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Original Article

Correlation of total serum immunoglobulin E level, sputum, and peripheral eosinophil count in assessing the clinical severity in bronchial asthma

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ABSTRACT

Context: Asthma is a chronic inflammatory disorder of the airway with involvement of various cellular populations and release of many inflammatory mediators. Eosinophils and serum immunoglobulin E (IgE) are considered a good marker of airway inflammation in asthma. The correlation of clinical assessment with various markers of airway inflammation in asthma is not well established in the Indian population. **Aims:** This study aims to study the correlation of serum IgE, sputum eosinophil count, and peripheral eosinophil count with clinical severity of Asthma. **Methods:** This is a cross-sectional study involving 76 stable asthmatic patients of 18–60 years of age attending the pulmonary medicine OPD. Spirometry measured at baseline. Participants were categorized according to the GINA criteria based on clinical symptoms and pulmonary function test. Blood samples were collected for peripheral eosinophil count, serum IgE levels, and sputum samples for eosinophil count. All three parameters were compared with severity of asthma. The correlation of sputum eosinophil count, peripheral eosinophil count, and serum IgE with severity of asthma was analyzed by Pearson's Chi-square test, Fisher's exact test, and the correlation coefficient was reported together with standard error of the estimate. **Results:** The mean age of patients in our study was 37.42 years and 56.6% were male. There was a significant inverse correlation between serum IgE levels and predicted forced expiratory volume 1 s (FEV_1). Sputum eosinophilia was significantly seen in severe persistent asthma patients (19.7%). There was a significant inverse correlation between sputum eosinophil count and predicted FEV_1 and forced vital capacity. We also found there was a significant association between peripheral eosinophil count, sputum eosinophil count, and elevated serum IgE (g100 IU/mL) with severe persistent asthma. **Conclusions:** The assessment of sputum eosinophil count is simple, inexpensive, noninvasive, and direct measurement of airway inflammation. It could be the preferred method in monitoring airway inflammation and guided management in day-to-day practice.

KEY WORDS: Asthma, peripheral eosinophil count, serum immunoglobulin E level, severity of asthma, sputum eosinophil count

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INTRODUCTION

Asthma is a chronic respiratory disorder of the airways characterized by bronchial hyper-responsiveness, respiratory symptoms, structural remodeling and reversible, and variable airflow limitation.[1,2] In the developed and developing nation, it is the most common respiratory disorder with evidence suggesting that over the last two decades its prevalence has increased worldwide.[3]

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Even with increased knowledge and understanding of asthma as a disease, it only remains controllable with proper treatment. The asthma control and severity staging are usually assessed by subjective including clinical assessment and quality of life questionnaires and objective measure such as spirometry, peak expiratory flow rate, and bronchoprovocation testing.[4] Treatment in asthma is currently guided based on clinical assessment and pulmonary function test (PFT). Current guidelines assess the level of asthma severity according to the severity of symptoms, use of rescue medication, asthma exacerbations, and severity of airflow obstruction.[1,2] The correlation between clinical, functional, and various biological markers of airway inflammation in asthma severity is not well established.[5-7] Over the last decade, various noninvasive markers for measurement of airways inflammation such as exhaled nitric oxide, sputum differential cytology, and serum proteins such as eosinophilic cationic protein have been used in monitoring of asthma.[8]

In this study, we wanted to evaluate the relationship between asthma severity and various inflammatory markers. There is not much data on the relation between clinical symptoms and functional parameters to biomarkers of airway inflammation. Therefore, this study was done with the intention to find the correlation of sputum and peripheral eosinophil count and serum immunoglobulin E (IgE) with severity of asthma.

Aim and objective

To study the correlation of serum IgE, sputum eosinophil count, and peripheral eosinophil count in assessing the clinical severity of asthma.

SUBJECTS AND METHODS

This was an institutional cross-sectional study which was conducted in pulmonary medicine outpatient department. All stable asthmatic patients of 18–60 years of age from January 2014 to August 2015 were enrolled in the study. A volunteer-written consent was taken from all the patients before the study. This study was approved by the Institutional Human Ethical Committee. Brief explanation of the procedure is given in Figure 1. Patients with acute exacerbation, clinical features, and spirometry suggestive of chronic obstructive pulmonary disease, those who did not give consent, those who were not able to perform spirometry correctly, patients with history of recent myocardial infarction, and patients on chronic corticosteroid therapy were excluded from the study [Flow Chart 1].

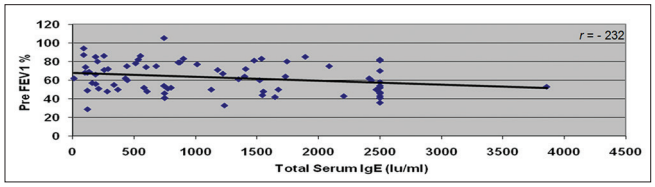


Figure 1: Correlation between total serum immunoglobulin E (IU/ml) and preforced expiratory volume 1 s %

A total of 132 participants were identified and invited to participate in the study, out of which 24 participants were unable to perform spirometry. Based on inclusion and exclusion criteria, 76 participants are enrolled, and all gave consent to participate in the study.

Assessment of severity of asthma

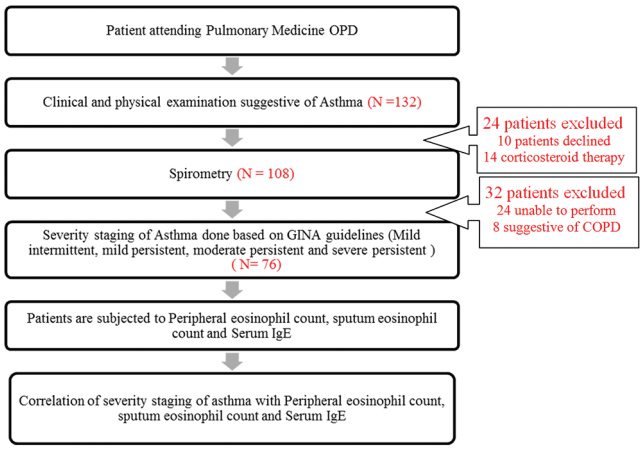
The severity of asthma was assessed according to the GINA criteria.[1] This includes frequency of diurnal and nocturnal symptoms, frequency of short-acting beta 2-agonist used, interference with daily activity and spirometry.

Spirometry

Patients were subjected to PFT with flow sensing MIR Spirobank II and were assessed for postbronchodilator reversibility after administering 200 μg of inhaled salbutamol by repeating the test after 15 min from the baseline.[4] The degree of reversibility in forced expiratory volume 1 s (FEV_1) of 12% and 200 ml from the prebronchodilator value was considered as diagnostic for asthma as per GINA guidelines.[4]

Sputum eosinophil

All the study participants were instructed to cough sputum into plastic containers. The sputum was homogenized by adding phosphate-buffered saline (PBS), vortexed for 30 s, and centrifuged for 10 min. We added 0.1% dithiothreitol to the cells in a ratio of 4:1, which was agitated for 20 min to break up the disulfide bonds and disperse the cells. Cells were washed once more with PBS and resuspended. The cell suspension was aspirated and filtered to remove any remaining debris. Supernatant was separated from cell pellet. Sputum sample was transferred to the slide and was distributed thinly and evenly over the slide. Staining was done by hematoxylin and eosin stain and analyzed using microscopy to determine the count for eosinophils.[9] The eosinophil count was then expressed as a percentage as it



Flow Chart 1: Brief explanation of the procedure

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is more accurate than absolute count.[9] Sputum eosinophil count ≥3% was considered abnormal.

Blood investigations

Under aseptic precaution, 5 ml of blood was taken from medial cubital vein into vacutainers from each patient and measured for peripheral eosinophil count and serum IgE and estimation of eosinophil percentage done by automated analyzer cellenium.

The total IgE levels were measured using Elecsys IgE II reagent kit in cobas e411 analyzers. The Elecsys IgE II assay uses monoclonal antibodies specifically directed against IgE. The reagents in the kit have been assembled into a ready for use unit that cannot be separated. The test is performed based on sandwich principle. Total IgE levels more than 100 IU/mL were taken as abnormal.[10,11]

RESULTS

A total number 76 cases were enrolled for the study. The demographic, baseline clinical, and functional characteristics are enumerated in Table 1. The mean age of patients in the present study was 37.42 years. Of the 76 patients in our study, 43 (56.6%) were male, and 33 (43.4%) were female. Out of 76 cases, 34 (44.7%) of the study population had severe persistent asthma.

Among 76 patients in our study, 73 (96.1%) patients had abnormal serum IgE levels. However, we did not observe a dose–response relationship between severity of asthma and serum IgE levels. We observed a statistically significant inverse correlation between total serum IgE levels and predicted FEV_1 ($P = 0.04$), which was, however, a weak correlation ($r = -0.23$).

Among 76 patients, 20 (26.3%) patients had abnormal sputum eosinophil count. We observed an abnormal sputum eosinophil count and severity of asthma had statistically significant ($P = 0.004$) [Figure 2]. Again, as in total IgE, we did not observe a dose–response relationship between elevated sputum eosinophil counts and asthma severity. We observed that there is a statistically significant inverse correlation between sputum eosinophil count and predicted forced expiratory volume in 1 s ($P = 0.004$) [Figure 3] and the predicted forced vital capacity (FVC) ($P = 0.011$). However, as in total IgE, the correlation was weak. More than half of the patients with severe asthma had normal sputum eosinophil counts suggesting that there could be specific phenotypes of asthma with elevated sputum eosinophils, which may not be a common feature among all asthmatics.

Chi-square test comparing peripheral eosinophil count, sputum eosinophil, and serum IgE with the severity of asthma shows significant association between peripheral eosinophil count and sputum eosinophil when serum IgE ≥100 IU/mL and severe persistent asthma [Table 2]. In our study, 44 (58%) patients had increase peripheral eosinophil count. Among 76 cases, 20 (26.3%) patients had a history of allergic rhinitis. We observed there was

Table 1: Demographic, baseline clinical, and functional characteristic data

	Severity of asthma				Total (76)
	Intermittent (12)	Mild persistent (4)	Moderate persistent (26)	Severe persistent (34)	
Age	34.5±11.07	38.5±13.72	38.31±12.5	37.65±14.18	37.42±12.95
Sex (male/female)	9/3	4/0	13/13	17/17	43/33
Serum IgE (IU/mL)	896.58±786.24	1736.58±1083	821.81±663.48	1390.45±1011	1136.16±909.01
Peripheral eosinophil %	6.42±2.81	10.5±4.44	7.15±3.27	8.06±3.37	7.62±3.37
Sputum eosinophil count %	0.25±0.86	3.5±4.73	0.62±1.67	4.49±7.62	2.44±5.6
FVC % predicted	98.83±9	89±12.68	79.38±8.22	59.5±10.38	74.07±17.44
FEV_1 % predicted	85.58±8.21	80.75±0.96	69.42±6.2	47.94±6.98	62.96±16.11
FEV_1/FVC % predicted	87.67±7.67	91.5±10.34	87.35±7.61	82.79±12.17	85.58±10.22
Post-FVC % predicted	106.75±13.61	97.25±9.25	86.88±8.19	69.03±11.86	82.58±17.59
Post-FEV_1 % predicted	101.67±10.73	94.25±0.96	81.92±5.98	63.94±10.17	77.64±16.52
Post-FEV_1/FVC % predicted	96.12±8.85	97.25±8.54	96.04±7.6	86.97±21.15	92.06±15.87
History of allergic rhinitis (yes/no)	3/9	3/1	7/19	7/27	20/56
Smoker/never smoker	2/10	1/3	2/24	3/31	8/68

FEV_1: Forced expiratory volume 1 s; FVC: Forced vital capacity; IgE: Immunoglobulin E

Table 2: Correlation of asthma severity with peripheral eosinophil count, sputum eosinophil count, and serum IgE by Chi-square test

Interpretation	Total serum IgE (IU/ml)		Value	df	Asymptotic significant (two-sided)	Exact significant (two-sided)	Exact significant (one-sided)
Severe persistent	≥100	Pearson Chi-square	9.632[b]	1	0.002		
		Continuity correction[a]	7.520	1	0.006		
		Likelihood ratio	10.937	1	0.001		
		Fisher's exact test				0.003	0.002
		Linear-by-linear association	9.349	1	0.002		
		Number of valid cases	34				

[a]Computed only for 2×2 table, [b]0 cells (0%) have expected count less than 5. The minimum expected count is 5.29. IgE: Immunoglobulin E

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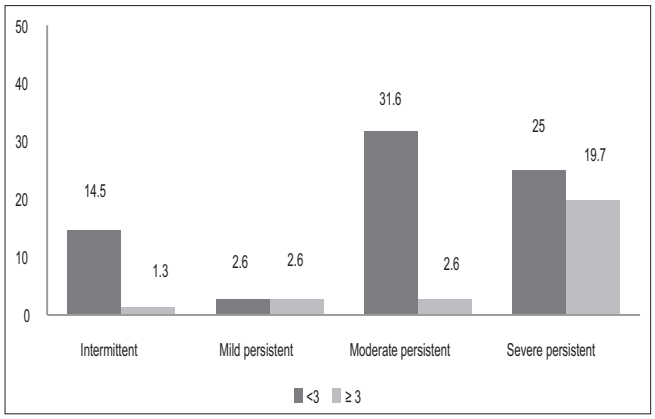

Figure 2: Comparison between sputum eosinophil count (%) and severity of asthma

no significant correlation between peripheral eosinophil count and lung function test ($r = -095$).

DISCUSSION

Asthma is a complex chronic respiratory disorder characterized by airway hyperresponsiveness and variable airflow obstruction. It is a Type 1 hypersensitivity reaction. Several methods of assessing airway inflammation have been proposed in literature. Noninvasive methods of assessment of airway inflammation are much safer, easier, and a convenient tool for monitoring in patients, especially those with more severe asthma.

Correlation of sputum eosinophil count and severity of asthma

We found higher percentage of sputum eosinophil count in 26.3% cases of the study population that included predominantly moderate and severe persistent asthma. We observed that Manise *et al*.[12] in their study reported almost similar distribution.

We observed high sputum eosinophil count (>3) was significantly seen in more patients with severe persistent asthma (19.7%) though more than half of them had normal sputum eosniophils. Similar results were observed in various studies.[13-17] On the other hand, Gibson *et al*.[18] and Palomino *et al*.[19] have reported conflicting results. In our study, there was no significant difference in sputum eosinophil level in intermittent and moderate persistent asthma, and we did not observe a dose–response relationship between asthma severity and proportion of patients with higher sputum eosinophilia, suggesting an asthma phenotype with sputum eosinophilia which may be seen in any asthma severity. Various authors also have reported similar findings.[15,20] The importance of identifying this phenotype of asthma with elevated sputum eosinophilia could be related to steroid responsiveness, which future studies should demonstrate in the Indian population. In our present study, though there was a significant inverse correlation between sputum

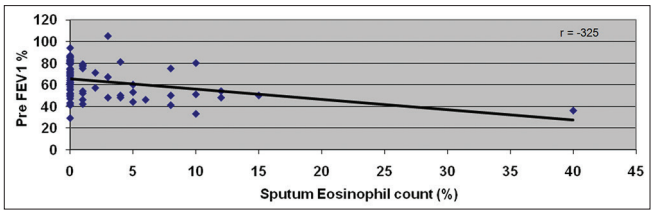

Figure 3: Correlation between sputum eosinophil count (%) and preforced expiratory volume 1 s %

eosinophil count and predicted forced expiratory volume in 1 s ($P = 0.011$) and predicted FVC ($P = 0.015$), the correlation has been weak. Various studies have also reported significant correlation between sputum eosinophil count and predicted FEV_1 ($P < 0.05$).[15,21-24]

Correlation of serum immunoglobulin E and severity of asthma

We found that 96.1% of study population had levels of total serum IgE of >100 IU/ml. This is in concurrence with the observation made by various authors.[12,19,25] A similar distribution was reported by Kartasamita *et al*.[26]

A study in the general population in South India showed the mean total serum IgE to be much higher than the Western population at 522.19 IU/ml.[27] We observed very high levels of total serum IgE in our asthmatic population as well with a mean of 1136.16 IU/ml. We have not included controls from the general population to assess the mean total IgE levels in the general population. Certain populations in the world from Asia (including India) and Africa are very high IgE producers. These high levels of IgE are hypothesized to be protective against various insults, such as detoxification and neutralization of venoms, expulsion of ectoparasites, and degradation of xenobiotics.[28]

In our study, we observed higher levels of serum IgE in all patients of mild persistent ($n = 4$) and severe persistent asthma ($n = 34$). The observed distribution had no significant correlation between serum IgE and severity of asthma. Similar results were obtained by various authors.[19,29] On the contrary, some authors have documented positive correlation between total serum IgE and severity of asthma.[30,31]

We also observed that mean value of serum IgE in mild persistent asthma was higher when compared with other group of asthma severity staging. This could probably due to associated history of allergic rhinitis in 3 out of 4 patients in mild persistent group.

Elevated total IgE may probably be a nonspecific reaction secondary to airway inflammation in asthmatics.[32] It may be proposed that relative higher IgE levels confined at the site of local inflammation and serum levels may not always necessarily reflect the level in lungs. It is also known that IgE binds to mast cells with relatively high affinity. This

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could provide a possible explanation as why circulating IgE may not yield an conclusive evidence of the severity of inflammation.[33] In our present study, we observed there was a significant inverse correlation between serum IgE and predicted forced expiratory volume in 1 s, which, however, was a weak correlation. Various authors have reported similar findings that the higher serum IgE levels had significantly lower FEV_1 <60% predicted ($P < 0.05$).[34-38]

Correlation of peripheral eosinophil count and severity of asthma

In our study, we observed increased peripheral eosinophil count in 57.9% of the study population. We observed wide difference in peripheral eosinophil percentages among various group of asthma severity staging. This is in concurrence with the observation made by Palomino *et al*.[19] We conclude that there is no correlation between peripheral eosinophil levels and asthma severity or lung functions.

One of the reasons could be due to elevation of peripheral eosinophil count in other conditions such as allergic rhinitis, parasitic infestation which may not be related to asthma severity.[39] Eosinophils are present in the intravascular space for a brief period only.[40] One of the hypotheses could be influx of peripheral blood eosinophils rapidly into the tissues at the site of local inflammation suggests that the relationship between peripheral blood eosinophil count with airway inflammation may be transitory.[41]

Correlation of sputum eosinophil count, peripheral eosinophil count, and serum immunoglobulin E with severity of asthma

We found a significant association between peripheral eosinophil count, sputum eosinophil count, and serum IgE (g100 IU/mL) with severe persistent asthma. Khadadah *et al*.[42] in their study reported positive correlation between total blood eosinophil counts, serum total IgE levels, and eosinophilic cationic protein.

In our present study of 76 asthmatics selected as a convenient sampling from the hospital, 44.7% patients had severe persistent asthma, 34.2% patients had moderate persistent asthma, 5.3% patients had mild persistent asthma, and 15.8% patients had intermittent asthma. In our study, 10.8% of patients had smoking history (current or ex-smoker). The effect of smoking on serum IgE has been reported in adult patients.[43] It was not possible to assess the impact of smoking on serum IgE levels, due to the relatively smaller number of smokers in various groups of asthma severity.

This study has few important limitations: (1) The evaluation of allergic bronchopulmonary aspergillosis was not done in patients with high serum IgE. (2) Asthmatic patients other than eosinophilic phenotype were not evaluated. (3) Patients with increased level of eosinophila were not evaluated for parasitic infestation. (4) The patients were recruited from the hospital clinic. (5) We did not recruit equal numbers of patients in the four groups of asthma severity. Very small numbers in mild intermittent and mild persistent asthma influenced our ability to compare across groups for a dose–response relationship. (6) Normal age-matched controls from the general population were not included in the study. (7) We did not use an ultrasonic nebulizer for sputum induction in the evaluation of sputum eosinophilia and only spontaneously generated sputum was used. (8) We did not repeat sputum eosinophilia to assess the repeatability of our measurements.

CONCLUSION

Eosinophilic inflammation is a characteristic feature of asthma. Assessment of sputum eosinophil count is simple, inexpensive, noninvasive, and direct measurement of airway inflammation that could help to identify specific phenotypes in asthma that could be more steroid responsive, which needs to be demonstrated in future studies. It could be the preferred method in monitoring airway inflammation and guided management in day-to-day practice.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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