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Diagnostic accuracy of blood eosinophils in comparison to other common biomarkers for identifying sputum eosinophilia in patients with chronic cough

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ABSTRACT

Background: Sputum eosinophilia is a treatable trait for chronic cough. It is currently not clear whether the blood eosinophil counts could be used to identify sputum eosinophilia in patients with chronic cough. This study aimed to evaluate the diagnostic accuracy of blood eosinophils in comparison to other common type 2 biomarkers for identifying sputum eosinophilia in patients with chronic cough.

Methods: In this prospective study, a total of 658 patients with chronic cough were enrolled. Induced-sputum test, routine blood test, total immunoglobulin E (TIgE), and fractional exhaled nitric oxide (FeNO) level were measured. The percentage of sputum eosinophils (Eos%) $\geq$ 2.5% was defined as sputum eosinophilia. The area under the curve (AUC) of blood eosinophil counts, TIgE, and FeNO alone or in combination for predicting sputum eosinophilia were analyzed.

Results: The AUC of blood eosinophil counts for predicting sputum eosinophilia in chronic cough patients was moderate [0.826 (0.767–0.885)], as compared to that of FeNO [0.784 (0.720–0.849), $P = 0.280$] and TIgE [0.686 (0.613–0.760), $P = 0.001$]. When combining blood eosinophil counts and FeNO for detecting sputum eosinophilia, a significantly larger AUC [0.868 (0.814–0.923), with a sensitivity of 84.2% and a specificity of 82.8%] was yielded, as compared to each single marker alone (all $P < 0.05$).

Conclusions: Blood eosinophil counts have a moderate diagnostic value for identifying sputum eosinophilia in patients with chronic cough, while a combination of blood eosinophil counts and FeNO measurement can provide additional predictive value.

Keywords: Eosinophils, Fractional exhaled nitric oxide testing, Immunoglobulin E, Biomarkers, Cough

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INTRODUCTION

Chronic cough, defined as a cough lasting for more than 8 weeks, is the most common complaint for patients to visit the respiratory specialist clinic. It has been estimated that the global prevalence of chronic cough was 9.6%.[1] Chronic coughers without a history of smoking and angiotensin-converting enzyme inhibitor (ACEI) treatment, and had no abnormalities on chest radiogram, cough variant asthma (CVA), upper airway cough syndrome (UACS), nonasthmatic eosinophilic bronchitis (NAEB), gastro-esophageal reflux-related cough (GERC), and atopic cough (AC) were the common causes.[2,3] In addition, up to 50% of chronic cough patients (eg, CVA and NAEB) might had an eosinophilic airway inflammation and responded well to corticosteroid therapy.[2,4] Thus, sputum eosinophilia might represent an important treatable trait in chronic coughers.[5,6]

Induced sputum cell counts is the most reliable strategy for identifying eosinophilic inflammation of the airways. However, induced sputum test could not be widely applicable due to its time-consuming and labor-intensive processes. Moreover, some patients with chronic cough could present with dry cough, making it difficult to obtain enough sputum for cell differential analysis. Thus, identifying a simple and reliable biomarker to predict eosinophilic airway inflammation will provide clinical significance for chronic coughers.

Blood eosinophil counts have been used to identify eosinophilic airway inflammation and guide therapeutics in asthmatics and Chronic Obstructive Pulmonary Disease (COPD) patients.[9–14] A meta-analysis revealed that blood eosinophil counts have moderate accuracy in predicting sputum eosinophils of 3% or more in asthmatic patients.[15] In patients with stable COPD, blood eosinophil counts at a threshold of 0.3×10^9/L could help identifying the presence or absence of sputum eosinophilia.[16] At an optimal cut-off value of 0.316×10^9/L, Balazs et al found that blood eosinophil counts are a good surrogate for identifying sputum eosinophilia (>3%) in stable COPD.[17] Nevertheless, the role of peripheral eosinophil counts in predicting sputum eosinophilia in patients with chronic cough is still unclear. Other type 2 inflammatory biomarkers, for example, fractional exhaled nitric oxide (FeNO) and total immunoglobulin E (TIgE), have also been applied to identify eosinophilic airway inflammation in asthmatic patients.[7,8] However, the diagnostic value of these biomarkers in predicting sputum eosinophilia in chronic cough patients remains unknown. Thus, in our present study, we aimed to investigate the diagnostic accuracy of blood eosinophil counts and its comparisons to other common type 2 inflammatory biomarkers in predicting sputum eosinophilia in patients with chronic cough.

METHODS

Study design

In this prospective study, patients with chronic cough were enrolled between June 2006 to January 2020. The clinical demographics, laboratory data, and diagnosis as well as treatment responsiveness were recorded. Information related to this prospective database has been reported in our previous publication,[18] and some patients had been enrolled in 2 clinical studies (NCT01404013 and ChiCTR1800014845). The study has been approved by the Ethics Committee (Number: 202019). All patients have provided their informed consent during this study.

Subjects

In the current study, the inclusion criteria were as follows: (1) Age between 16 and 70 years; (2) Cough as the sole or predominant symptom lasting more than 8 weeks; (3) No obvious abnormality on chest X-ray; (4) No smoking history; and (5) Patients had induced sputum test and performed at least 1 of the following measurements: complete blood count, FeNO, and TIgE. Patients who had been treated with steroids or leukotriene receptor antagonists (LTRAs) in the past 4 weeks were excluded.

Measurements of clinical biomarkers

Sputum was induced and processed as described in our previous study.[19] Briefly, after inhalation of 400 μg salbutamol, the patients were instructed to inhale 3% saline for 15 min via an ultrasonic nebulizer and the sputum could be induced. Sputum cell differential was obtained by counting 400 non-squamous cells. The percentage of sputum eosinophil (Eos%) $\geq$ 2.5% was defined as sputum eosinophilia.[20] The blood differential cell

counts were performed by collecting venous blood with a hematology analyzer (DxH800, Beckman Coulter, US). During the study period, the instruments had undergone quality control and the experimental data were reliable. Absolute blood eosinophil counts were expressed as 10^9 cells·L^{-1}. Serum level of total immunoglobulin E (TIgE) was measured by ImmunoCap (Phadia AB, Uppsala, Sweden) and the results were expressed as KU/L. The level of fractional exhaled nitric oxide (FeNO) was determined with NIOX VERO (Aerocrine, Sweden) in accordance with the standard procedure described in ATS guideline.[21] In addition, the spirometry was performed according to ATS/ERS guideline.[22] The pulmonary ventilation parameters were also recorded.

Statistical analysis

Statistical analyses were conducted by using SPSS (version 18.0), GraphPad Prism (version 8.0), R (version 4.1.0), and MedCalc (19.4.1). The FeNO level, sputum Eos%, blood eosinophil counts, and TIgE level were expressed as median and interquartile ranges (IQR). A Mann-Whitney test was applied to compare the level of FeNO, blood eosinophils, and TIgE between groups. Chi-square tests or Fisher's exact test for categorical variables. The correlation of the two parameters was determined by the Spearman rank correlation. The optimal cutoff points of FeNO, blood eosinophils, and TIgE for identifying sputum eosinophilia were obtained by the receiver operating characteristic (ROC) curve, by which the sensitivity, specificity, and positive and negative likelihood ratio were calculated. Areas under the receiver operating characteristics curves (AUC) of blood eosinophil counts, FeNO, and TIgE alone or combined, for detecting sputum eosinophilia, were calculated and analyzed. The STARD 2015 guideline for reporting diagnostic accuracy studies was applied.[23] DeLong tests were used to compare AUCs between different biomarkers and to evaluate whether any of the 2 or 3 biomarkers combined can improve the predictive accuracy. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline demographics and clinical characteristics

A total of 658 patients were enrolled, among which 495 patients performed FeNO measurement, 473 patients had routine blood test and 311 patients had TIgE measurement, respectively. Meanwhile, 201 patients completed all of the above measurements.

The demographics and baseline characteristics were described in Table 1. Among 658 patients enrolled in this study, 310 (47.1%) patients had sputum eosinophilia. As compared to patients without sputum eosinophilia, patients with sputum eosinophilia exhibited female predominance (59.0% vs 50.0%, $P = 0.023$) and shorter median cough duration (18.0 months vs 30.0 months, $P < 0.01$). There were no significant differences in terms of age, BMI, and pulmonary functions between the subgroups (all $P > 0.05$).

As compared to patients without sputum eosinophil, those with sputum eosinophilia had a significantly higher level of blood eosinophil counts [0.3 (0.2–0.4) x10^9/L vs. 0.10 (0.1–0.2) x10^9/L, $P < 0.01$], FeNO level [38.0 (22.0–82.5) ppb vs 16.0 (11.0–23.0) ppb, $P < 0.01$] and TIgE level [85.8 (32.7–206.3) KU/L vs. 43.1 (15.9–102.0) KU/L, $P < 0.01$], respectively (Fig. 1).

Correlation analysis of sputum eosinophil and other biomarkers

Correlation analysis showed that the percentage of sputum eosinophils (sputum Eos%) were positively and moderately correlated with blood eosinophil counts [$r_s = 0.538$ (95%CI: 0.472–0.603), $P < 0.0001$], with FeNO [$r_s = 0.551$ (95%CI: 0.484–0.611), $P < 0.0001$] and TIgE [$r_s = 0.316$ (95%CI: 0.209–0.416), $P < 0.0001$], respectively.

Diagnostic accuracy of blood eosinophil counts and other biomarkers in identifying sputum eosinophilia

Overall, the ROC, the optimal threshold and associated sensitivity (Sen), specificity (Spe), positive predictive value (PPV), and negative predictive value (NPV) of each biomarker for predicting sputum eosinophilia were summarized in Table 2 and Fig. 2. We also investigate the exploratory cut-off points at a higher specificity of 95% (Table 2). When the cut-off value of blood eosinophil counts was 0.155×10^9/L, an optimal sensitivity (78.9%) and specificity (70.3%) were yielded. The optimal cut-off level of FeNO in predicting sputum eosinophilia was 26.5 ppb, with a sensitivity of 69.1% and a specificity of 80.0%,

respectively. The diagnostic value of TIgE in predicting sputum eosinophilia is limited, with a sensitivity of 52.2% and specificity of 72.2% at an optimal cut-off point of 80.05 KU/L.

Comparisons of diagnostic accuracy of biomarkers alone or in combination

In subgroup analysis of 201 patients who undertook all biomarker measurements, the AUC under the ROC showed that FeNO and blood eosinophil counts had similar diagnostic value ($z = 1.080$, $P = 0.280$), while the AUC for TIgE was significantly lower than that of FeNO ($z = 2.369$, $P = 0.018$) and blood eosinophil counts ($z = 3.207$, $P = 0.001$), respectively. Furthermore, combining FeNO and blood eosinophil counts significantly improved the diagnostic value for identifying sputum eosinophilia as compared to FeNO alone ($z = 3.462$, $P = 0.000$), blood eosinophil counts alone ($z = 2.007$, $P = 0.045$) and TIgE alone ($z = 4.636$, $P < 0.001$). Meanwhile, adding TIgE to the combination model of FeNO and blood eosinophil counts did not improve the AUC ($z = 0.334$, $P = 0.738$) (Table 3 and Fig. 3).

DISCUSSION

To our knowledge, the present study is the first to evaluate the accuracy of blood eosinophil counts and other type 2 inflammatory biomarkers,

Characteristic	Total	Patients with sputum eosinophilia	Patients without sputum eosinophilia
N	658	310	348
Female, %	54.3	59.0*	50.0
Age, year	41.2 ± 13.1	40.6 ± 13.6	41.7 ± 12.7
BMI	23.1 ± 3.4	23.0 ± 3.4	23.2 ± 3.3
Duration, months	24.0 (7.0–66.0)	18.0 (5.0–54.0) **	30.0 (10.0–72.0)
AR, % (n = 631)	40.0	44.5 **	31.0
Sputum Eos%	1.8 (0.3–9.0)	9.5 (4.5–26.0) **	0.4 (0.0–1.0)
Sputum Neu%	62.0 (36.5–83.1)	56.8 (27.9–78.5) **	67.9 (43.1–87.9)
FeNO, ppb (n = 495)	21.0 (13.0–42.0)	38.0 (22.0–82.5) **	16.0 (11.0–23.0)
Blood eosinophil counts, 10^9/L (n = 473)	0.2 (0.1–0.3)	0.3 (0.2–0.4) **	0.1 (0.1–0.2)
TIgE, KU/L (n = 311)	60.1 (22.6–171.0)	85.8 (32.7–206.3) **	43.1 (15.9–102.0)
FVC% pred (n = 593)	100.4 ± 16.0	99.6 ± 17.5	101.1 ± 14.5
FEV_1% pred	98.2 ± 39.3	98.8 ± 54.4	97.8 ± 14.9
FEV_1/FVC	82.4 ± 9.3	82.0 ± 9.1	82.9 ± 9.4
MMEF% pred	74.0 ± 24.4	71.4 ± 24.0	76.6 ± 24.5

Table 1. Demographics and clinical characteristics of the patients with or without sputum eosinophilia. *Female and AR were presented as percentage (%); Age, BMI, FVC% pred, FEV_1% pred, FEV_1/FVC and MMEF% pred were presented as mean ± SD; Duration, sputum Eos%, sputum Neu%, FeNO, blood eosinophil counts and TIgE were presented as median (IQR). BMI: body mass index; AR: allergic rhinitis; Eos: eosinophil; Neu: neutrophil; FeNO: fractional exhaled nitric oxide; TIgE: total immunoglobulin E; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MMEF: maximal mid-expiratory flow; PEF: peak expiratory flow. Patients with sputum eosinophilia vs patients without sputum eosinophilia: *, $P < 0.05$; **, $P < 0.01$.*

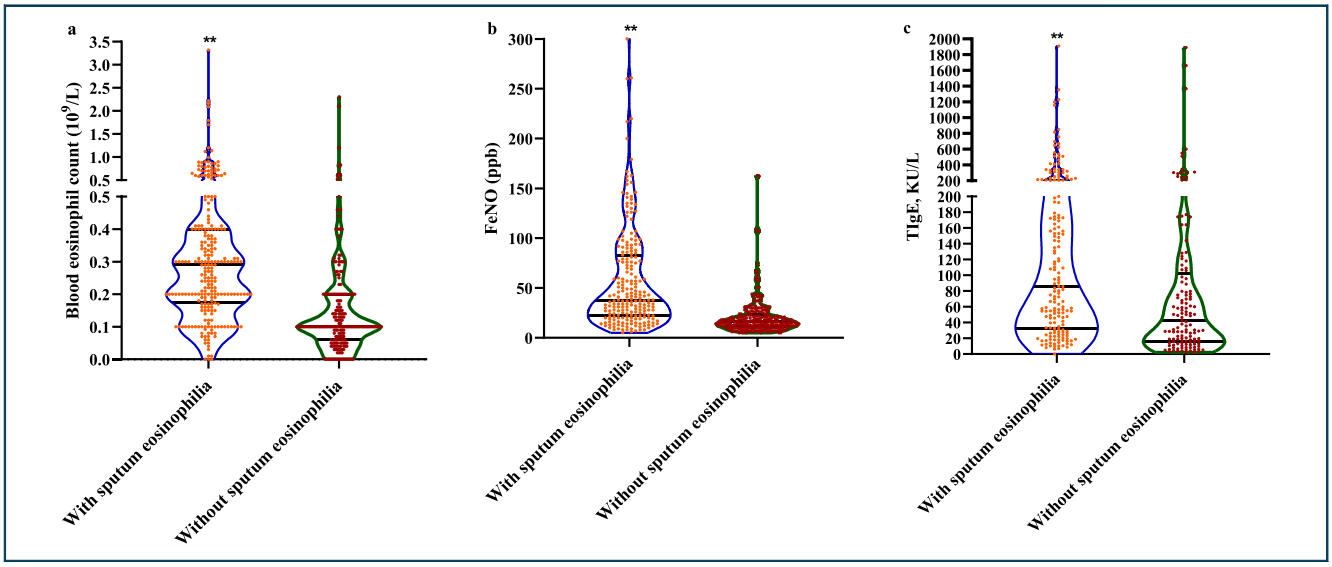

Fig. 1 Levels of different biomarkers in patients with sputum eosinophilia and without sputum eosinophilia. a: Blood eosinophil counts were increased significantly in patients with sputum eosinophilia as compared to those without sputum eosinophilia, $^{**}P < 0.01$; b: The level of FeNO in patients with eosinophilia was significantly higher than those without sputum eosinophilia, $^{**}P < 0.01$; c: The level of total IgE in patients with eosinophilia was significantly increased as compared to those without sputum eosinophilia, $^{**}P < 0.01$

including FeNO and TIgE, in identifying sputum eosinophilia in a large sample of chronic cough patients. Our study first revealed that blood eosinophil counts have a moderate predictive value in identifying sputum eosinophilia in patients with chronic cough. Combining FeNO and blood eosinophil counts could effectively improve diagnostic accuracy.

Since eosinophilic airway inflammation usually responded well to corticosteroid therapy in patients with chronic cough,[5,24,25] and routine blood test is cheap and easy to access, our finding is of great importance for the management of chronic cough patients, especially in the settings where induced sputum test and FeNO measurement are not available.

Previously studies have shown that blood eosinophil levels are correlated well with sputum eosinophils in patients with asthma or COPD.[7,16,17,26–28] A recent study enrolling 142 adult chronic coughers found that there was a weak correlation between the blood eosinophil counts and sputum eosinophil ($r = 0.30$).[29] In the present study, we found that the level of blood eosinophil counts was moderately correlated with the percentage of sputum eosinophils ($r = 0.54$) in chronic coughers. Additionally, our results revealed that blood eosinophil counts $\geq 0.155 \times 10^9$/L indicated a more likelihood of airway eosinophilia-related chronic cough, with an optimal sensitivity (78.9%) and specificity (70.3%). When the cut-off value of blood eosinophil counts was set at 0.470×10^9/L, the specificity could be up to 95.0%. In asthmatic patients, eosinophil counts greater than 300 cells/μL has been shown to indicate an eosinophilic airway inflammation,[30] with a sensitivity higher than 70% and specificity higher than 90%. We found that the specificity could be up to 89.6% while the sensitivity was 40.2% when the cutoff point of blood eosinophils was set as 300 cells/μL in chronic coughers.

The current study showed that the optimal cut-off value of FeNO for identifying sputum eosinophilia in chronic coughers was 26.5 ppb with a moderate sensitivity of 69.1% and a specificity of 80.0%, respectively. The AUCs of blood eosinophil counts were similar to that of FeNO, indicating that blood eosinophils counts can be used as a simple biomarker to identify sputum eosinophilia in patients with chronic cough. Eosinophil-related conditions such as cough variant asthma and eosinophilic bronchitis are common causes of chronic cough;[2,31] however, it is not easy to diagnose those conditions in clinical settings. Relevant investigations including bronchial challenge test, induced sputum test, or FeNO measurement are either expensive or unavailable in many medical cares. In this case, blood eosinophil counts can be used as a simple and cheap surrogate to identify eosinophilic

	AUC (95% CI)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
FeNO, ppb (n = 495)	0.799 (0.759–0.839)	26.5	69.1 (62.5–75.0)	80.0 (74.7–84.5)	73.4 (66.8–79.2)	76.4 (71.0–81.1)
		50.0	39.5 (33.1–46.4)	**94.9** (91.4–97.1)	86.1 (77.5–91.9)	66.2 (61.3–70.9)
Blood eosinophil counts, 10^9/L (n = 473)	0.780 (0.738–0.823)	0.155	78.9 (73.2–83.7)	70.3 (63.7–76.1)	75.0 (69.2–80.0)	74.6 (68.1–80.3)
		0.300	40.2 (34.2–46.6)	89.6 (84.7–93.2)	81.5 (73.3–87.6)	57.0 (51.6–62.2)
		0.470	20.7 (16.0–26.4)	**95.0** (91.1–97.4)	82.5 (70.1–90.6)	51.5 (46.5–56.4)
TIgE, KU/L (n = 311)	0.653 (0.591–0.714)	80.05	52.2 (44.7–59.7)	72.2 (63.6–79.4)	71.5 (62.8–78.9)	53.0 (45.5–60.4)
		100.0	46.6 (39.2–54.2)	75.2 (66.8–82.1)	71.6 (62.3–79.3)	51.3 (44.1–58.5)
		317.5	15.2 (10.4–21.5)	**94.7** (89.1–97.7)	79.4 (61.6–90.7)	45.5 (39.5–51.6)

Table 2. Predictive accuracy of single biomarker for sputum eosinophilia. *Data expressed as (95% CI). AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value; FeNO: fraction of exhaled nitric oxide; TIgE: total immunoglobulin E.*

inflammation and guide treatment options for chronic coughers.

Allergic diseases are usually characterized by an elevated IgE level and eosinophilic inflammation. In the present study, we showed that the TIgE in chronic cough patients with sputum eosinophilia was significantly higher than those patients without sputum eosinophilia, but the correlation between TIgE and percentages of sputum eosinophil was weak (r_s = 0.336). Thus, the diagnostic value of TIgE in predicting sputum eosinophilia was low, which was similar to the findings reported in asthmatic patients.[7] If we set a high specificity of 95%, the optimal cut-off point of TIgE level would be 317.5 KU/L and the sensitivity was only 15.2%, indicating that TIgE level is not an ideal surrogate for eosinophilic airway inflammation in chronic cough.

The accuracies of type 2 inflammatory biomarkers in predicting eosinophilic airway inflammation in asthma varied in different studies.[7,8,15,26,32–34] Hastie et al reported that FeNO, blood eosinophil counts, and TIgE were poor surrogates for accurately predicting sputum eosinophilia in severe asthma, both separately and combined.[8] Westerhof et al showed that blood eosinophils and FeNO had a comparable accuracy of identifying sputum eosinophilia in asthma, irrespective of asthma phenotype.[7] These conflicting results might be attributed to the different disease severities, medication histories, and races of the enrolled patients. However, results from a meta-analysis revealed that FeNO, blood eosinophils and IgE had moderate diagnostic accuracy for predicting airway eosinophilia in adult patients with asthma.[15] In our present study, blood eosinophil counts and FeNO demonstrated a moderate and comparable diagnostic accuracy in identifying eosinophilic airway inflammation in chronic cough patients, and both of them were superior to that of TIgE. Although the sensitivity and specificity of each marker were not very high, combining FeNO and blood eosinophil counts significantly improved the diagnostic accuracy, showing the largest AUC (0.868 [0.814–0.923]), associated with an increased sensitivity (84.2% [75.9%–90.1%]) and specificity (82.8% [72.8%–89.7%]). Our findings were consistent with the findings in recent studies

	AUC (95% CI)	Positive thres-hold	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
FeNO, ppb	0.784 (0.72–0.849) *	26.5	72.8 (63.5–80.5)	77.0 (66.5–85.1)	80.6 (71.4–87.5)	68.4 (58.1–77.2)
Blood eosinophil counts, 10^9/L	0.826 (0.767–0.885) **	0.205	68.4 (59.0–76.6)	87.4 (78.1–93.2)	87.6 (78.6–93.4)	67.9 (58.3–76.2)
TIgE, KU/L	0.686 (0.613–0.760)	80.05	57.9 (48.3–67)	73.6 (62.8–82.2)	74.2 (63.6–82.6)	57.1 (47.4–66.3)
FeNO + blood eosinophil counts	0.868 (0.814–0.923) #, $, &	0.491[1]	84.2 (75.9–90.1)	82.8 (72.8–89.7)	86.5 (78.4–92.0)	80.0 (70.0–87.4)
FeNO + TIgE	0.792 (0.728–0.856)	0.496[1]	74.6 (65.4–82.0)	78.2 (67.8–86.0)	81.7 (72.7–88.4)	70.1 (59.8–78.8)
Blood eosinophil counts + TIgE	0.837 (0.778–0.895)	0.569[1]	68.4 (59.0–76.6)	88.5 (79.4–94.1)	88.6 (79.7–94.1)	68.1 (58.6–76.4)
FeNO + blood eosinophil counts + TIgE	0.868 (0.814–0.923)	0.491[1]	84.2 (75.9–90.1)	82.8 (72.8–89.7)	86.5 (78.4–92.0)	80.0 (70.0–87.4)

Table 3. Predictive accuracy of the biomarkers alone or combined in the subgroup analysis (n = 201). *Data expressed as (95% CI). AUC: Area under curve; PPV: positive predictive value; NPV: negative predictive value; FeNO: Fraction of exhaled nitric oxide; TIgE: Total immunoglobulin E. *: vs TIgE, $P < 0.05$. **: vs TIgE, $P < 0.01$. #: vs Blood eosinophil counts, $P < 0.05$. $: vs FeNO, $P < 0.01$. &: vs TIgE, $P < 0.01$. [1]All test combinations were log transformed, these values correspond to an individual's probability of sputum eosinophilia, as obtained by the formulas provided in online Supplementary Figure E1.*

focusing on asthmatics or COPD patients.[35,36] Thus, we can readily identify most of the patients with chronic cough who might have eosinophilic airway inflammation by performing the FeNO measurement and blood routine test when the induced sputum test was not applicable.

We admit the limitations of this study. First, the data of the present study were collected in a single center. Thus, the results might not reflect the real condition in different regions, but the findings derived from this study with the largest sample size could provide important clinical implications for the management of chronic cough. Further validation study in multiple centers will be worth conducting in the future. Secondly, we did not observe directly the validity of blood eosinophils counts and other biomarkers in predicting the

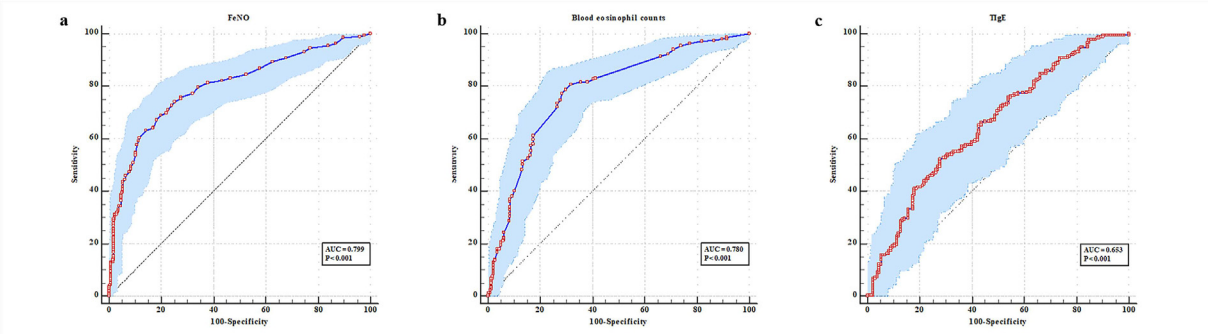

Fig. 2 ROC curve for FeNO (a, n = 495), blood eosinophil counts (b, n = 473) and TIgE (c, n = 311) in predicting sputum eosinophilia. The shadow indicated 95% CI

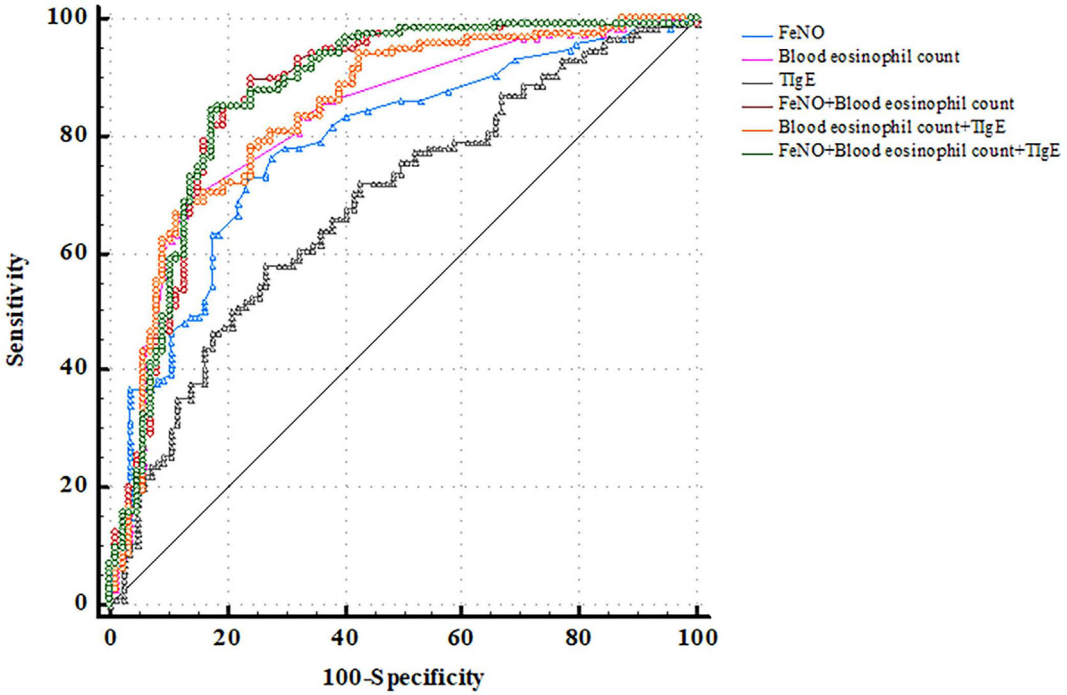

Fig. 3 ROC curves of each biomarker alone or in combination for predicting sputum eosinophilia (n = 201)

response to corticosteroids in patients with chronic cough. However, in the current study, we enrolled the patients with sputum eosinophilia who all experienced full investigations related to the etiological diagnosis of chronic cough and responded to corticosteroids. Future studies are warranted to investigate the role of blood eosinophil counts in predicting treatment responsiveness in chronic coughers. Thirdly, blood eosinophil counts might be affected by many factors, such as drugs, daytime variations or seasonal variations.[37] We could not rule out the effects of these inevitable factors as we only analyzed the baseline data in the current study.

CONCLUSION

In summary, our study revealed that blood eosinophil counts have similar moderate diagnostic accuracy as FeNO in identifying sputum eosinophilia in patients with chronic cough. Blood eosinophil counts can be used as a simple and cheap surrogate to guide the treatment of chronic cough in clinical practice, especially in community clinics and secondary hospitals. A combination of blood eosinophil counts and FeNO measurement can improve the diagnostic accuracy for identifying sputum eosinophilia.

Abbreviations

FeNO, fractional exhaled nitric oxide; TIgE, total immunoglobulin E; AUC, area under the receiver operating characteristics curve; CVA, cough variant asthma; UACS, upper airway cough syndrome; NAEB, nonasthmatic eosinophilic bronchitis; GERC, gastro-esophageal reflux related cough; AC, atopic cough; LTRAs, leukotriene receptor antagonists.

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Availability of data and materials

Data and materials for generating the results of this paper will be available upon reasonable request to the correspondence author.

Authors' contributions

FY, FZF contributed to the study conception and design, data acquisition, data analysis and interpretation, manuscript drafting and revising; WHL contributed to the data analysis and interpretation, manuscript revising; RLH contributed to the data acquisition, data analysis and interpretation; MJ contributed to the data analysis and interpretation, manuscript review; FZF, HKX, ZC contributed to the data acquisition, manuscript review; WL

contributed to the sputum induction and differential cell count, manuscript review; FKL developed the concept and design the study, and contributed to the critical revision of the manuscript. All authors provided the final review and approval of the manuscript to be submitted.

Ethics approval and consent to participate
The study has been approved by the Ethic Committee of the First Affiliated Hospital of Guangzhou Medical University (Number: 202019). All patients have provided their informed consent during this study.

Authors' consent for publication
All authors approved the manuscript and gave their consent for publication.

Declaration of competing interest
The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100819.

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