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Diagnostic value of EOS count and serum VEGF in bronchial asthma and their correlation with inflammatory factors and lung function indicators

Longqun Liu[1†], Chenfei Zhang[2†], Jian Xu[3*] and Wei Hu[4*]

Abstract

Objective To probe the diagnostic value of direct eosinophils (EOS) count and vascular endothelial growth factor (VEGF) in bronchial asthma (BA) and their correlation with inflammatory factors and lung function indicators.

Methods A total of 66 patients with BA (BA group) were retrospectively gathered, who were further divided into mild ($n=25$), moderate ($n=31$), and severe ($n=10$) subgroups based on asthma severity. Additionally, 60 healthy individuals undergoing physical examinations during the same period were enrolled as the normal group. The EOS count, serum VEGF, inflammatory factors [interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-10 (IL-10)], and lung function indicators [forced expiratory volume in one second (FEV1%) as a percentage of the predicted value, FEV1/forced vital capacity (FVC)] were compared among different groups. Spearman correlation analysis was performed to assess the correlation between EOS count, serum VEGF, and inflammatory factors, as well as lung function indicators in the BA group. Receiver operating characteristic (ROC) curves and Delong's test were adopted to analyze the diagnostic value of EOS and VEGF individually and in combination for BA and the severity of BA.

Results Versus the normal group, the BA group exhibited higher EOS count and serum levels of VEGF, IL-6, and IL-7, but lower levels of IL-10, FEV1%, and FEV1/FVC. In the severe subgroup, EOS count and serum VEGF, IL-6, and IL-7 levels were higher than those in the moderate and mild subgroups, while the moderate subgroup had higher values than the mild subgroup. IL-10, FEV1%, and FEV1/FVC were lower in the severe subgroup versus the moderate and mild subgroups, and the moderate subgroup had lower levels than the mild subgroup (all $p<0.05$). Spearman correlation analysis unveiled positive correlations between EOS count and VEGF with IL-6 and IL-7 ($r>0$, $p<0.05$), but negative correlations with IL-10, FEV1%, and FEV1/FVC ($r<0$, $p<0.05$). ROC curve analysis displayed that the areas under the curve (AUCs) for EOS count and serum VEGF individually in diagnosing BA were 0.767 and 0.807. The AUC for the combined diagnosis of both (0.875) was significantly greater than the AUC for each test used alone ($p<0.05$).

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The AUC for using EOS count alone to diagnose the severity of BA in patients was 0.936, while the AUC for using serum VEGF alone was 0.963. The AUC for the combined diagnosis of both (1.000) was significantly greater than the AUC for EOS count alone ($p < 0.05$).

Conclusion There is a correlation between EOS count, serum VEGF, inflammatory levels, and lung function indicators in patients with BA. The combined detection of EOS count and serum VEGF levels has guiding significance for clinical diagnosis and disease assessment.

Clinical trial number Not applicable.

Keywords Bronchial asthma, Eosinophil count, Vascular endothelial growth factor, Inflammatory factors, Lung function, Combined detection

Introduction

Bronchial asthma (BA) is a heterogeneous disease marked by airflow obstruction, airway hyperresponsiveness and persistent respiratory inflammation [1]. The clinical manifestations of the disease are varying degrees of airway narrowing (dyspnea and wheezing) and cough. Prolonged asthma may induce airway remodeling and become refractory [2]. The heterogeneity of asthma poses a number of diagnostic challenges, particularly in distinguishing chronic asthma from other lung diseases (e.g., chronic obstructive pulmonary disease) marked by disruption of normal lung function and structure [1]. As one of the most general chronic inflammatory airway diseases, the incidence of BA is increasing year by year globally, imposing a heavy healthcare burden on individuals and society [3].

The molecular pathways involved in asthma are highly heterogeneous, with various factors contributing to the physiologic and pathological changes that define this chronic condition. Key contributors include excessive secretion of cytokines, genetic factors such as gene polymorphisms, infiltration of inflammatory cells (e.g., eosinophils [EOS]), and vascular endothelial growth factor (VEGF) [4]. Notably, VEGF and eosinophil-derived neurotoxin (EDN) have emerged as pivotal mediators in the pathophysiology of asthma. Elevated levels of both VEGF and EDN in asthmatic patients are strongly linked to airway hyperresponsiveness and disease severity. The diversity of VEGF polymorphisms further complicates asthma treatment, contributing to variability in patient response to glucocorticoid and leukotriene antagonist therapies. Given these roles, targeting EOS and VEGF holds promise as a novel therapeutic strategy for asthma management [5].

A common phenotype of asthm, eosinophilic asthma, is characterized by the presence of eosinophilia. EOS, once viewed primarily as stable, fully differentiated effector cells, are now recognized key players in in severe eosinophilic asthma and related eosinophil-driven diseases [6]. These immune cells tare critical in the initiation and progression of asthma [7], engaging in the inflammatory response of the airway wall by releasing mediators and cytokines [8]. Data suggest that blood EOS counts in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease may serve as a useful biomarker for predicting readmission risk [9]. Moreover, EOS has been identified as a primary target for therapeutic intervention in BA [10]. Measuring blood EOS count is a noninvasive and relatively reliable marker of eosinophilic airway inflammation. A single measurement of peripheral blood EOS greater than or equal to 150 cells/μL has been shown to predict a positive response to antieosinophilic therapy in patients with severe eosinophilic asthma [11]. Thus, both the quantify and activity of EOS are strongly correlated with asthma severity and prognosis.

VEGF, a potent stimulator of angiogenesis, tissue remodeling, and permeability, plays an essential role in wound healing and tissue cytoprotection. It is also considered a critical role in Th2-driven inflammation. Beyond its roles in promoting edema and angiogenesis, VEGF induces eosinophilic inflammation, myocyte proliferation, subepithelial fibrosis, mucus degeneration, airway hyperresponsiveness, and dendritic cell activation through both IL-13-dependent and non-independent mechanisms. Overexpression of VEGF can lead to Th2 inflammatory disorders, including asthma, by exacerbating these pathological processes [12]. In summary, EOS count and VEGF plays crucial roles in the pathogenesis of asthma and may serve as important diagnostic biomarkers. Furthermore, there appears to be a significant correlation between these markers and other inflammatory factors involved in asthma's development.

Moreover, research data highlight several key characteristics of lung function in asthma: reversible airflow limitation with bronchodilator use, variable airflow limitation, and airway hyperresponsiveness. The latter refers to an exaggerated reaction of the airways to aerosol excitants, resulting in a significant reduction in airflow, whereas normal individuals exhibit little or no response to such excitants [13]. Pulmonary function testing that demonstrates variable airflow obstruction is the most common method for diagnosing asthma [14]. However, there have been relatively few studies investigating the

combined diagnostic value of EOS and VEGF in BA, particularly their correlation with inflammatory factors and lung function indices. This study aimed to probe the diagnostic value of EOS count and serum VEGF in BA and their correlation with inflammatory markers and lung function parameters. By examining the quantity and activity of EOS and VEGF in BA patients, this study seeks to provide new insights and approaches for the diagnosis and treatment of asthma.

Materials and methods

Ethics statement

The Ethics Committee of the 904 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army granted approval for this study (approval number: 20191220) and in accordance with the Declaration of Helsinki, with patients and their families providing their informed consent.

Baseline information

A total of 66 BA patients diagnosed and treated in the 904 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army from April 2020 to May 2021 were retrospectively gathered as the BA group, including 29 males and 37 females, with an average age of (43.71 ± 12.19) years old. Among them, 49 patients had completed high school or below level, and 17 patients had completed above high school level. Inclusion criteria: ① patients with clear diagnostic criteria [15]; ② those who stopped glucocorticosteroids 2 weeks before the examination; ③ those aged 18–70 years old; ④ those with no history of smoking and other allergic diseases; ⑤ those without comorbid psychiatric diseases and cognitive disorders; ⑥ those with complete clinical data; ⑦ those who agreed to participate in the study and signed the informed consent form, as approved by the Ethics Committee of the hospital. Exclusion criteria: ① those who excluded other lung diseases such as chronic obstructive pulmonary disease, tuberculosis, bacterial/fungal infections of the lungs; ② those combined with endocrine or immune system diseases; ③ those suffering from malignant tumors; ④ those complicated with cardiac, hepatic, renal abnormalities and severe diseases; ⑤ those on long-term immunosuppressants. At the same time, 60 healthy individuals undergoing physical examinations during the same period were selected as the normal group, including 25 males and 35 females, with the age of (45.58 ± 9.82) years old. Among them, the education level of 48 subjects with the level of high school and below, and 12 subjects with the level of high school and above. Before the examination, the normal subjects had no occurrence of BA, rhinitis, respiratory infections, etc., within the past month, had not used hormonal drugs in the last 1 month, had no obvious positive signs in the physical examination, and had no history of cardiopulmonary diseases, smoking, familial asthma, or allergies. Baseline data such as gender, age, and education level did not differ significantly between the BA and normal groups ($p > 0.05$), and the groups were balanced and comparable.

Methods of subgroup division of the BA group

Referring to the asthma severity classification standard [16], according to forced expiratory volume in one second (FEV1%) as a percentage of the predicted value, all BA patients were separated into the mild ($n = 25$, FEV1% > 80%), moderate ($n = 31$, FEV1% between 60% and 80%), and severe ($n = 10$, FEV1% < 60%) subgroups.

Research methods

Blood sample was collected from study subjects in the early morning after fasting. Ethylene diamine tetraacetic acid (EDTA) was used as the anticoagulant tube for the peripheral blood samples (2 mL). EOS count was measured adopting the BC-5000 automatic hematology analyzer provided by Shanghai Langyi Medical Device Co., Ltd. (Shanghai, China). The blood sample (4 mL) was centrifuged at 3500 revolutions per minute for 10 min, and the supernatant was gathered and stored in an Eppendorf tube at -80 °C. VEGF, interleukin-6 (IL-6), IL-7, and IL-10 were tested employing bythe enzyme-linked immunosorbent assay (ELISA) method with kits purchased from Beijing Tiangen Biochemical Technology Co., Ltd (Beijing, China). FEV1% and FEV1/forced vital capacity (FVC) were measured by adopting the AS-505 pulmonary function tester produced by Canon (Japan). All tests were conducted by technicians in the clinical laboratory of our hospital.

Statistics

Statistical analyses were implemented by applying SPSS 26.0 software. For qualitative data, descriptions were provided as [n (%)], and the χ^2 test was implemented for comparisons. The normality of quantitative data were assessed using the Kolmogorov-Smirnov test (K-S test). Normally distributed quantitative data were summarized adopting mean ± standard deviation ($\bar{x} \pm s$). Independent sample t-tests were employed for comparisons between two groups, while a one-way Analysis of Variance was employed for comparisons among three or more groups. For skewed distribution quantitative data, M ($p25$, $p75$) was applied for description, and the Mann-Whitney U-test was adopted for comparisons between two groups, with the Kruskal-Wallis test utilized for comparisons among three groups. Spearman analysis was utilized to assess correlations. The diagnostic value was evaluated through ROC curves and the Delong test. Statistical significance was deemed present when the p-value < 0.05.

Table 1 Comparison of EOS count, serum VEGF, inflammatory factors and lung function between the BA group and normal group

Indicator	BA group ($n=66$)	Normal group ($n=60$)	Z/t	p
EOS ($\times10^9$/L)	0.27 (0.09, 0.37)	0.12 (0.05, 0.16)	-5.176	< 0.001
VEGF (pg/mL)	230.54 (170.99, 282.08)	140.19 (94.45, 187.76)	-5.935	< 0.001
IL-6 (pg/mL)	37.36 ± 6.21	10.95 ± 2.33	30.995	< 0.001
IL-7 (pg/mL)	13.48 ± 2.12	6.31 ± 1.25	22.815	< 0.001
IL-10 (pg/mL)	5.72 ± 1.30	18.86 ± 3.40	-29.139	< 0.001
FEV1 (%)	74.50 (68.75, 82.00)	97.00 (87.00, 99.00)	-8.323	< 0.001
FEV1/FVC (%)	72.00 (67.00, 76.00)	85.50 (82.00, 89.00)	-9.347	< 0.001

Table 2 Comparison of EOS count, serum VEGF, inflammatory factors and lung function in different subgroups of BA group

Indicator	Mild subgroup ($n=25$)	Moderate subgroup ($n=31$)	Severe subgroup ($n=10$)	Z/t	p
EOS ($\times10^9$/L)	0.11 (0.07, 0.23)	0.31 (0.20, 0.37)[a]	0.49 (0.43, 0.60)[ab]	30.282	< 0.001
VEGF (pg/mL)	173.66 ± 58.18	241.06 ± 62.16[a]	377.00 ± 64.66[ab]	39.815	< 0.001
IL-6 (pg/mL)	33.68 ± 3.86	37.56 ± 5.56[a]	45.98 ± 3.94[ab]	23.964	< 0.001
IL-7 (pg/mL)	12.24 ± 1.63	13.69 ± 2.00[a]	15.93 ± 1.03[ab]	16.182	< 0.001
IL-10 (pg/mL)	6.49 ± 1.05	5.64 ± 1.11[a]	4.06 ± 0.63[ab]	20.009	< 0.001
FEV1 (%)	82.00 (81.00, 84.50)	72.00 (69.00, 75.00)[a]	55.00 (54.00, 57.25)[ab]	54.694	< 0.001
FEV1/FVC (%)	77.00 (74.00, 79.00)	70.00 (67.00, 73.00)[a]	63.50 (61.00, 65.25)[ab]	42.138	< 0.001

Note: [a]$p < 0.05$ vs. Mild subgroup; [b]$p < 0.05$ vs. Moderate subgroup

Results

EOS count, serum VEGF, inflammatory factors and lung function between the BA group and normal group

EOS count, serum VEGF, IL-6, and IL-7 were higher in the BA group versus in the normal group, while IL-10, FEV1%, and FEV1/FVC were lower in the BA group versus in the normal group ($p < 0.05$) (Table 1).

EOS count, serum VEGF, inflammatory factors and lung function in different subgroups of BA group

EOS count, serum VEGF, IL-6 and IL-7 in the severe subgroup were higher in comparison with in both the moderate and the mild subgroups, and those in the moderate subgroup were higher than those in the mild subgroup. IL-10, FEV1%, and FEV1/FVC in the severe subgroup were lower versus in both the moderate and the mild subgroups, and those in the moderate subgroup were lower versus those in the mild subgroup ($p < 0.05$) (Table 2).

Correlation between EOS count, serum VEGF and inflammatory factors

Spearman's correlation unveiled that in BA patients, both EOS count and serum VEGF were positively correlated with I.

L-6 ($r = 0.579$, 0.636, $p < 0.001$), also positively correlated with IL-7 ($r = 0.541$, 0.594, $p < 0.001$) and negatively correlated with IL-10 (r = -0.473, -0.518, $p < 0.001$) (Fig. 1).

Correlation between EOS count, serum VEGF and lung function indices

Spearman's correlation displayed that in BA patients, EOS count and serum VEGF were negatively correlated with FEV1% (r = -0.607, -0.639, $p < 0.001$) and also negatively correlated with FEV1/FVC (r = -0.483, -0.495, $p < 0.001$) (Fig. 2).

Diagnostic value of EOS count and serum VEGF single and in combination in BA

ROC curves were plotted using EOS count and serum VEGF as the test variables, and the presence of BA (BA group and normal group) as the dependent variable. The ROC curves uncovered that the AUC (95% CI) of EOS count and serum VEGF single in the diagnosis of BA were 0.767 (0.685–0.850) and 0.807 (0.732–0.881) ($p < 0.001$), with the sensitivity of 65.2% and 69.7%, and the specificity of 86.7% and 71.7%, respectively. The AUC (95% CI) for the combined diagnosis of BA using EOS and VEGF was 0.875 (0.812–0.938), with a sensitivity of 80.3% and a specificity of 88.3%. Delong's test disclosed that the AUC of the combination was greater than the AUC of EOS, VEGF single diagnosis ($Z = 2.849$, 2.586, $p < 0.05$) (Table 3; Fig. 3).

Analysis of the diagnostic value of EOS count and serum VEGF in assessing the severity of BA

ROC curves were plotted using EOS count and serum VEGF as the test variables, and the severity of BA in patients (mild-moderate group and severe group) as the dependent variable. The results demonstrated that the AUC (95% CI) for EOS count alone in diagnosing the severity of BA in patients was 0.936 (0.874–0.997), with a sensitivity of 90.0% and a specificity of 85.7%. The AUC (95% CI) for serum VEGF alone in diagnosing the severity of BA in patients was 0.963 (0.915-1.000), with a sensitivity of 100.0% and a specificity of 80.4%. The AUC (95%

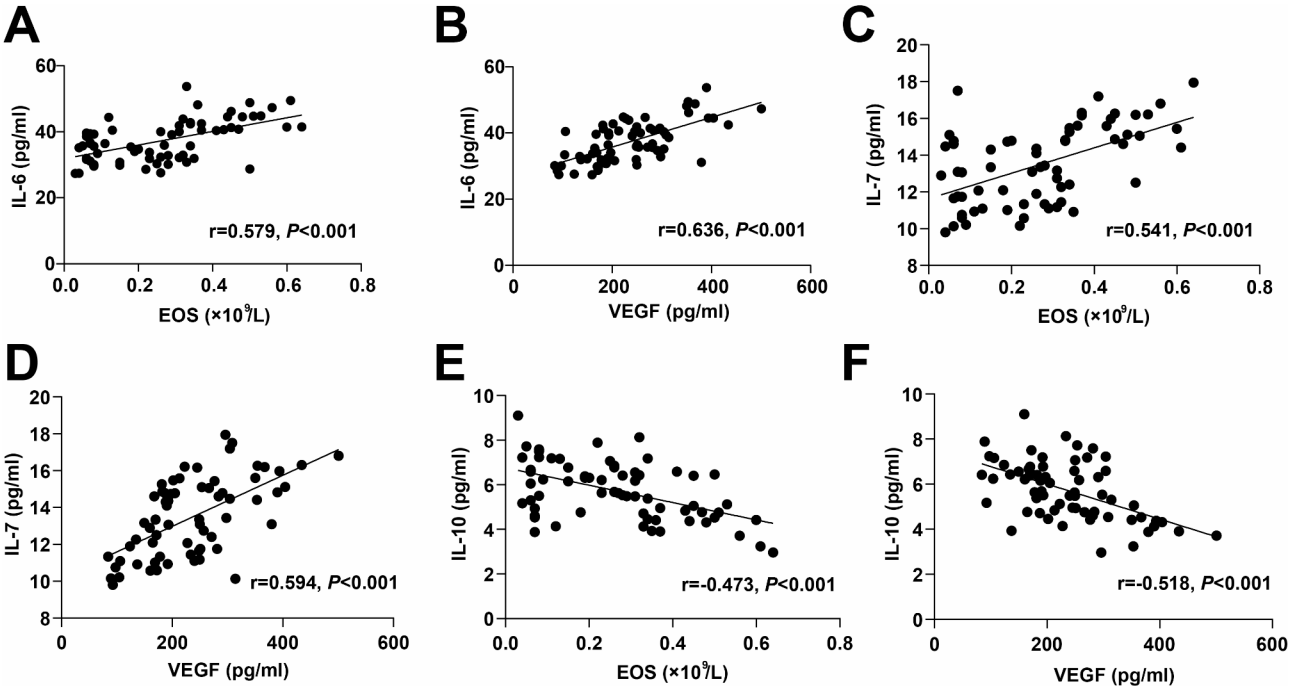

Fig. 1 Correlation of EOS, VEGF and inflammatory factors. Note: (**A**) Scatterplot of correlation between EOS and IL-6; (**B**) Scatterplot of correlation between VEGF and IL-6; (**C**) Scatterplot of correlation between EOS and IL-7; (**D**) Scatterplot of correlation between VEGF and IL-7; (**E**) Scatterplot of correlation between VEGF and IL-10; (**F**) Scatterplot of correlation between VEGF and IL-10

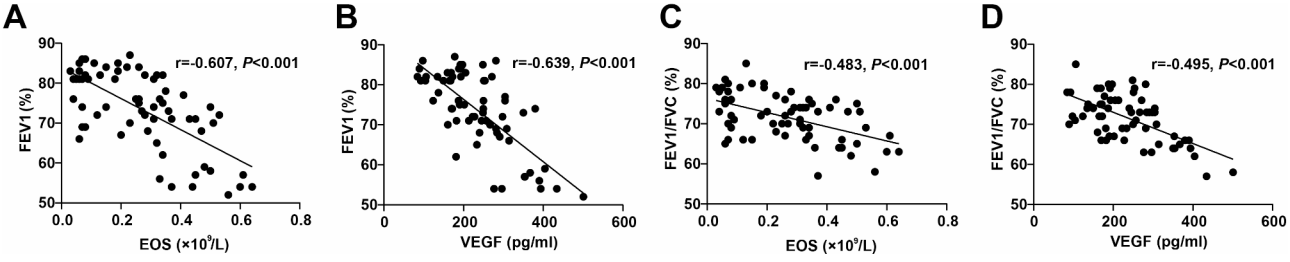

Fig. 2 Correlation between EOS, VEGF and lung function indexes. Note: (**A**) Scatterplot of correlation between EOS and FEV1%; (**B**) Scatterplot of correlation between VEGF and FEV1%; (**C**) Scatterplot of correlation between EOS and FEV1/FVC; and (**D**) Scatterplot of correlation between VEGF and FEV1/FVC

Table 3 ROC curve results of EOS count, serum VEGF single and combined diagnosis of BA

Indicator	AUC	Youden Index	Sensitivity/%	Specificity/%	95%CI	*p*
EOS	0.767	0.519	65.2	86.7	0.685–0.850	< 0.001
VEGF	0.807	0.465	69.7	71.7	0.732–0.881	< 0.001
Combination	0.875	0.686	80.3	88.3	0.812–0.938	< 0.001

CI) for the combined diagnosis of BA severity using both was 1.000 (1.000–1.000), with a sensitivity of 100.0% and a specificity of 100.0% (Table 4; Fig. 4). The AUC for the combined diagnosis was greater than that for EOS count alone (Z = 2.034, $p = 0.042$), and only slightly greater than that for serum VEGF alone (Z = 1.527, $p = 0.127$).

Discussion

BA is a heterogeneous disease marked by airway hyperresponsiveness and chronic airway inflammation [17]. Studies have pointed out that asthma comprises three primary components: airway remodeling, airway hyperresponsiveness and airway inflammation. Persistent airway inflammation causes damage and deterioration to normal airway tissues, leading to thickening of the airway wall, reduced reversibility, and heightened airway hyperresponsiveness. The development of irreversible airway narrowing, along with the accompanying increase in airway hyperresponsiveness, are significant factors contributing to severe asthma [18]. Therefore, in addition to effective pharmacologic target therapy, the development of several biomarkers is crucial.

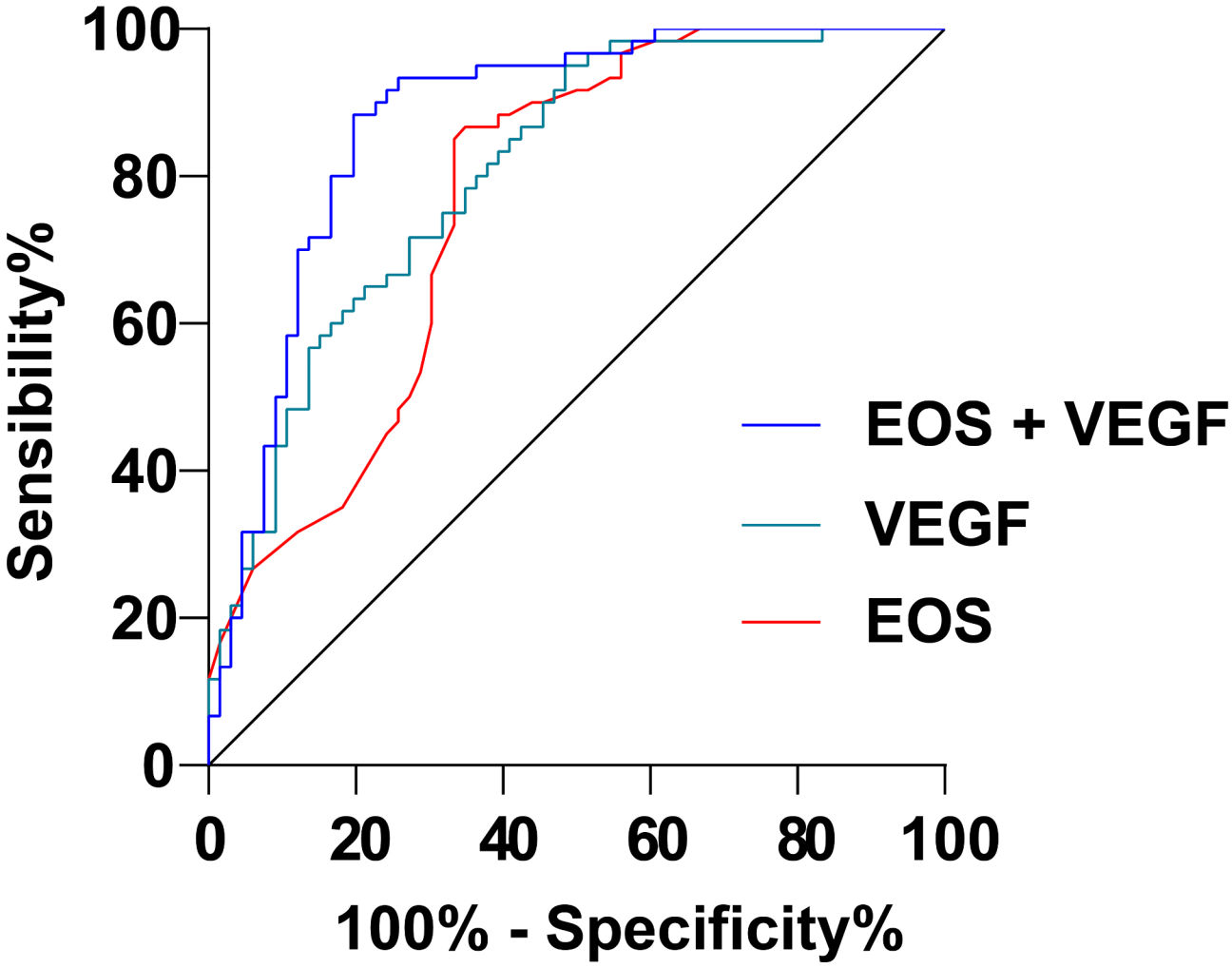

Fig. 3 ROC curve of EOS, VEGF single and combined diagnosis of BA

Table 4 Analysis of the diagnostic value of EOS count and serum VEGF in assessing the severity of BA

Indicator	AUC	Youden Index	Sensitivity/%	Specificity/%	95%CI	*p*
EOS	0.936	0.365	90.0	85.7	0.874–0.997	< 0.001
VEGF	0.963	0.465	100.0	80.4	0.915-1.000	< 0.001
Combination	1.000	1.000	100.0	100.0	1.000–1.000	< 0.001

In recent years, the roles of EOS and serum VEGF in the pathogenesis of asthma have gradually gained attention with the in-depth study of asthma pathophysiologic mechanisms. Asthma is usually caused by allergic and/or eosinophilic inflammation, and both may be present in severe diseases [19]. It has been proposed that elevated EOS is linked to numerous diseases, ranging from relatively common organ-specific diseases (e.g., severe eosinophilic asthma) to rare multisystemic diseases (e.g., eosinophilic hypercellularity syndrome and eosinophilic granulomatosis with polyangiitis). Patients with these multisystem diseases are often concerned with markedly elevated EOS, and they suffer from high morbidity and mortality due to delayed diagnosis or inappropriate treatment [20]. As previously mentioned, VEGF is involved in airway repair and asthma. A study discloses that VEGFSNP rs3025020 and rs3025039 may be associated with the development of asthma, suggesting a role for VEGF in asthma [21]. Furthermore, airway subepithelial vascular proliferation and angiogenesis are part of the asthmatic airway wall structure. The increase in bronchial mucosal vascularization is closely related to the expression of angiogenic factors such as VEGF [22]. In this study, we unveiled that EOS count and serum VEGF levels were higher in the BA group versus in the normal group, implying that EOS count and serum VEGF may have a significant impact on the pathogenesis of BA. Further analysis of BA subgroups of different severity

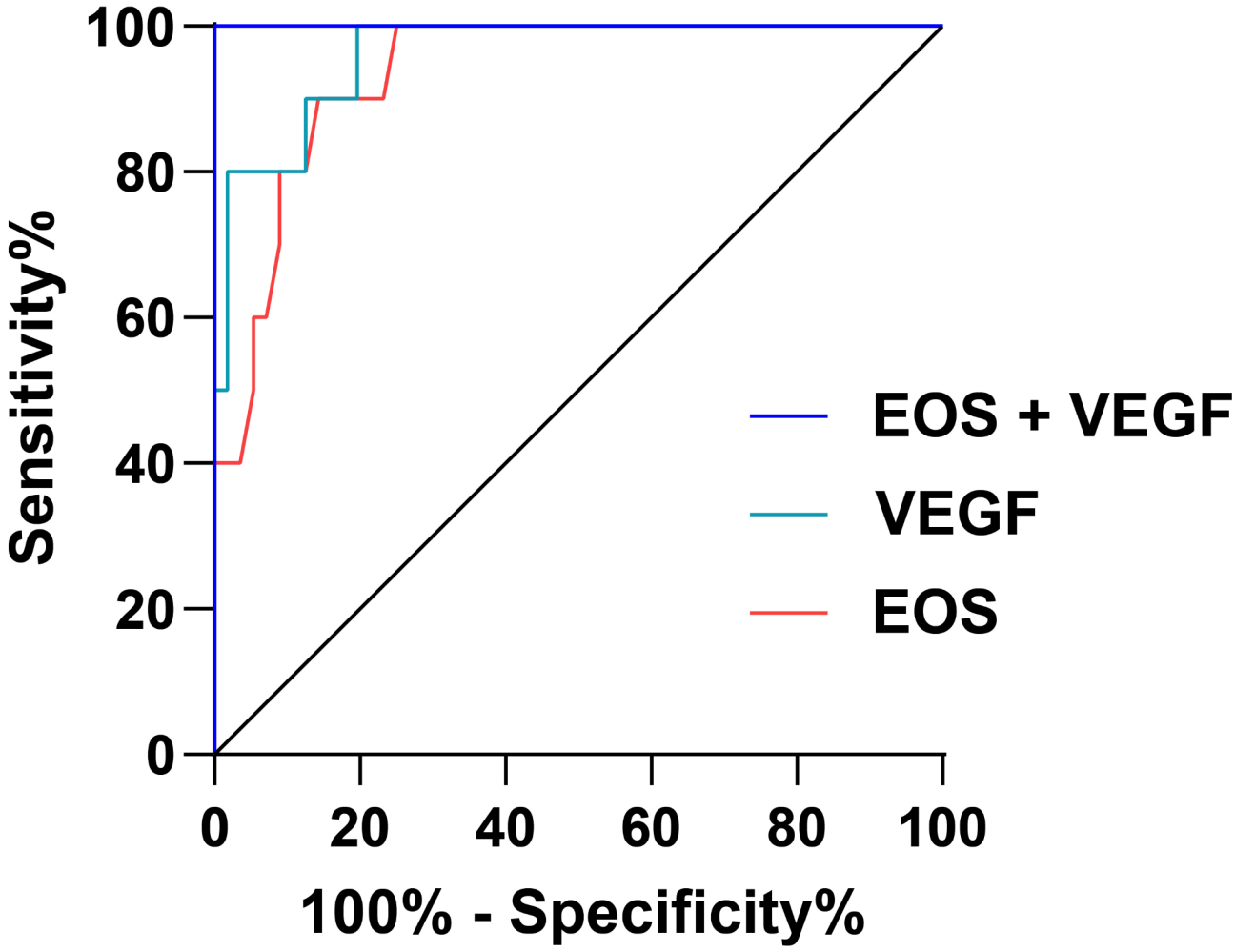

Fig. 4 ROC Curves for EOS, VEGF, and their combination in diagnosing the severity of BA

revealed that the highest EOS count and serum VEGF levels were found in the severe subgroup, followed by the moderate subgroup, and the lowest in the mild subgroup, indicating that EOS count and serum VEGF were positively correlated with the severity of BA.

With the proposed definition of the severe eosinophilic asthma phenotype, the severe eosinophilic asthma phenotype is characterized by high blood EOS and elevated exhaled nitric oxide levels. This phenotype is related to a T2 inflammatory signature expressed by IL-4, IL-5, and IL-13 [23]. E Koczy-Baron et al. uncover that overexpression and enhanced release of VEGF were assessed in various allergic inflammatory conditions including asthma, and that systemic release of vascular endothelial growth factor from allergy patients with different clinical presentations may vary, which may depend on the severity/activity and extent of the inflammatory response [24]. This implies that VEGF may be concerned with multiple inflammatory factors in the pathogenesis of asthma. In this study, the Spearman correlation unveiled that EOS and VEGF were positively correlated with inflammatory factors IL-6 and IL-7 and negatively correlated with anti-inflammatory factor IL-10. This suggested that EOS and VEGF might be involved in the inflammatory response in BA and might influence the disease process by regulating the levels of inflammatory factors. Moreover, Spearman correlation also demonstrated that both EOS and VEGF were negatively correlated with lung function indices FEV1% and FEV1/FVC. This implied that the higher the EOS count and serum VEGF levels, the worse the lung function of the patient might be. So-Hee Lee et al. evaluate the relationship between EOS and the decline in lung function (FEV1 metric) using a well-established health screening database. They conclude that EOS is linked with FEV1 decline and sustained high EOS is an independent risk factor for accelerated FEV1 decline [25]. Elevated VEGF, as mentioned earlier, is often accompanied by increased airway hyperresponsiveness, among other things [5]. These pathologic changes lead to exacerbation of the patient's symptoms such as dyspnea, cough and wheezing [2] and affect lung function. Taken together, EOS count and serum VEGF testing can be an important

indicator for assessing lung function and disease severity in BA patients.

In our study, we analyzed the diagnostic value of EOS count and serum VEGF single and in combination in BA. ROC curve analysis displayed that the AUC of EOS count and serum VEGF single for diagnosis of BA had a certain diagnostic value. The AUC of EOS count and serum VEGF in combination was greater than that of a single diagnosis, which indicated that the combined test could improve diagnostic accuracy, and that the detection of EOS count and serum VEGF levels in BA patients is of guiding significance for clinical diagnosis. Moreover, we also found that the AUC for using EOS count alone to diagnose the severity of BA in patients was 0.936, while the AUC for using serum VEGF alone was 0.963. The AUC for the combined diagnosis of both (1.000) was significantly greater than the AUC for EOS alone.

In conclusion, this study underscores the diagnostic value of EOS count and serum VEGF in BA and their correlation with inflammatory factors and pulmonary function indicators, which is the originality of this study. Specifically, there is a correlation between EOS count and serum VEGF and inflammation levels and lung function indices in patients with BA, and the combined detection of EOS count and VEGF serum levels is of great significance in confirming the clinical diagnosis and evaluating the disease. Therefore, this study provides new evidence for the diagnostic value of EOS count and VEGF in BA and their correlation with inflammatory factors and lung function indices and offers new ideas for the in-depth study and treatment of this disease. Future studies could further explore the specific mechanisms of EOS count and VEGF in BA, as well as potential therapeutic approaches against these targets.

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Author contributions
Longqun Liu finished the study design. Chenfei Zhang finished the experimental studies. Jian Xu finished the data analysis. Wei Hu finished the manuscript editing. All authors read and approved the final version of the manuscript.

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Data availability
The experimental data used to support the findings of this study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the 904 Hospital of the Joint Logistics Support Force of the Chinese People's Liberation Army granted approval for this study (approval number: 20191220) and in accordance with the Declaration of Helsinki, with patients and their families providing their informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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