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The characterization of asthma with blood eosinophilia in adults in Latin America

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ABSTRACT

Objective: To identify and characterize asthma with blood eosinophilia in adults. **Methods:** This cross-sectional study consisted of 164 asthma patients, aged 18 years or older. Multivariate analyses by logistic regression were performed to identify clinical characteristics and biomarkers associated with asthma with blood eosinophilia (defined as asthma and a peripheral blood eosinophil count ≥ 400 cells/mm³). To evaluate the diagnostic accuracy of these biomarkers, the sensitivity, specificity and predictive values were calculated. Additionally, the area under the receiver operating characteristic (ROC) curve (AUC) was estimated for each biomarker. **Results:** Overall, 37.8% (95%CI: 30.7–45.4%) of asthma patients had blood eosinophilia. The following factors were associated with this characteristic: patient age < 50 years (OR 3.25; 95% CI: 1.33–7.94), a serum level of IgE ≥ 300 UI/mL (OR 2.32; 95%CI: 1.14–4.75), and an Asthma Control Test (ACT) score < 20 points (OR 3.10; 95%CI: 1.35–4.75); asthma with blood eosinophilia was also associated with a baseline FEV₁/FVC $< 70\%$ (OR 2.68; 95%CI: 1.28–5.59). On the other hand, age < 50 years and ACT score < 20 showed the highest sensitivity (above 80% each). Serum IgE level ≥ 300 UI/mL had the highest specificity (almost 68%). Finally, those with an ACT score < 20 had the highest AUC (68%). **Conclusions:** In our study population, one-third of asthmatic adults had asthma with blood eosinophilia. Furthermore, the prevalence was greater in those ≤ 50 years of age; these patients experienced more severe, more poorly controlled asthma and had higher total serum IgE levels.

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1. Introduction

Eosinophilic asthma (EA) is characterized by the increased presence of eosinophils in the bronchial mucus. Eosinophils can be identified by a bronchoscopy or in induced sputum. Because these techniques are complex, other more easily detectable parameters, related to bronchial eosinophilia have emerged, such as: the analysis of peripheral blood eosinophilia, the fraction of exhaled nitric oxide (FeNO) [1–3], or, eosinophils in nasal lavage [4]. These easier testing methods also allow us to more easily study this phenomenon. Several cutoff points regarding eosinophils in the blood have been proposed as a means of distinguishing between EA and noneosinophilic asthma (NEA) [2,3,5,6]. Notably, an eosinophil count

≥ 400 cells/mm³ is the most recommended cutoff value. Based on previous studies, the frequency of eosinophilic asthma has been estimated to be between 16% and 50% among all asthma patients, depending on methods and cutoff values used to define EA and the study populations [3,7–10].

Various clinical factors have been associated with EA: sinusitis, nasal polyps, and respiratory disease exacerbated by aspirin [1]; moreover, EA tends to be more frequent among men and is linked to an increase in asthma severity [3,10]. According to race, Afro-Americans are the most commonly affected group [11]. Last, EA is associated with a higher probability of asthma exacerbations [5–7]. However, it must be borne in mind that asthma with blood

eosinophilia is not exactly synonymous with eosinophilic asthma, as we discussed above. As such, in our article we decided to be puristic, and refer to asthma with blood eosinophilia (asthma-w-bloodEO) to the disease fulfilling these characteristics.

With the surge of several specific biological agents for asthma, now more than ever, determining the predominant inflammatory pattern in asthma is important for its research and treatment. Some of these biological treatment modalities will take blood eosinophilia into consideration as a parameter for the selection of their ideal candidate. Notably, despite the fact that asthma-w-bloodEO is an important subtype, its detection and characterization lack standardization; on the other hand, in Latin American, studies aimed at analyzing this problem are scarce. Thus, our objective was to determine the prevalence of asthma with blood eosinophilia in Mexican asthma patients aged 18 years or older and to evaluate biomarkers to distinguish asthma-w-bloodEO from asthma-non-bloodEO.

2. Material and methods

2.1. Design and patient

A cross-sectional study was conducted in a university hospital, we analyzed the data corresponding to 164 patients with asthma; all of them were recruited consecutively from October 2014 to January 2016. We included patients who received treatment for the first time, were aged ≥ 18 years, and those that had not used oral systemic steroids during the previous month; pregnant women were excluded. Additionally, a personal history of atopic diseases was documented; we also inquired about the evolution and the clinical characteristics of their asthma.

2.2. Asthma diagnosis

To establish an asthma diagnosis, in line with asthma guidelines we took the following symptoms into consideration: wheezing, coughing, shortness of breath or chest tightness. Notably, these had to be fluctuating in intensity and frequency [12]. Moreover, all patients had to have a forced spirometry test results compatible with airflow limitation reversible with a short-acting bronchodilator administered by inhaler. We diagnosed asthma-w-bloodEO when, in addition to the aforementioned, the patient had a peripheral blood eosinophil count over 400 cells/mm³ [9,10,13].

2.3. Pulmonary function test

Prior to carrying out the procedures, each patient was instructed to suspend the use of inhaled long and short acting beta-2 agonists, for at least twelve hours. Spirometry was conducted in the morning with the use of a Master Screen-Body PFT (Jaeger®, Care Fusion, Baesweiler, Germany); the subjects were sitting while their nostrils were closed. In total, each patient performed a maximum of 8 blows or until at least 3 of the criteria of acceptability and reproducibility were met. To identify the reversibility of the obstruction, the patient inhaled 400 μ g of salbutamol by metered-dose inhaler and spacer; 15 min later, the procedure was repeated. If the forced expiratory volume in the first second (FEV₁) improved by 12% or more and was greater than 200 ml, the reversibility test result was considered positive [14].

2.4. Periphery blood total IgE, eosinophilia and allergy

Morning blood samples were sent to the main laboratory in the hospital in order to quantify the serum total IgE levels and the total peripheral blood eosinophil count. The IgE serum level was determined with the use of the magnetic particle-based chemiluminescence technique (Access Total IgE®, Beckman Coulter) following the manufacturer's instructions.

Allergy was defined as the presence of at least one positive skin prick test to at least one of the tested aeroallergens. These were administered and interpreted by an allergist that adhered to international standards [15].

2.5. Asthma severity

The severity of asthma was established based on the degree of obstruction, as expressed by FEV₁ (percentage of predicted) in a forced spirometry. Patients were placed in different categories based on the recommendations provided by the Global Initiative for Asthma (GINA) guidelines: mild intermittent, mild persistent, moderate persistent or severe persistent [16]. The Asthma Control Test (ACT) was also employed. A total point count ≥ 20 defined well-controlled asthma; values below 20 were considered uncontrolled [17]. The patient's severity was also determined based on their personal history of at least one hospitalization due to asthma in the previous year.

2.6. Statistical analyses

During the comparison of the clinical characteristics and the severity of asthma among patients with asthma-w-bloodEO and asthma-non-bloodEO, we applied Student's *t* test or the Mann-Whitney U test (based on the distribution of continuous variables), and the Chi [2] (when we estimated proportions).

To identify the factors associated with asthma-w-bloodEO (dependent variable), we used multivariate models with binary logistic regression, for which the independent variables were: age, presence of allergic sensitization, allergic rhinitis, total serum IgE level, ACT score and FEV₁/FVC.

In these models, the strength of the association between variables was estimated by the odds ratio (OR). Afterward, the variables that were identified as associated during the multivariate analyses were also studied for their utility as biomarkers for asthma-w-bloodEO, considering peripheral blood eosinophils ≥ 400 cells/mm³ as the gold standard (surrogate variable).

We estimated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the receiver operating characteristic (ROC) curve of age, IgE level, ACT score and FEV₁/FVC to evaluate the asthma-w-bloodEO diagnostic accuracy. The same cutoff point of each biomarker used in the multivariate analysis was considered. When necessary, 95% confidence intervals (95% CI) were calculated in the statistical analysis. The data was processed with the IBM SPSS Program,

version 20.0 for Windows (IBM Co., Armonk, NY, USA).

2.7. Ethics

This study was approved by the Ethics Committee at The Hospital Civil de Guadalajara "Dr. Juan I. Menchaca." To participate, each patient was asked to sign a written consent form.

3. Results

Overall, 62 out of 164 asthma patients had asthma-w-bloodEO (37.8%; 95% CI: 30.7%–45.4%); for asthma-non-bloodEO the mean age was 41.2 years, whereas for asthma-w-bloodEO it was 35.5 years ($p=0.011$), Table 1. The frequency for allergy sensitization was higher in asthma-w-bloodEO than it was for asthma-non-bloodEO (90.3% vs. 74.5%, $p=0.013$). The total serum IgE concentration was significantly higher in those with blood eosinophilia.

Table 2 offers a comparison between asthma-w-bloodEO and non-bloodEO, based on severity. The hospitalization rate during the previous year did not differ between the groups. With the use of ACT, we observed a higher number of controlled patients with asthma-non-bloodEO compared to those who had blood eosinophilia ($p=0.001$). In the respiratory function tests, there were no significant differences between the two groups regarding the pre- and postbronchodilator FVC and FEV₁ with the exception of the baseline FEV₁/FVC, which was lower in the

Table 1. Clinical characteristics of patients with asthma.

	Total <i>n</i> = 164	Asthma with blood eosinophils		<i>p</i>
		Yes <i>n</i> = 62	No <i>n</i> = 102	
Age, years $\pm$ SD	39.0 $\pm$ 14.0	35.5 $\pm$ 12.1	41.2 $\pm$ 14.8	0.011
Sex (female), <i>n</i> (%)	131 (79.9)	50 (80.6)	81 (79.4)	0.848
Current smoker, <i>n</i> (%)	10 (6.1)	4 (6.5)	6 (5.9)	0.883
Co-morbidity, <i>n</i> (%)				
Allergic rhinitis	127 (77.4)	52 (83.9)	75 (73.5)	0.124
Food allergy	25 (15.2)	12 (19.4)	13 (12.7)	0.253
Atopic dermatitis	10 (6.1)	4 (6.5)	6 (6.4)	0.883
Urticaria	1 (0.6)	1 (1.6)	0 (0)	0.380
Body mass index (Kg/m ²), mean $\pm$ SD	29.2 $\pm$ 5.9	28.8 $\pm$ 5.2	29.5 $\pm$ 6.3	0.426
Obesity, <i>n</i> (%)	70 (42.7)	27 (43.5)	43 (42.2)	0.861
Allergy sensitization, <i>n</i> (%)	132 (80.5)	56 (90.3)	76 (74.5)	0.013
IgE serum levels				
Median (P ₂₅ –P ₇₅)	170.9	300 (88 - 475)	153 (50 - 339)	0.022
IgE ≥ 100 UI/mL	104 (63.4)	45 (72.6)	59 (57.8)	0.057
IgE ≥ 200 UI/mL	75 (45.7)	33 (53.2)	42 (41.2)	0.133
IgE ≥ 300 UI/mL	65 (39.6)	32 (51.6)	33 (32.4)	0.014
Duration of asthma (years), mean $\pm$ SD	12.6 $\pm$ 10.1	11.5 $\pm$ 9.7	13.3 $\pm$ 10.3	0.258
Age of asthma onset ≥ 18 years, <i>n</i> (%)	114 (69.5)	43 (69.4)	71 (69.6)	0.973

n: The number of occurrences.

SD: Standard deviation.

P₂₅–P₇₅: Percentile 25 – percentile 75.

p values obtained through the chi square test or the Student's *t* test or the Mann-Whitney U test, as deemed necessary.

Obesity was defined as IMC ≥ 30 Kg/m².

Table 2. Severity of asthma based on the presence of blood eosinophilia.

	Total <i>n</i> = 164	Asthma with blood eosinophils		<i>p</i>
		Yes <i>n</i> = 62	No <i>n</i> = 102	
Hospitalization due to asthma in previous year, <i>n</i> (%)	51 (31.1)	23 (37.1)	28 (27.5)	0.196
Asthma control test, points				
≥ 20, <i>n</i> (%)	52 (31.7)	10 (16.1)	42 (41.2)	0.001
Mean ± DE	16.0 ± 5.3	14.1 ± 4.9	17.2 ± 5.1	< 0.001
Median (P ₂₅ –P ₇₅)	16 (12–21)	14 (10–18)	17 (14–22)	< 0.001
Respiratory function test, mean ± SD				
% predicted baseline				
FVC	89.4 ± 17.6	89.9 ± 19.7	89.1 ± 16.3	0.780
FEV ₁	73.7 ± 18.3	71.1 ± 19.5	75.5 ± 16.3	0.142
FEV ₁ /FVC	68.1 ± 10.3	65.5 ± 10.3	69.8 ± 9.97	0.008
% predicted post-β ₂ agonist				
FVC	97.0 ± 17.9	97.0 ± 19.5	97.1 ± 17.0	0.970
FEV ₁	87.3 ± 18.3	85.2 ± 20.5	89.5 ± 17.4	0.159
FEV ₁ /FVC	73.9 ± 9.4	72.8 ± 10.5	75.5 ± 9.3	0.092
Reversibility, %, mean ± SD	20.7 ± 11.4	21.4 ± 10.0	20.3 ± 12.3	0.554
Asthma severity, <i>n</i> (%)				0.515
Mild intermittent	7 (4.3)	3 (4.8)	4 (3.9)	
Mild persistent	53 (32.3)	17 (27.4)	36 (35.3)	
Moderate persistent	66 (40.2)	25 (40.3)	41 (40.2)	
Severe persistent	38 (23.2)	17 (27.4)	21 (20.6)	

SD: Standard deviation.

P₂₅–P₇₅: Percentile 25 – percentile 75.

FVC: Forced vital capacity.

FEV₁: Forced expiratory volume at 1 s.*p* values obtained through the chi square test or the Student's *t* test or the Mann-Whitney U test, as deemed.**Table 3.** Multivariate models of factors associated to asthma with blood eosinophils.

	Model I			Model II		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Age <50 years	2.7	1.08–6.8	0.033	3.25	1.33 – 7.94	0.010
Allergy sensitization	2.33	0.70–7.81	0.169	—	—	0.079
Allergic Rhinitis	1.13	0.39–3.28	0.826	—	—	0.261
IgE ≥300 UI/mL	2.11	1.01–4.39	0.047	2.32	1.14 – 4.75	0.021
Asthma control test under 20 points	3.12	1.34–7.28	0.008	3.09	1.35 – 7.06	0.007
FEV ₁ /FVC baseline under the 70% predicted	2.75	1.31–5.79	0.007	2.68	1.28 – 5.59	0.009

OR: odds ratios estimated through logistic regression.

CI: Confidence interval. FVC: Forced vital capacity.

FEV₁: Forced expiratory volume at 1 s.

Model I, through the “Enter” method. Model II, obtained through “Forward conditional” method. The OR of the variables that were used as adjusters are not shown in Model II.

Table 4. Evaluation of asthma with blood eosinophils biomarkers.

Cut-off Point*	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Age <50 years	0.61 (0.52–0.70)	85.5 (76.7–94.3)	42.6 (33.8–51.4)	43.1 (34.3–51.8)	85.2 (76.3–94.1)
IgE ≥300 UI/mL	0.61 (0.52–0.69)	51.6 (39.2–64.1)	67.6 (58.6–76.7)	49.2 (37.1–61.4)	69.7 (60.6–78.8)
ACT <20 points	0.68 (0.59–0.76)	83.9 (74.7–93.0)	41.2 (31.6–50.7)	46.4 (37.2–55.7)	80.8 (70.1–91.5)
FEV ₁ /FVC baseline, < 70% predicted	0.63 (0.54–0.71)	62.9 (50.9–74.9)	56.9 (47.3–66.5)	47.0 (36.2–57.7)	71.6 (61.8–81.4)

AUC: Area under the curve.

PPV: Positive predictive value.

NPV: Negative predictive value.

CI: Confidence interval.

ACT: Asthma control test.

FVC: Forced vital capacity. FEV₁: Forced expiratory volume at 1 s.

*Cut-off point for the result of a biomarker to be considered positive for eosinophilic asthma.

asthma-w-bloodEO group ($p = 0.008$). According to GINA criteria, almost one-fourth of the patients had severe asthma; however, when we compared the two groups based on their severity categories, we did not observe any statistical significance ($p = 0.515$).

Table 3 shows the factors associated with asthma-w-bloodEO: total serum IgE level ≥ 300 UI/mL

($p = 0.02$), age over 50 years ($p = 0.01$), ACT score < 20 points ($p < 0.01$), and predicted FEV₁/FVC baseline $< 70\%$ ($p < 0.01$). Instead, aeroallergen sensitization and allergic rhinitis did not show a statistically significant association.

Table 4 displays the variables that were identified during multivariate analysis allowing us to evaluate

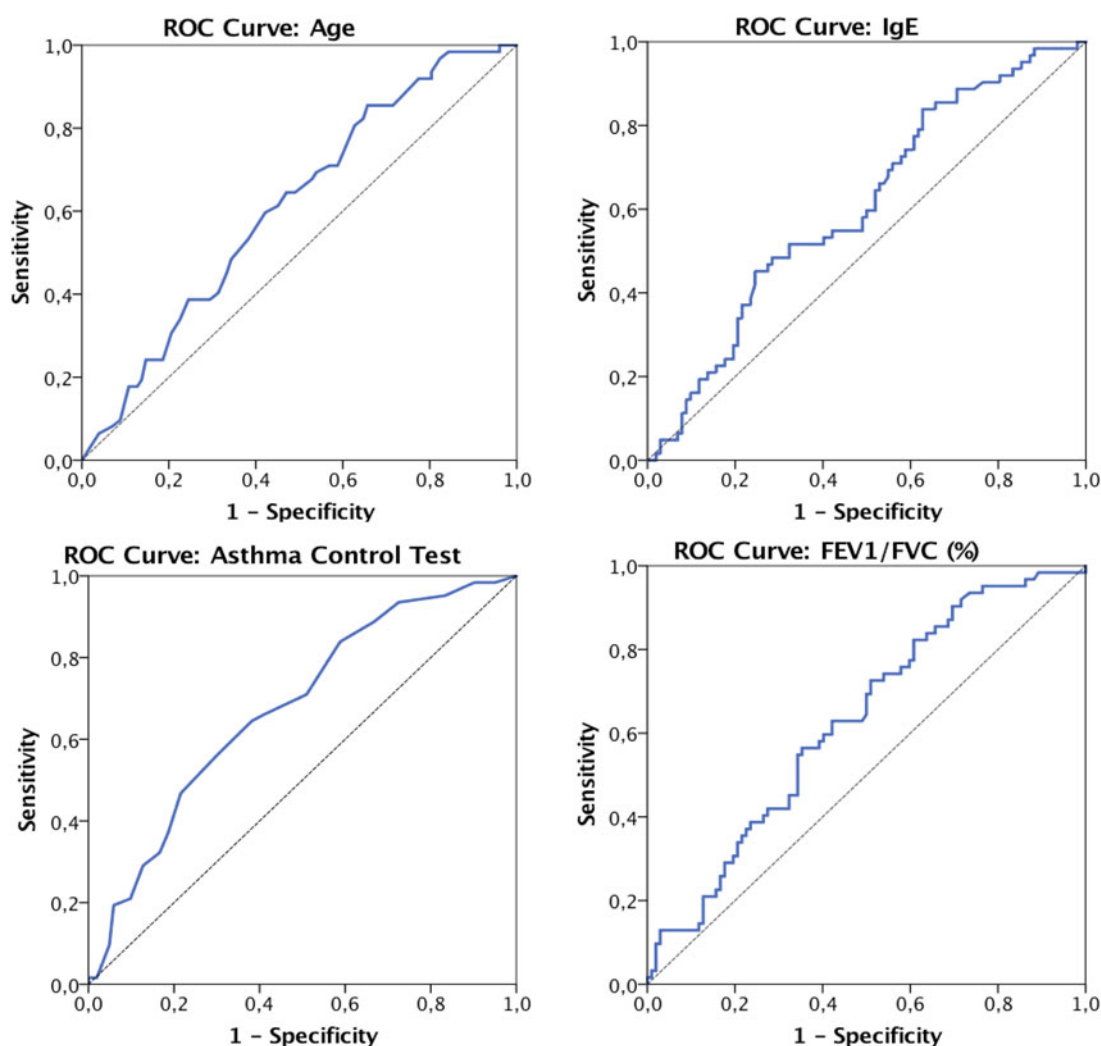


Figure 1. Receiver operating characteristic (ROC) curves for age, IgE, asthma control test and FEV₁/FVC ($n = 164$).

Table 5. Evaluation of the biomarkers combined asthma with blood eosinophils.

Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
IgE ≥ 300 UI/mL + ACT < 20 points	46.8 (34.3–59.2)	81.4 (73.8–88.9)	60.4 (46.6–74.2)	71.5 (63.3–79.8)
IgE ≥ 300 UI/mL + ACT < 20 points + FEV ₁ /FVC baseline, $< 70\%$ predicted	25.8 (14.9–36.7)	93.1 (88.2–98.0)	69.6 (50.8–88.4)	67.4 (59.6–75.1)
Age < 50 years + IgE ≥ 300 UI/mL + ACT < 20 points + FEV ₁ /FVC basal, $< 70\%$ predicted	21.0 (10.8–31.1)	97.1 (93.8–100)	81.2 (62.1–100)	66.9 (59.3–74.5)

AUC: Area under the curve.

PPV: Positive predictive value.

NPV: Negative predictive value.

CI: Confidence interval.

ACT: Asthma control test.

FVC: Forced vital capacity. FEV₁: Forced expiratory volume at 1 s.

their utility as biomarkers of asthma-w-bloodEO. Their sensitivity, specificity and predictive values were taken into account by using the same cutoff point used in Table 3.

The clinical characteristics of age < 50 years and ACT score < 20 points showed the highest sensitivity

(above 80% each), while an IgE level ≥ 300 UI/mL had the highest specificity (almost 68%). Notably, none of the biomarkers displayed a PPV $> 50\%$; the highest NPV was found for ACT score < 20 points, with a value of almost 81%. The ACT score demonstrated greater precision in its capability of

distinguishing between subjects with and without blood EO, more so than any of the other biomarkers evaluated (Figure 1).

Last, in Table 5, we display the biomarkers and clinical characteristics related to asthma-w-bloodEO. Interestingly, specificity increased as we combined a higher number of criteria (positive biomarkers); for example, IgE level ≥ 300 UI/mL combined with ACT score < 20 presented 81.4% specificity. However, if we added the predictive FEV₁/FVC baseline of $< 70\%$, the specificity rose even further to 93.1%, and when we added an age of < 50 , the specificity reached 97.1%. Similar results were observed for PPV: when the four criteria were met, the PPV for asthma-w-bloodEO increased to 81.2%.

4. Discussion

Our study exposed that in our population adult patients with asthma-w-bloodEO are younger than patients with asthma-non-bloodEO. Additionally, the asthma severity of asthma-w-bloodEO patients was greater, which was reflected by a higher frequency of bronchial obstruction in pulmonary function tests, and the control over their asthma was decreased. Last, a serum IgE level ≥ 300 UI/mL was identified as a factor associated with increased risk of asthma-w-bloodEO. Notably, the percentage of adult asthma patients with blood EO was relatively high in our population.

It is problematic to base the definition of EA on the eosinophil count in peripheral blood as there is no consensus on the cutoff point that should be used to identify this disorder. The eosinophil count has varied considerably among previous studies that examined the disease, ranging from 90 to 450 eosinophils/mm³ [2,18]. We decided to work with 400 cells/mm³ as our cutoff point as there is growing acceptance of this threshold and because of its acceptable sensitivity and high specificity (36% and 95%, respectively) in sputum samples that are used to detect sputum eosinophilia; a blood eosinophil cutoff point of less than 90 cells/mm³ showed a higher sensitivity (96%), however at the expense of specificity (26%) [2]. Additionally, an eosinophil count in peripheral blood is an easily accessible technique that can be used outside of hospitals as it is far less complex than the induced sputum technique or the bronchoscopy. As already exposed in our introduction we would like to stress the importance of correct terminology, avoiding the term eosinophilic asthma when asthma-w-bloodEO is meant. In many clinical

situations the identification of asthma-w-bloodEO versus asthma-non-bloodEO can be enough.

Thus far, the association between age and EA has been continuously debated. Some studies show that EA frequency is higher during the young adult stage, while others have not mentioned this fact. We have found that EA is predominant among patients under the age of 50, when compared to patients aged 50 years or older. Similarly, other studies have concurred with our findings; they state that patients with EA are considerably younger than patients with NEA [7,19,20]. However, it is important to note that there are studies in which an association between age and EA is not established [3,9,21]. Groot et al., initially observed that EA was more common in older patients than it was in younger patients, although this association lost significance after the multivariate analyses. It is likely that these results were influenced by their definition of EA as well as the time during which a patient develops asthma. So far, the eosinophil cutoff point in peripheral blood has not been standardized when defining EA; moreover, there is no set definition for early or late onset asthma.

One of the most relevant aspects of our study is that with our multivariate analysis, we were able to identify that a total serum IgE level of 300 UI/mL was the cutoff point for its independent association with asthma-w-bloodEO. We also analyzed other possible cutoff points of IgE levels (100 UI/mL and 150 UI/mL); however, we found no significant associations with these values (the results for the rest of the models are not presented). We then evaluated the utility of this cutoff point of IgE level as a possible biomarker for asthma-w-bloodEO and compared it to the clinical characteristics, such as age, ACT score, and FEV₁/FVC. Overall, each biomarker that was evaluated in our study displayed a low differentiation capability (approximately 60%); however, the IgE level showed higher specificity (59% to 77%) and positive predictive value (PPV from 37% to 56%). Other studies have evaluated the utility of IgE levels as an indicator of EA; however, Westerhof et al., found that the IgE level was the least precise indicator of eosinophilia in sputum samples when compared to biomarkers such as eosinophils in the blood and the FeNO levels. By contrast, in our study, the area under the curve (AUC) that was used to identify blood eosinophilia was 0.69 [2]. A recent meta-analysis showed similar findings that concurred with the latter result of decreased precision of the IgE level as a factor associated with eosinophils in the blood and FeNO; in this case, the AUC was 0.65 [22]. When compared to

NEA, additional studies have observed total concentrations of IgE >150 UI/mL in EA patients [6,23]. Thus, our results suggest a practical approach that would be easy to implement in hospitals and small clinics, as it would allow physicians to adequately identify EA in patients.

There are several tools that can be used to evaluate the level of asthma control, such as symptoms, the frequency of unscheduled hospital visits, and visits to the emergency room due to acute asthma, among others. In this study, we compared the level of control that our patients with asthma-w-bloodEO and asthma-non-bloodEO had over their disease with the use of the ACT, which allowed us to observe that those with bloodEO have significantly reduced control over their disease compared with those without bloodEO. Previous studies have shown that individuals with uncontrolled asthma have a significantly higher eosinophil count in their sputum samples [3,24,25]. Interestingly, in our population the severity of asthma as defined by the GINA guidelines was not associated with bloodEO. That is, asthma-w-bloodEO is linked to the degree of asthma control but not to the severity of the disease [24]. Moreover, we also found that FEV₁/FVC is significantly reduced in patients with asthma-w-bloodEO. Previous studies have proven that is an indicator of an obstruction in the respiratory region, which was strongly correlated to eosinophilia in sputum samples but not with eosinophilia in the blood [26]. In a different study, a group of patients with eosinophilia in their blood showed a reduction in FEV₁/FVC, but this was observed only in the postbronchodilator test [6]. It seems that eosinophilia found in the blood of asthmatic patients might be associated with reduced efficiency of the respiratory tract; however, the association is not as strong as the one observed between eosinophilia in sputum samples and the airway's diameter. Last, we compared asthma control with each patient's history of hospitalization during the previous year; however, we found no link between the two. Based on the available evidence, the increased presence of eosinophilia in the blood is correlated to an increased risk of asthma exacerbations [5–7].

While it's true that in our study most of the patients with asthma-w-bloodEO showed sensitization to at least one aeroallergen, this did not prove to be a statistically significant risk factor. Usually, atopic asthma is regulated by Th2 lymphocytes, which favor IgE production; however, recent evidence indicates that in non-atopic asthma eosinophils can be activated through other means [2], such as innate type 2

lymphoid cells [27,28]. Thus, asthma-w-bloodEO emerges as a partially independent phenotype to atopy.

In this particular study, almost 40% of the asthma patients had asthma-w-bloodEO. This finding significantly contrasts with the percentages reported in previous observation-based studies. Prior studies report far lower frequencies, which ranged anywhere from 16% to 26% [7–10]. On the other hand, in a retrospective study, Schleich et al. found that the frequency of EA was slightly higher at 50% in Belgian patients [3], a percentage that is similar to ours. A possible explanation for this might be due to the clinical similarities among our patients, as none of them had taken oral steroids at least one month prior to their inclusion in our study, which made it easier for us to identify eosinophilia in the peripheral blood. Notably, we believe that having selected patients from allergy services had little influence over the frequency of eosinophilia, since, as our results show, atopy was not strongly associated with bloodEO. We consider that this last point should be taken into consideration when trying to categorize the asthma phenotype.

Since our study included only first-time allergy patients, the use of asthma control medication could not be determined, which is necessary when defining the severity of the disease. Overall, the vast majority of patients only administered salbutamol as a means of control (data is not displayed in the tables). With respect to quantifying blood eosinophilia, we performed this test only once, which means there may have been individuals who were preemptively classified into the asthma-non-bloodEO group. Thus, due to the nature of our study and given our limited time frame, we were unable to determine the stability of eosinophilia.

Our findings confirm in a Latin-American population the suggestions of the international guidelines: to obtain routinely in all asthmatic patients a complete blood count in search of eosinophilia, as this might indicate more severe asthma and thus might indicate the need for more aggressive treatment, in some cases this might include biological.

Furthermore, this study shows that asthma-w-bloodEO in our population is more frequent in people under the age of 50 and those with a total serum IgE level over 300 UI/mL and that asthma-w-bloodEO patients have more poorly controlled asthma, as defined by an ACT score <20 points. It was also characterized by greater respiratory obstruction. We recommend that these factors be utilized when diagnosing or ruling out asthma-w-bloodEO in adult

patients. Moreover, we have demonstrated that the frequency of asthma-w-bloodEO, as defined by elevated eosinophil levels of at least 400 cells/mm³, in adult patients with asthma is common.

Authorship and contributor ship

Bedolla-Barajas designed the study; Ortiz-Peregrina, Hernández-Colín and Bedolla-Pulido were involved in data collection. Bedolla-Barajas and Morales-Romero wrote the manuscript and performed the statistical analysis. Larenas-Linnemann edited the manuscript for scientific content.

Conflict of interest

The authors declare that they have no conflicts of interest.

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