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Comparison between eosinophilic and neutrophilic asthma

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Abstract

Asthma is a common respiratory disease in general population that can be further subdivided into several cellular endotypes depending on sputum cell counts. The objective of this study to conduct a comparative analysis of eosinophilic and neutrophilic asthma endotypes in terms of their respective prevalence rates, patient characteristics, severity, and treatment response. Cross-sectional study included 59 patients with asthma who attended respiratory diseases out-patient clinic in Baghdad medical hospital between October 2022 and October 2023. The study included patients between 18 and 80 years with clinical history of asthma. Sputum sample was obtained from each patient and analyzed. In a study of 59 asthma patients, those with eosinophilic asthma had significantly younger ages and higher levels of blood basophils and sputum macrophages compared to those with neutrophilic asthma, who showed better asthma control. Significant correlations were found between sputum and blood eosinophils, as well as between sputum and blood neutrophils in eosinophilic and neutrophilic asthma, respectively. Other parameters did not show significant differences between the groups. In conclusion, Eosinophilic asthma is highly prevalent and poorly controlled. Patients with neutrophilic phenotype of asthma tend to be older than those with eosinophilic asthma.

Keywords: Asthma, Eosinophilic, Neutrophilic, Endotypes

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Introduction

Asthma remains a prevalent chronic respiratory disorder marked by its heterogeneity and complex pathophysiology, affecting millions worldwide with significant morbidity and healthcare costs. As the most common chronic respiratory disease globally, asthma's variability not only spans its symptoms and severity but also reflects deep-seated differences in its pathological and etiological underpinnings [1]. The condition is characterized by chronic airway inflammation and hyper responsiveness, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or early in the morning [1]. These symptoms are highly variable and can be triggered by a host of environmental factors including allergens, air pollution, and respiratory infections [2]. Epidemiologically, asthma affects approximately 358 million individuals worldwide, with prevalence rates that vary markedly across different regions and socioeconomic contexts [3]. In 2017, it was

responsible for over 450,000 deaths, making it the second leading cause of death among chronic respiratory diseases [4]. The disparity in asthma prevalence—from 15% to 20% in developed nations to 2% to 4% in less developed countries—underscores the influence of environmental and genetic factors in its pathogenesis [5]. Asthma is not a uniform disease but a syndrome composed of several phenotypic presentations, each associated with distinct inflammatory pathways and cellular activities [6]. This heterogeneity is evident in the differentiation between eosinophilic and neutrophilic asthma, which are characterized by distinct cellular infiltrates in the lungs and divergent responses to common treatments [7]. The traditional categorization of asthma into extrinsic and intrinsic types has been expanded into more nuanced endotypes, reflecting advances in our understanding of its molecular and immunological mechanisms [8]. The pathophysiology of asthma involves an intricate interplay of immune responses, where environmental triggers such as allergens or irritants provoke the release of IgE antibodies. These antibodies bind to receptors on mast cells and basophils in the airways, leading to the release of inflammatory mediators like histamine, leukotrienes, and prostaglandins, which contribute to airway constriction, mucus production, and further inflammation [9]. This response is divided into early and late phase reactions, the former occurring within minutes of exposure to allergens and the latter developing hours later, potentially leading to chronic inflammation and airway hyper responsiveness [9]. Clinically, asthma is diagnosed based on medical history, symptomatology, and confirmatory tests such as spirometry, which assesses the variability and reversibility of airflow obstruction [10]. Additional diagnostic tools may include peak flow monitoring, bronchial challenge tests, and exhaled nitric oxide measurements to evaluate airway inflammation [11]. Despite the array of diagnostic techniques available, the clinical heterogeneity of asthma can complicate diagnosis and management, emphasizing the need for personalized treatment approaches [12]. Management strategies for asthma are aimed at reducing exposure to triggers, controlling persistent inflammation, and relieving acute symptoms through stepwise therapeutic protocols that include bronchodilators, inhaled corticosteroids, and newer biologic agents [13]. The goal is to maintain long-term control over symptoms and prevent exacerbations, thereby improving quality of life and reducing the risk of severe outcomes [13]. Aim of the study to compare between eosinophilic and neutrophilic asthma endotypes with respect to prevalence, patients' characteristics, severity, and response to treatment.

Method

This cross-sectional study conducted between October 2022 and October 2023 at Baghdad Medical Hospital focused on 97 asthma patients attending a respiratory diseases outpatient clinic. After exclusions due to non-producibility of sputum or invalid specimens, 59 patients remained in the sample. These participants, aged between 18 and 80 with clinically confirmed asthma responsive to bronchodilators, were selected based on strict inclusion criteria, with exclusions for factors like recent chest infections, other respiratory diseases, severe comorbid conditions, and inability to undergo sputum induction. The research received approval from the Iraqi Board for Medical Specializations, and verbal consent was obtained from all participants. Patients underwent comprehensive evaluations, including history taking, physical examinations, pulmonary function tests (FEV1 & FVC) post-bronchodilator, complete blood counts, and sputum analysis following the method by Weiszhár

et al. The sputum induction involved pre-and post-bronchodilator lung function measurements, nebulization with hypertonic saline, and expectoration, with the procedure halted if significant symptoms or FEV1/PEF drops occurred. Sputum samples were processed to assess cell viability, total cell count, and differential count, using cytospin slides stained with Giemsa or Wright's stain. Eosinophilic asthma was identified in patients with eosinophils comprising ≥3% of total sputum cells, while neutrophilic asthma was indicated by ≥61% neutrophils. Asthma control was classified based on the Asthma Control Test (ACT) score into well-controlled, partially controlled, and uncontrolled categories. Data analysis was performed using Microsoft Excel 2010 and SPSS version 26. The study employed the Kolmogorov-Smirnov test for data normality, Chi-square or Fisher's exact tests for qualitative data, and Mann-Whitney U or T-tests for quantitative data analysis. Pearson correlation coefficients were calculated to explore relationships between variables, and Receiver Operating Characteristic (ROC) curves were used to examine the correlation between sputum and blood eosinophils. A p-value of less than 0.05 was deemed significant, underlining the rigorous statistical framework guiding the analysis and ensuring the reliability of the findings in understanding the characteristics and control of eosinophilic and neutrophilic asthma within the studied population.

Results

We enrolled 59 patients with asthma with mean age of 43.66 years and average body mass index of 27.68 kg/m^2. In this sample 26(44%) were male and 25(42.4%) were smoker. Description of general population is fully illustrated in table 1 and figure 1. In the sample 81% (n=48) of patients had eosinophilic asthma while only 19% (n=11) were diagnosed as having neutrophilic asthma (figure 3). Patients with eosinophilic variant of asthma had significantly lower mean age in comparison with those with neutrophilic asthma (42.52 vs 52.72, *p-value* 0.03) (figure 3). Asthma control was significantly better in neutrophilic asthma group (7 Well-controlled, 4 Partially controlled, and 0 Poorly controlled patient's vs 15 Well-controlled, 17 Partially controlled, and 16 Poorly controlled patients, *p-value* 0.02). Blood basophils and sputum macrophages percentage were significantly higher in eosinophilic asthma arm (0.0285 x 10^9 vs 0.0112 x 10^9, *p-value* 0.005 and 53.916% vs 24.454%, *p-value* <0.00001 respectively). Other parameters were not statistically different between the two groups (table 2). In patients with eosinophilic asthma sputum eosinophils percentage was significantly correlated with blood eosinophils (r=0.3469, *p-value* 0.015) (figure 4) and asthma control test scores (r=-0.4464, p-*value 0*.001) (figure 4). Cut-point for sputum eosinophils percentage was 1.7% with Sensitivity and Specificity of 85.1% and 63.6% respectively. In addition, there was a statistically significant association between sputum neutrophils percentage and blood neutrophils (r=0.2725, *p-value* 0.03). as in table 3.

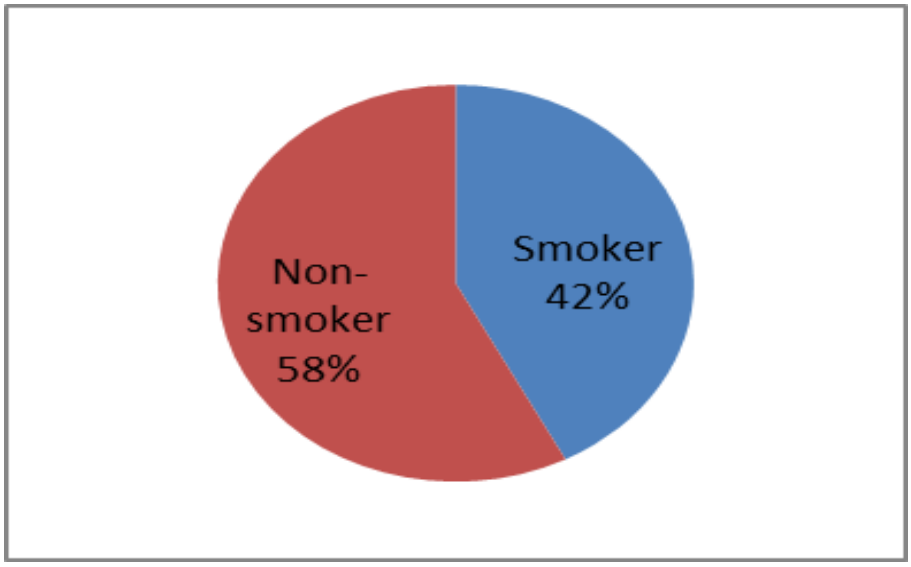

Figure 1.

(smoker to non-smoker ratio)

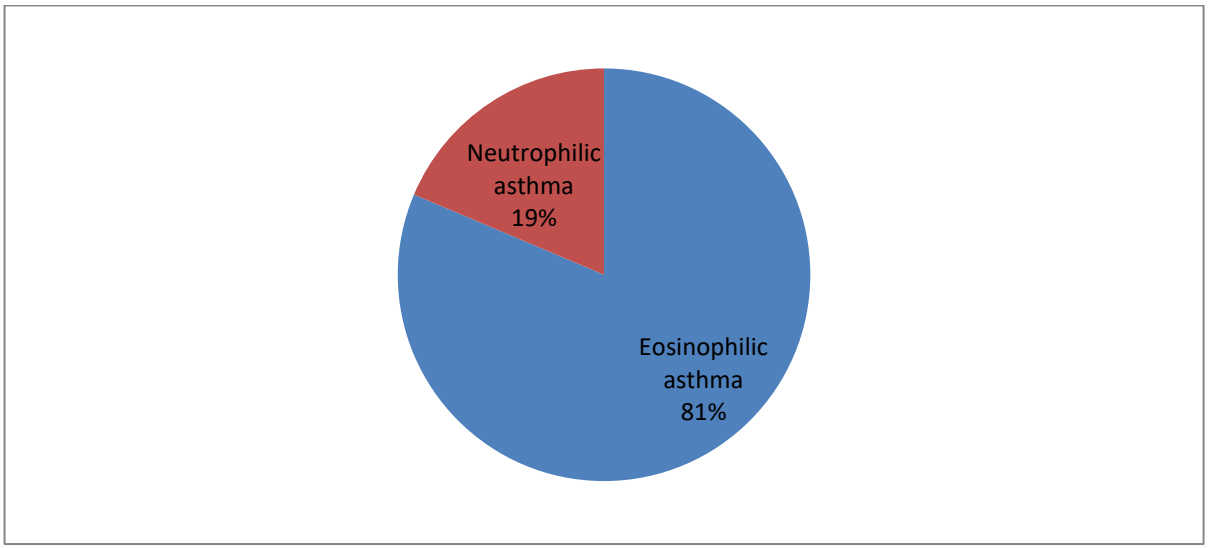

Figure 2.

(proportions of eosinophilic and neutrophilic asthma).

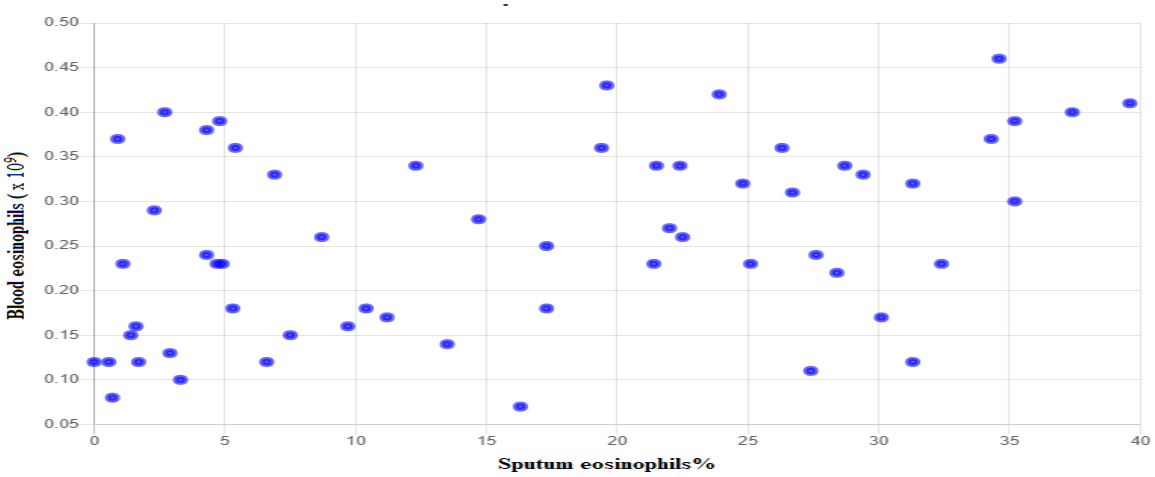

Figure 3.

(correlation of sputum eosinophils% and blood eosinophils)

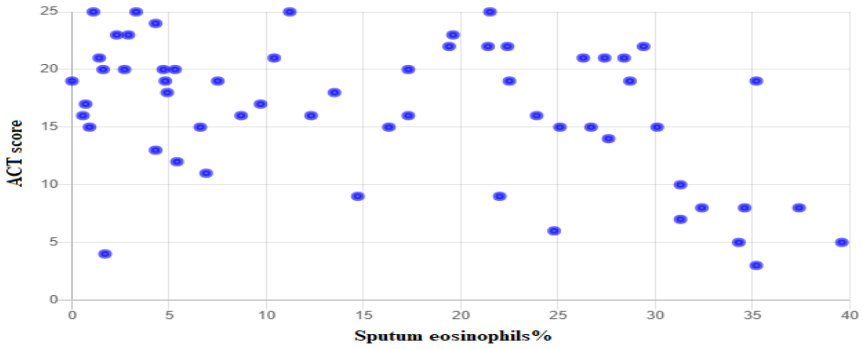

Figure 4.

(correlation of sputum eosinophils% and ACT score)

Table 1.

Demographic and Clinical Parameters

Variable	Patients (n=59)
Age (years)	Mean (range): 43.66 (21-77)
Sex (Male/female)	26 (44%) / 33 (56%)
BMI (kg/m^2)	Mean (range): 27.68 (19.1-34.3)
Asthma severity	Well-controlled: 22 (37.3%) Partially controlled: 21 (35.6%) Poorly controlled: 16 (27.1%)
Smoking status	Yes: 25 (42.4%) No: 34 (57.6%)
FEV1% predicted	Mean (range): 71.64 (52-99)
FEV1/FVC ratio	Mean (range): 64.68 (47-84.2)
Blood eosinophils (10^9/L)	Mean (range): 0.26 (0.07-0.46)
Blood neutrophils (10^9/L)	Mean (range): 4.17 (2.1-6.2)
Blood lymphocytes (10^9/L)	Mean (range): 1.85 (0.6-3.4)
Blood basophils (10^9/L)	Mean (range): 0.025 (0-0.07)
Sputum total cell count (10^6/mL)	Mean (range): 3.47 (0.7-9.1)
Sputum eosinophil%	Mean (range): 16.33 (0-39.6)
Sputum neutrophil%	Mean (range): 15.31 (0.7-83)
Sputum lymphocyte%	Mean (range): 2.70 (0-8.1)
Sputum macrophage%	Mean (range): 48.42 (10-73)

Table 2.

Comparison of Eosinophilic and Neutrophilic Asthma Patients

Variable	Eosinophilic Asthma Group (n=48)	Neutrophilic Asthma Group (n=11)	p-value
Age (years) Mean (range)	42.52 (21-77)	52.72 (23-75)	0.03
Sex (Male/female) n%	21 (43.75%) / 27 (56.25%)	5 (45.45%) / 6 (54.55%)	0.91
BMI (kg/m²) Mean (range)	27.77 (22-34.3)	27.3 (23.2-32.7)	0.81
Asthma severity (n%)	Well-controlled: 15 (31.25%) Partially controlled: 17 (35.42%) Poorly controlled: 16 (33.33%)	Well-controlled: 7 (63.64%) Partially controlled: 4 (36.36%) Poorly controlled: 0 (0%)	0.02
Smoking status Yes/No (n%)	18 (37.5%) / 30 (62.5%)	7 (63.64%) / 4 (36.36%)	0.11
FEV1% predicted Mean (range)	71.92 (52-99)	70.40 (50.3-96.7)	0.81
FEV1/FVC ratio Mean (range)	64.63 (47-84.2)	64.91 (47.2-83.7)	0.84
Blood eosinophils (10^9/L) Mean (range)	0.27 (0.07-0.45)	0.143 (0.08-0.40)	0.03
Blood neutrophils (10^9/L) Mean (range)	4.06 (2.6-5.6)	4.56 (2.1-6.2)	0.056
Blood lymphocytes (10^9/L) Mean (range)	1.868 (0.6-3.4)	1.794 (0.9-3.2)	0.6
Blood basophils (10^9/L) Mean (range)	0.0285 (0-0.09)	0.0112 (0-0.033)	0.005
Sputum total cell count (10^6/mL) Mean (range)	3.422 (0.7-9.1)	3.7 (0.7-8.3)	0.77
Sputum eosinophil% Mean (range)	19.747 (3.3-39.6)	1.441 (0-2.9)	<0.00001
Sputum neutrophil% Mean (range)	2.573 (0.3-9.2)	70.936 (63.7-83)	<0.00001
Sputum lymphocyte% Mean (range)	2.688 (0.4-6.8)	2.784 (0-7.4)	0.94
Sputum macrophage% Mean (range)	53.916 (33-76)	24.454 (10-43)	<0.000

Table 3.

Correlation of Variables.

Variable Pairs	Correlation Coefficient (r)	p-value
Sputum eosinophils% and Blood eosinophils	0.3469	0.015
Sputum eosinophils% and Asthma control test scores	-0.4464	0.001
Sputum neutrophils% and Blood neutrophils	0.2725	0.03
FEV1 and Sputum eosinophils%	0.209	0.097
FVC and Sputum eosinophils%	0.234	0.082
FEV1/FVC ratio and Sputum eosinophils%	0.158	0.214
FEV1 and Sputum neutrophils%	-0.287	0.028
FVC and Sputum neutrophils%	-0.312	0.018
FEV1/FVC ratio and Sputum neutrophils%	-0.331	0.012
Sputum eosinophils% and Sputum basophils%	0.712	<0.0001
Sputum eosinophils% and Sputum macrophages%	-0.482	0.0003
Sputum neutrophils% and Sputum macrophages%	0.509	0.0002

Discussion

This comprehensive study, conducted at Baghdad Medical Hospital, involved a cross-sectional analysis of 97 asthma patients, resulting in a final sample of 59 individuals after exclusions. The study, approved by the Iraqi Board for Medical Specializations, identified a predominant prevalence of the eosinophilic asthma phenotype (81.4%) compared to the neutrophilic subtype (18.6%), consistent with the findings of Dawood et al. (64%) but higher than other regional studies which showed varied prevalence due to different diagnostic criteria and study designs [14]. The demographic profile revealed that patients with neutrophilic asthma were significantly older, which aligns with findings from Shi et al. and Schleich et al., suggesting that age could be an independent factor influencing sputum neutrophilia [15,16]. This phenomenon could be attributed to age-related tissue remodeling and increased microvascular permeability, enhancing neutrophil recruitment to the pulmonary airways [17]. Contrary to other studies where the paucigranulocytic phenotype was more prevalent [18], our findings highlight a higher occurrence of eosinophilic asthma. Differences in

phenotype prevalence across studies suggest that demographic features, methodology, sample size, and geographic area play significant roles in the distribution of asthma variants [19]. Notably, our study found no significant differences in BMI and sex between the eosinophilic and neutrophilic groups, supporting similar observations by Rafaat et al. and Shi et al. [16,20]. Asthma control appeared to be negatively correlated with the eosinophilic phenotype, echoing findings by Refaat et al., Dawood et al., and Padró-Casas et al. [14,20,21]. Eosinophils, by promoting airway remodeling and hyperresponsiveness, contribute to persistent airway damage through degranulation and toxic molecule secretion [22]. Despite this, eosinophilic asthma showed only partial responsiveness to bronchodilators and inhaled corticosteroids, with systemic corticosteroids required for effective control [23]. In terms of pulmonary function, our study did not find a correlation between FEV1, FVC, or the FEV1/FVC ratio and asthma phenotypes, contrasting with findings by Dawood et al. and Schleich et al., which could be attributed to our study's smaller sample size [14,15]. Significant correlations were noted between sputum and blood eosinophils, as well as between sputum and blood neutrophils, reinforcing the reliability of sputum analysis as a diagnostic tool in asthma phenotyping [15,16]. The study also reported higher percentages of sputum basophils and macrophages in the eosinophilic group compared to the neutrophilic group. These findings align with those of Sakuzi et al., who noted a positive correlation between sputum basophils and eosinophils, suggesting that basophils may play a crucial role in initiating and amplifying eosinophil-guided inflammation through IL-4 secretion [24]. Moreover, the differential expression of cytokines and chemokines by group 2 innate lymphoid cells, driven by basophil-derived IL-4, could facilitate the recruitment and survival of eosinophils at inflammation sites, further supported by increased VCAM-1 expression induced by basophils [24]. This mechanism highlights the intricate interplay between basophils and eosinophils in perpetuating asthma's inflammatory cascade, emphasizing the complexity of asthma pathophysiology and its implications for targeted therapy.

Conclusion

Eosinophilic asthma is highly prevalent and poorly controlled. Patients with neutrophilic phenotype of asthma tend to be older than those with eosinophilic asthma.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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