentation, gross endoscopic appearance and histopathological density of esophageal eosinophilia, clinical atopy disease burden and allergy sensitization profiles of pediatric patients with EoE. Gender⁽³⁾ and age^(4,5) are known predictors of variable EoE presentation with a higher proportion of males and Black-African Americans diagnosed at an age of <18 years. The focus on racial diversity in this study will help understand the phenotypic variability in the manifestation and atopic sensitization of pediatric EoE, from the perspective of race.

METHODS:

Study Design:

This was single center retrospective study at a municipal hospital and tertiary referral center, Jacobi Medical Center in The Bronx, New York. The center serves a low income, predominantly immigrant population in its pediatrics outpatient department. A review of patients presenting for routine well-child checks (n=14,379, between 3/1/2018-7/26/2019) consisted of; 34% Black/African-American, 34% Hispanic/LatinX, 8% Asian and only 7% white. After approval by the local IRB (Albert Einstein College of Medicine) data was obtained through retrospective chart review of electronic medical records (EMR) of pediatric patients presenting to the Pediatric Gastroenterology Division between March 2008 to July 2019.

Eligibility:

Subjects were included in the analysis if aged <21 years at time of EoE diagnosis. The diagnosis of EoE was based on histopathologic report of ≥ 15 eosinophils per high power field (hpf) on

biopsy in either mid- or lower-esophageal specimens with suggestive clinical features ⁽⁹⁾.

Subjects with missing information on age or race, or if histopathological correlation to clinical suspicion of EoE was not met, were excluded from the analysis.

Variables:

The following data was collected: age at first clinical atopic diagnosis (defined as any one of allergic rhinitis, atopic dermatitis, asthma or food allergies), age at EoE diagnosis, gender, weight, height, body mass index (BMI) category (per age and gender specific growth curves), presenting complaint, atopic condition(s) such as allergic rhinitis, atopic dermatitis, asthma, food/environmental allergic sensitizations, absolute eosinophil count (AEC) and total serum IgE level (documented within six months prior to endoscopy), treatment received pre-endoscopy i.e. proton pump inhibitor (PPI), gross endoscopic finding (initial/diagnostic endoscopy) and eosinophils/hpf in mid- and lower-esophageal biopsies (where a range was provided, the higher end value was taken as the peak).

Statistical Analysis:

StataIC 11 was used for statistical computation. Continuous, non-parametrically distributed variables were expressed in medians and interquartile ranges (IQR) and means with standard deviation (SD) were used for parametric variables. Kruskal-Wallis test and Fisher's Exact test were performed for comparison of continuous non-parametric variables or categorical variables, respectively. T-test or ANOVA were applied for comparison of continuous parametric variables. Numerical data that was recorded as an inequality expression ($<$, $\leq$, $>$ or $\geq$) was converted into the number without the respective symbol to allow inclusion in an otherwise continuous variable.

This was relevant for only total serum IgE i.e. an IgE serum level documented as >2,000 was converted to 2,000 to allow inclusion into statistical computations.

For the description of race, the World Health Organization (WHO) definition was used for White, Black/African-American, Hispanic/LatinX and Asian, with one additional category created; “mixed race” for those that identified as being multi-racial. For statistical comparison four groups were used; Black/African-American, Hispanic/LatinX, Asian and “other”. Other included White and mixed race.

RESULTS:

Demographics:

Out of the 41 patients identified in the EMR over the eleven-year period, seven patients did not meet eligibility criteria and were excluded due to lack of racial identification (n=2) and histopathological criteria with <15/hpf eosinophils (n=5). The subjects (n=34) at time of EoE diagnosis were between the ages of 0.58 to 20 years, with a median [IQR] of 5 [3,8] years [Table 1]. Subjects were predominantly male (76.4%), with a male to female ratio of 3:1. The majority (64.7%) were classified as being in a healthy BMI category i.e. BMI between 5th to the 85th percentile for age and gender. Between racial groups abnormal BMI category relative to age and gender approached statistically significant differences, with Black/African-Americans more likely to have an abnormal BMI; either within the overweight (85th – 95th percentile) or obese (>95th percentile) category for age and gender (p = 0.073). Racial identity was primarily Hispanic/LatinX (32%), followed by Asian (29%), Other (21%) and Black/African American (18%). Other included White (6%) and mixed race (15%). Overall, the proportions of each race

group among children with EoE were relatively similar when compared to the general referral base to the Pediatric Allergy Division. Referrals for any reason between 3/1/18-7/26/19; n=724, 41% were Hispanic/LatinX, 28% were Black/African-American, 7% were Asian and 8% were White [Table 2].

Atopy History and Allergy Sensitization:

Subjects were found to have an extensive atopy history [Table 1]. The median [IQR] age for initial atopy manifestation (allergic rhinitis, atopic dermatitis, asthma or food allergies⁽¹⁰⁾) was 2 [1,5] years for all races combined. There was no significant difference between the racial groups for age at first atopy ($p = 0.481$). Compared to our non-EoE Pediatric cohort the burden of allergic rhinitis and asthma were similar (allergic rhinitis in 35% of EoE patients, and 30% in Non-EoE patients; asthma in 53% of EoE patients and 32% of non-EoE patients). Children with EoE showed higher rates of atopic dermatitis compared to the children without EoE (47% atopic dermatitis in EoE, 6% atopic dermatitis in non-EoE patients). The median [IQR] age for EoE diagnosis in all races combined was 5 [3,8] years. Nevertheless, at the time of EoE diagnosis for Black/African-Americans were noted to be older (median 13 years, IQR 5,18) than the other racial groups combined (median 5 years, IQR 2,8) ($p=0.012$) [Table 1]. Although analysis was only approaching statistical significance ($p = 0.07$) when comparing age between all racial groups. The interval between initial atopy diagnosis to EoE diagnosis was calculated and defined as “inter-atopy interval”. This interval was identified to be shortest for the Black/African-American race, at a median 0 [0,5] years. However, as the median inter-atopy interval was similar for each racial cohort (i.e. 0-1 year), there was no statistical difference ($p = 0.943$).

There was no difference in the number of atopic diagnoses with a mean [95% CI] of 2 [1.6-2.4] prior to the diagnosis of EoE ($p = 0.47$). The extent of food allergen sensitization was determined

by skin prick test results or serum specific IgE testing. For a standard panel of the eight most common food allergens, 20 children (59%) had undergone skin prick testing (SPT) while 25 children (74%) had serum IgE allergy testing performed. Fifteen children (44%) had both SPT and serum IgE. Overall, 31 children (90%) had documented food allergy testing performed. Any positive test result was counted towards this analysis. Between the racial groups there was no difference in the total number of food sensitizations, when the 8 common food allergens milk, egg, soy, peanut, wheat, fish mix, shellfish or tree nuts were taken into account ($p = 0.139$) [Table 2]. Similarly, there was no difference between the racial groups in regards to sensitization to grains (rye, barley, rice and oat) ($p = 0.81$) [Table 3].

Twenty-five children (74%) had SPT and/or serum IgE tests results available for environmental allergens. Nineteen children (56%) had SPT performed and 6 children (18%) had serum IgE performed, while only 2 children (5%) had both SPT and serum IgE. Environmental allergy testing demonstrated that Black/African-Americans were more likely to be sensitized for weeds ($p = 0.037$), dog ($p = 0.009$) and mold ($p = 0.006$). When environmental allergens were grouped into predominant indoor (dustmite, cat, dog, cockroach, mouse and mold) and outdoor (pollen of tree, grass or weeds) sensitizations there was no significant racial difference; $p = 0.494$ and $p = 0.133$, respectively. [Table 3]

Clinical Presentation:

Subjects demonstrated a broad presenting symptomatology prompting evaluation for EoE; faltering growth or weight loss (29.4%), emesis (26.5%), feeding issues (17.6%), dysphagia (14.7%), abdominal pain (8.8%) and hematemesis (2.9%). [Figure 1] There was no statistical difference between the racial cohorts in the presenting symptom/sign that prompted referral to subspecialty services (Fishers Exact t-test, $p = 0.59$). The majority of each cohort, except

Hispanic/LatinXs presented with faltering growth or weight loss. In contrast, Hispanic/LatinXs predominantly presented with emesis (45%). To determine if age predicted symptomatology, the subjects were stratified into two groups based on median age of EoE diagnosis (≤ 5 years and >5 years). Emesis was observed to occur more frequently in children ≤ 5 (n=9, 45%) years and faltering growth/weight loss (n=6, 43%) in children >5 years ($p = 0.03$).

Evaluation:

Routine complete blood cell count was performed prior to endoscopy in all children. Manual differential for baseline peripheral blood AEC was available in 27 (80%) children, with a mean (SD) of 537/ μ L (330/ μ L). [Table 4] Defining ≥ 350 / μ L as eosinophilia, 65% of children (n=19) demonstrated evidence of serum eosinophilia on routine complete blood count. In children with available data on total serum IgE (n=33, 97%), the mean serum IgE level was 753IU/mL with a range of 14 to $>2,000$ IU/mL. Although Asians and Black/African-Americans appeared to have higher rates of abnormal total IgE levels compared to the other racial groups this difference was not significant ($p=0.075$), nor was significance reached when comparing Asians to non-Asians ($p = 0.09$) or Black/African-Americans to non-Black/African-Americans ($p = 0.278$).

Prior to establishing the diagnosis of EoE with endoscopy and biopsy, 54% (n=18) were prescribed a daily PPI. Data was missing on one subject. Pre-endoscopy treatment with a PPI did not vary by race ($p = 0.276$). Gross endoscopy was abnormal in the majority of children (n=25, 74%) with evidence of either mucosal edema, friable mucosa on passage of the endoscope, white exudate or plaques, erosions, furrowing, felinezation and strictures reported. Albeit not statistically significant, Asians were more likely to have a normal gross endoscopy with only 50% showing evidence of the aforementioned features on analysis ($p=0.122$); however, significance was reached when comparing Asians to non-Asians ($p = 0.048$). Sub-analysis on the

multiple gross endoscopic features per race was not performed; however friable mucosa was the most frequent finding in 38% (n=13) of children.

Histopathological data of eosinophilia/hpf in each of the two esophageal biopsy sites (mid-esophagus and lower-esophagus) were analyzed [Table 5]. The overall median [IQR] number of eosinophils in the mid-esophagus was 20 eosinophils/hpf [IQR 10,41]. Black/African-American subjects were found to have more prominent mid-esophageal eosinophilia at 50/hpf [20,80/hpf] when compared to other racial cohorts ($p = 0.048$). Hispanics/LatinXs had milder mid-esophageal eosinophilia involvement, 10/hpf [IQR 3,20/hpf]. The lower esophagus had a higher overall median eosinophilia/hpf with 40 eosinophils/hpf [IQR 20,40]. Evidence of lower esophageal eosinophilia was most prominent for Hispanic/LatinXs demonstrating a median of 40/hpf [IQR 20,40/hpf], when compared to Black/African-Americans 35/hpf [IQR 19,80/hpf] and Asians 35/hpf [IQR 20,40/hpf] ($p = 0.044$).

DISCUSSION:

This observational study on pediatric EoE patients allowed us to make several race-specific observations. Some of these findings are confirmatory of that documented in the literature, while others are described for the first time. The documentation of these differences will help with a race-specific phenotypic description in pediatric EoE.

Prior studies have indicated that the time gap between EoE symptom onset to formal EoE diagnosis on endoscopy is age and race dependent.⁽⁷⁾ While the symptom onset could not have been established by chart review in some of our patients, we found that Black/African-Americans were diagnosed with EoE at an older age than their non-Black/African-American peers, which appears to contradict the existing literature.^(4,5)

Previous studies have indicated that the clinical presentation of EoE may vary by race with Black/African-Americans more likely to present with feeding issues and faltering growth, while Whites more commonly present with dysphagia.⁽³⁻⁵⁾ Our cohort confirmed these findings among Black/African-Americans, but additionally identified emesis as a more common presentation in Hispanic/LatinX patients. In general, emesis was more frequently the presenting sign before the age of 5 years while faltering growth was more commonly the primary symptom in older children.

Our cohort confirmed extensive allergy sensitizations in pediatric EoE⁽¹¹⁾ with similar patterns of food sensitization, supporting the strong evidence for empiric elimination diets in treatment across pediatric cohorts in absence of allergy testing.⁽¹²⁻¹⁴⁾ Regarding environmental allergy testing Black/African-Americans were found to have higher rates of sensitization to the common aeroallergens such as weeds, dog and mold. This is important as both seasonal diagnostic patterns^(15,16) and animal models⁽¹⁷⁾ have been described, suggestive that exposure to aeroallergens can exacerbate EoE.⁽¹⁴⁾

Gross endoscopic findings are common and extremely variable in EoE^(18,19), however, no feature is pathognomic. On initial diagnostic endoscopy, we confirmed that non-Whites^(3,6), and specifically Asians were more likely to have a normal gross endoscopy. On histopathological analysis of eosinophils/hpf, the findings of this study confirmed other investigators' reports that Black/African-Americans have a higher density of eosinophils/hpf in the mid-esophagus.⁽⁵⁾ In addition, we found a higher density of eosinophils/hpf in the lower-esophagus among Hispanic/LatinXs patients.

Our study has several limitations, such as its small sample size and retrospective design. Nevertheless, our preliminary findings may help in considering a larger, prospective cohort study

in highly diverse populations. In addition, a quality of this study lies in involving exclusive pediatric EoE patients, the racial diversity of patients and a comprehensive multidisciplinary input.

In summary, this retrospective study of children with EoE suggests that; 1) Black/African-Americans may be more likely to present at an older age in years at diagnosis, 2) Hispanic/LatinXs appear more likely to present with emesis, 3) Black/African-Americans may be more likely to have aeroallergen sensitization and 4) Hispanic-LatinXs may have higher densities of lower-esophageal eosinophilia.

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Figure 1: Clinical Presentation of Pediatric Eosinophilic Esophagitis, by race.

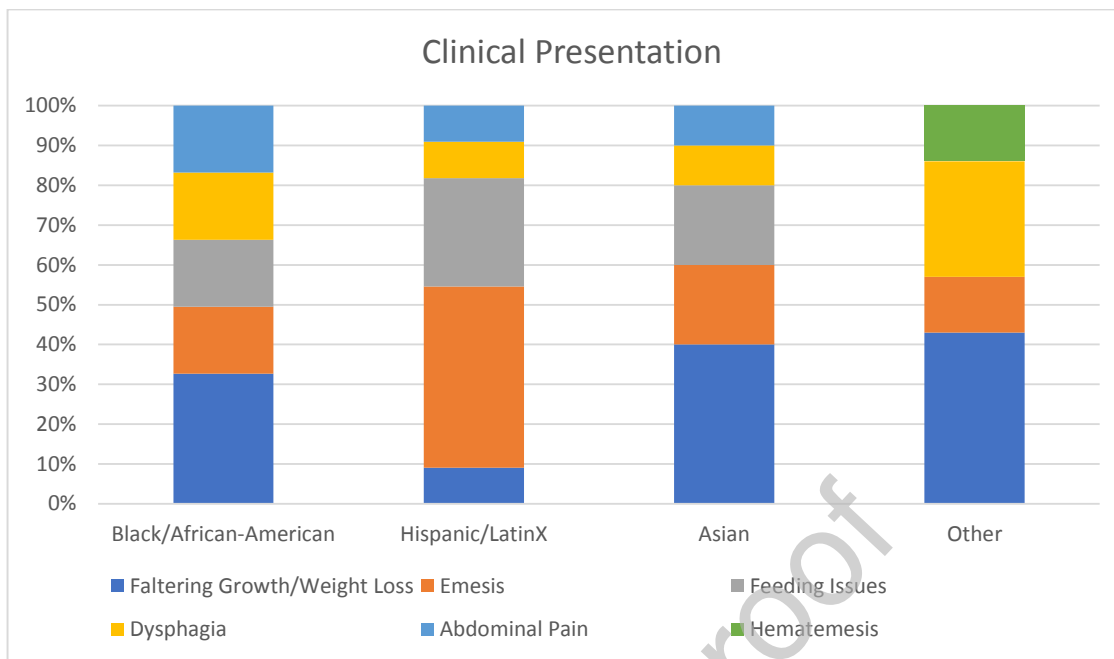


Table 1: Phenotypic Atopy Profiles in Pediatric EoE.

	Black/African-American	Hispanic/LatinX	Asian	Other	p-value
Number of patients [n(%)]	6 (18)	11 (32)	10 (29)	7 (21)	NA
Male Gender [n(%)]	6 (100)	9 (82)	6 (60)	5 (71)	0.364
Age (yrs) first atopy [median(IQR)]	8 (2, 14)	2 (0.33, 6)	2.5 (1.5, 4)	2 (0, 5)	0.481
Age (yrs) at EoE Diagnosis [median(IQR)]	13 (5, 18)	4 (1.5, 9)	5 (3, 7)	3 (1.5, 8)	0.07
Time in years between initial atopy diagnosis to EoE diagnosis [median(IQR)]	0 (0, 5)	0.75 (0, 3)	0.25 (0, 4)	1 (0, 2)	0.943
Allergic Rhinitis [n(%)]	2 (33)	5 (46)	4 (40)	2 (29)	0.961
Atopic Dermatitis [n(%)]	1 (17)	6 (55)	4 (40)	5 (71)	0.272
Asthma [n(%)]	2 (33)	6 (55)	5 (50)	5 (71)	0.65
Allergies [n(%)]	4 (67)	9 (82)	5 (50)	4 (57)	0.462

Table 2: Demographic distribution of pediatric patients with and without EoE.

Race	Patient with EoE (n=34)	Patients without EoE (n=724)
Black/African American [n(%)]	6(18)	204(28)
Hispanic/LatinX [n(%)]	11(32)	299(41)
Asian [n(%)]	10(29)	52(7)
White [n(%)]	2(6)	63(8)
Other [n(%)]	5(15)*	106(15)**

* All identified as “mixed race”. ** Proportion was Alaskan (4%) and unknown/declined (96%).

Table 3: Allergy Profile Testing in Pediatric EoE.

[n(%)tested]	Black/African-American	Hispanic/LatinX	Asian	Other	p-value
Food Sensitizations					
Milk	1 (33)	4 (44)	4 (50)	3 (50)	1.000
Egg	2 (50)	7 (70)	4 (44)	4 (57)	0.725
Soy	3 (75)	4 (40)	6 (67)	4 (67)	0.608
Peanut	2 (50)	2 (50)	4 (44)	5 (71)	0.198
Wheat	2 (50)	4 (40)	4 (44)	5 (57)	0.954
Fish	2 (40)	1 (10)	2 (22)	1 (17)	0.561
Shellfish	4 (80)	2 (20)	3 (33)	2 (40)	0.201
Tree Nut	3 (100)	3 (33)	5 (63)	2 (67)	0.278
Total of common food [mean(SD)]	3.2 ($\pm$ 3.2)	2.5 ($\pm$ 2.1)	3.2 ($\pm$ 2.2)	3.6 ($\pm$ 2.2)	0.139
Grain Sensitizations					
Rye	3 (75)	1 (17)	5 (63)	1 (33)	0.259
Barley	3 (75)	1 (20)	3 (43)	1 (33)	0.500
Rice	1 (50)	0 (0)	2 (67)	1 (25)	0.455
Oat	3 (75)	4 (80)	4 (50)	2 (50)	0.670
Total Grain [mean(SD)]	1.6 ($\pm$ 1.9)	0.5 ($\pm$ 0.9)	1.4 ($\pm$ 1.5)	0.7 ($\pm$ 1.1)	0.810
Environmental Sensitizations					
Tree	3 (100)	2 (29)	4 (44)	3 (60)	0.255

Grass	1 (50)	2 (29)	0 (0)	3 (60)	0.069
Weeds	3 (100)	3 (43)	1 (11)	3 (60)	0.037
Dustmite	3 (100)	4 (57)	2 (25)	1 (20)	0.093
Cat	2 (67)	5 (71)	3 (38)	1 (20)	0.344
Dog	3 (100)	6 (86)	1 (14)	1 (20)	0.009
Cockroach	3 (100)	4 (57)	4 (44)	2 (40)	0.465
Mouse	1 (33)	6 (86)	2 (25)	3 (60)	0.132
Mold	2 (100)	2 (29)	0 (0)	0 (0)	0.006
Total Indoor Environmental [mean(SD)]	2.3 (± 2.6)	2.5 (± 2.6)	1.2 (± 1.3)	1.1 (± 1.9)	0.494
Total Outdoor Environmental [mean(SD)]	1.2 (± 1.3)	1.0 (± 1.2)	0.5 (± 0.7)	1.2 (± 1.6)	0.133

Table 4: Serum Markers of Atopy in Pediatric EoE.

	Black/African-American	Hispanic/LatinX	Asian	Other	p-value
Absolute Eosinophil Count $\geq 350/\mu\text{L}$ [n(%)]	3 (60)	4 (50)	7 (78)	5 (71)	0.785
Total Serum IgE ≥ 300 IU/mL [n(%)]	4 (80)	3 (27)	8 (80)	4 (57)	0.075

Table 5: Abnormal Gross Endoscopy and Histopathological Eosinophilia in pediatric EoE.

	Black/African-American	Hispanic/LatinX	Asian	Other	p-value
Abnormal Gross Endoscopy [n(%)]	5 (83)	8 (73)	5 (50)	7 (100)	0.122
Midesophageal Eosinophilia [median(IQR)]	50 (20, 80)	10 (3, 20)	22.5 (15, 41)	41 (3, 41)	0.048
Lower Esophageal Eosinophilia [median(IQR)]	35 (19, 80)	40 (20, 40)	35 (20, 40)	41 (30, 41)	0.044