



Biomarkers of type 2 inflammation as predictors of response to biologics for severe eosinophilic asthma

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Pre-treatment BEC is not associated with response to anti-IL-5/IL-5R α or anti-IL-4R α in SEA patients. F_{ENO} effects vary by outcome domain and biological therapy. Combining these biomarkers does not improve prediction. <https://bit.ly/3GG9kaT>

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Abstract

Background The relationship between pre-treatment levels of blood eosinophil count (BEC), fractional exhaled nitric oxide (F_{ENO}) and sputum eosinophils (Sp-EOS) and treatment response to monoclonal antibodies (mAbs) in severe eosinophilic asthma (SEA) remains unclear. We evaluated pre-treatment levels of BEC, F_{ENO} , Sp-EOS and their combinations as predictors of treatment responses in patients with SEA undergoing anti-interleukin (IL)-5/IL-5R α or anti-IL-4R α antibody therapies.

Methods The study included 153 adult patients with SEA (59 anti-IL-5/IL-5R α and 94 anti-IL-4R α users). Logistic regression models were used to evaluate the association between predictors and 12-month treatment responses and clinical remission across four domains: exacerbation rate, maintenance of oral corticosteroid dose, forced expiratory volume in 1 s (FEV₁) and asthma control test (ACT) improvement.

Results Pre-treatment BEC and Sp-EOS were not associated with treatment responses in either mAb group. For combined data from anti-IL-5/IL-5R α and anti-IL-4R α users, the adjusted odds ratios (95% confidence intervals) for a 1-unit increase in log-transformed F_{ENO} were 1.8 (1.21–2.74) for FEV₁ response and 2.15 (1.29–3.75) for ACT response. For anti-IL-4R α users, these values were 2.34 (1.39–4.17) and 3.6 (1.73–8.84),

respectively. No significant association between F_{ENO} and treatment response was found among anti-IL-5/IL-5R α users. Additionally, no associations were observed between BEC, Sp-EOS or F_{ENO} and clinical remission across mAb categories. Combining biomarkers did not significantly enhance predictive ability.

Conclusion In patients with SEA treated with anti-IL-4R α antibodies, pre-treatment F_{ENO} may be a good predictor for certain treatment response domains.

Introduction

Severe asthma (SA) is a chronic inflammatory condition of the airways that requires the use of high-dose inhaled (ICSs) or oral corticosteroids (OCSs) for maintenance therapy. However, despite such treatment, patients continue to experience frequent recurrent exacerbations and have a decline in respiratory function [1]. This complex pathological condition involves numerous interconnected factors and diverse individual responses to various exposures and treatments [2]. Recent studies have focused on specific cytokines in the type 2 (T2) inflammatory pathway, identifying a T2-high phenotype and developing monoclonal antibodies (mAbs) that specifically inhibit these cytokines [3, 4]. mAbs targeting downstream cytokines, such as interleukin (IL)-5, IL-4 and IL-13, compared to placebo decrease exacerbation rates, reduce maintenance oral corticosteroid (mOCS) use and improve lung function in patients with severe eosinophilic asthma (SEA) [5–8]. However, individual responses to these agents vary widely within the population. Therefore, identifying the predictors that can forecast the therapeutic response to such treatment is essential for personalising therapy for SEA patients.

The variability in response to biological treatments may stem from inconsistencies in defining the concept of “response”. Reduction in exacerbation frequency is considered the most critical outcome in treating SEA [1]. However, recent therapeutic goals for SEA have used a more multidimensional approach due to the heterogeneous nature of asthma. The proposed recommendations on the definition of “response” focus on four domains: reduction in exacerbation frequency, decrease in long-term OCS use, improvement in asthma control and increase in forced expiratory volume in 1 s (FEV₁) [9–11]. The responder rate varies greatly depending on the domains included in the criteria, and many individuals do not respond in one domain but show a significant improvement in another domain [10, 12]. Recently, there has been emerging interest in combining these response factors to achieve long-term clinical remission and complete disease elimination. A consensus framework defined clinical remission as requiring at least 12 months of assessment, with no exacerbations or mOCS, along with optimised/stabilised lung function, and the absence of significant symptoms [13]. Furthermore, estimates of the effect size of the relationship between predictors and outcomes in randomised controlled trials (RCTs) and real-world studies differ, especially in the context of the heterogeneous nature of asthma [14].

Patient characteristics before mAb administration are used to identify potential predictors of response [15]. The *post hoc* analyses from RCTs revealed that pre-treatment blood eosinophil count (BEC) levels in patients with SA were associated with the extent of exacerbation reduction among anti-IL-5/IL-5R α or anti-IL-4R α users [16–19]. Meanwhile, high baseline fractional exhaled nitric oxide (F_{ENO}) levels may be independently associated with a better response in patients treated with anti-IL-4R α [20]. High BEC and F_{ENO} levels before mAbs administration have been recommended for optimising treatment response [1]. However, the relationship between baseline BEC and F_{ENO} levels and response outcomes is mostly based on secondary analyses from RCTs. Additionally, whether the relationship between pre-treatment T2 inflammation biomarkers and clinical treatment responses persists remains unclear for SEA patients eligible for biological add-on therapy (*i.e.*, those with high pre-treatment T2 inflammation biomarkers). BEC and F_{ENO} are indirect markers of eosinophilic airway inflammation and can be influenced by other pathological factors [21, 22]. The induced sputum eosinophil (Sp-EOS) level is considered a direct proxy for eosinophilic airway inflammation [23], but whether combining this biomarker with currently available biomarkers can improve the prediction of response to mAb treatment is unknown.

In this study, we investigated the predictive power of three main T2 inflammatory biomarkers (BEC, Sp-EOS and F_{ENO}) in forecasting the various domains of treatment responses and clinical remission to either anti-IL-5/IL-5R α or anti-IL-4R α mAbs in SEA patients.

Methods

Participants

The Precision Medicine Intervention in Severe Asthma (PRISM) study is a nationwide ongoing multicentre (23 centres) prospective cohort study since May 2020 [24]. Adults with SA were enrolled based on diagnoses by respiratory experts as either “controlled” with high-dose continuous ICS or a second anti-asthma drug, or “uncontrolled” despite active treatment. Patients who had used any biologics for asthma treatment in the past 3 months, had prolonged OCS use in the past 4 weeks (exceeding a total of

90 mg prednisolone), or had hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis or any other severe respiratory diseases were excluded. Biologics were indicated for SEA patients according to the Global Initiative for Asthma recommendations [1]. In this analysis, we evaluated patients treated with anti-IL-5/IL-5R α (mepolizumab, reslizumab or benralizumab) or anti-IL-4R α (dupilumab), who completed a 12-month follow-up. The criteria for administration, dosage and usage protocol of biologics are presented in supplementary table 1S. In brief, mepolizumab was administered to patients with a baseline BEC of ≥ 150 cells· μL^{-1} or ≥ 300 cells· μL^{-1} in at least one test within the previous 12 months. Reslizumab was indicated for patients with a BEC >400 cells· μL^{-1} , and benralizumab for patients with a baseline BEC >150 cells· μL^{-1} . Dupilumab was indicated for patients with a baseline BEC >150 cells· μL^{-1} or $F_{\text{ENO}} >25$ ppb. A total of 153 SEA patients met the inclusion criteria, comprising 59 anti-IL-5/IL-5R α users (22 patients on mepolizumab, 28 patients on reslizumab and nine patients on benralizumab) and 94 anti-IL-4R α users. The number of patients per biologics group at each hospital is listed in supplementary table 2S. The Institutional Review Board at each study site approved the study protocol and registered it on ClinicalTrials.gov (registration number NCT05164939) [25]. All participants provided informed written consent.

Measurements

Baseline characteristics collected before treatment included BEC, Sp-EOS, F_{ENO} , asthma control test (ACT) score, pre-bronchodilator FEV₁, age, sex, age at diagnosis, body mass index (BMI), number of exacerbations in the previous year, ICS use (in budesonide equivalent dose; Bude_eq), OCS use (in prednisolone equivalent dose; Pred_eq) at baseline and history of comorbidities, such as allergic rhinitis, gastroesophageal reflux and nasal polyps. BEC values, measured in cells per microlitre, were derived from standard complete blood cell counts. F_{ENO} measurements were performed using an airway inflammation monitor (Niox Vero, SE-754, Uppsala, Sweden), adhering to the American Thoracic Society/European Respiratory Society guidelines and technical standards. Sp-EOS percentages were obtained from induced sputum samples collected after nebulised hypertonic saline inhalation. Supplementary table 3S shows detailed instructions for calculating Bude_eq and Pred_eq.

Definition of outcome

The definition of “responder” in this analysis was based on four consensus domains: reduction in exacerbation rate, reduction in mOCS, improvement in FEV₁ and improvement in the ACT score [10]. An “EXA-OCS-Res” referred to patients who, after 12 months of treatment, met one of the following conditions: 1) a $\geq 50\%$ reduction in the annual exacerbation rate; 2) a $\geq 50\%$ reduction in mOCS use; or 3) no history of exacerbations in the year before treatment, maintaining this status throughout the 12-month follow-up. An “FEV₁-Res” was defined as a patient who, after 12 months of treatment, had a predicted pre-bronchodilator FEV₁ of $\geq 80\%$, or that increased by at least 100 mL and by $\geq 10\%$ at the 12-month visit compared with pre-treatment. An “ACT-Res” was defined as a patient who, after 12 months of treatment, had an ACT score of ≥ 20 , or that increased by at least 3 points at the 12-month visit compared with pre-treatment. Clinical remission (Clin-Rem) was defined as patients who had no exacerbations and did not use mOCS throughout the follow-up period, while also fulfilling the criteria for FEV₁-Res and ACT-Res at the 12-month checkup.

Statistical analysis

Statistical analyses were conducted using R version 4.3.1, with statistical significance set at $p < 0.05$. Descriptive analysis compared the baseline patients’ characteristics among biologics groups and between responders and non-responders in each domain. T-tests and rank sum tests were employed for normally and non-normally distributed continuous variables, respectively. For categorical variables, Fisher’s exact tests were applied. Logistic regression examined the association between predictors and their combination with the outcome. Seven models were performed for each response domain with predictors as (M1) BEC, (M2) Sp-EOS, (M3) F_{ENO} , (M4) BEC+Sp-EOS, (M5) BEC+ F_{ENO} , (M6) Sp-EOS+ F_{ENO} and (M7) all three biomarkers. The models were adjusted for covariates including age and sex. The predictors (BEC, Sp-EOS and F_{ENO}) were log-transformed owing to their skewed distribution. The area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated for each model and compared with the AUC of other models using the DeLong test [26]. The sensitivity–specificity equality criterion (SSEC) was used to estimate the optimal cut-off and corresponding sensitivity and specificity for baseline BEC, Sp-EOS and F_{ENO} in predicting each domain outcome [27]. The same analyses were performed separately on overall data, anti-IL-5/IL-5R α users and anti-IL-4R α users. Because the “responder” and “remission” labels were quite skewed, logistic regression models were more likely to favour the majority labels. To address this issue, we applied the random over-sampling examples (ROSE) technique to adjust the data with the ratio of outcomes as 1:1 to avoid overfitting [28]. The analysis of the data after applying the ROSE technique was reported as a sensitivity analysis.

Results

Patients

At baseline, patients had a mean age of 54 years and a high mean BMI ($25 \text{ kg}\cdot\text{m}^{-2}$), with nearly 90% having a BEC level $>150 \text{ cells}\cdot\mu\text{L}^{-1}$, 75% having an $\text{FEV}_1 <80\%$, and 75% having an ACT score <20 points. Anti-IL-5/IL-5R α and anti-IL-4R α users did not differ regarding demographics, lung function, history of exacerbations and ICS/OCS doses used. Anti-IL-5/IL-5R α users had a higher baseline BEC, with a notably higher proportion of BEC $>300 \text{ cells}\cdot\mu\text{L}^{-1}$ (88% versus 64%, $p=0.001$). They also had higher baseline Sp-EOS and F_{ENO} compared to anti-IL-4R α users (all $p<0.05$; table 1).

Rate and baseline characteristics of responders

Figure 1 illustrates the response rate by each response domain and the remission rate. After 12 months of treatment, $>85\%$ of patients met the criteria for EXA-OCS-Res and ACT-Res, and $>75\%$ fulfilled the criteria for FEV_1 -Res. Only $\sim 40\%$ of them achieved clinical remission according to the combined criteria of all four domains. Across all response domains and clinical remission, the response and clinical remission rates in the anti-IL-5/IL-5R α group were slightly higher compared with the anti-IL-4R α group.

At baseline, EXA-OCS responders had a higher proportion of females (both in the overall dataset and among anti-IL-5/IL-5R α users) and experienced more exacerbation events in the previous year (in the overall dataset and among anti-IL-4R α users) compared with non-responders (table 2, supplementary tables 4S and 5S). For FEV_1 -Res and ACT-Res, responders had higher FEV_1 values and elevated BEC levels (both absolute counts and the proportion of patients with $>300 \text{ cells}\cdot\mu\text{L}^{-1}$, all $p<0.05$), as well as higher F_{ENO} levels (both absolute values and the proportion of patients with $F_{\text{ENO}} >25 \text{ ppb}$, all $p<0.05$) in the overall dataset and among anti-IL-4R α users. Among anti-IL-5/IL-5R α users, no group differences were found for FEV_1 -Res; however, for ACT-Res, responders had higher Sp-EOS levels (table 2, supplementary

TABLE 1 Baseline characteristics of anti-interleukin (IL)-5/IL-5R α and anti-IL-4R α users

Variable	Total	n	anti-IL-5/IL-5R α	anti-IL-4R α	p-value
Male, n (%) ⁺	66 (43.1)	59/94	20 (33.9)	46 (48.9)	0.093
Age, y [#]	53.8 $\pm$ 10.3	59/95	52.4 $\pm$ 10.6	54.8 $\pm$ 10.1	0.177
Age _{diag} , y [#]	42 $\pm$ 13.3	57/89	43.0 $\pm$ 18.0	42.0 $\pm$ 20.0	0.756
BMI, kg $\cdot\text{m}^{-2}$ [#]	24.9 $\pm$ 3.8	59/94	24.3 $\pm$ 3.6	25.3 $\pm$ 3.9	0.098
FEV_1 , % [#]	63.9 $\pm$ 19.6	59/94	63.1 $\pm$ 19.2	64.4 $\pm$ 19.9	0.670
$\text{FEV}_{1\text{u80}}$, n (%) ⁺	116 (75.8)	59/94	47 (79.7)	69 (73.4)	0.441
BEC, cells $\cdot\mu\text{L}^{-1}$ [¶]	538 (581.5)	59/94	674.0 (645.5)	428.5 (379.0)	<0.001
BEC ₁₅₀ , n (%) ⁺	137 (89.5)	59/94	56 (94.9)	81 (86.2)	0.107
BEC ₃₀₀ , n (%) ⁺	112 (73.2)	59/94	52 (88.1)	60 (63.8)	0.001
Sp-EOS, % [¶]	7 (27)	47/78	15.0 (36.0)	4.5 (21.8)	0.010
Sp-EOS _{2%} , n (%) ⁺	80 (64)	47/78	35 (74.5)	45 (57.7)	0.083
F_{ENO} , ppb [¶]	53.5 (60.2)	58/94	62.0 (69.0)	45.5 (70.2)	0.038
F_{ENOa25} , n (%) ⁺	121 (79.6)	58/94	52 (89.7)	69 (73.4)	0.022
ACT, points [#]	16.1 $\pm$ 4.9	59/94	15.3 $\pm$ 5.2	16.6 $\pm$ 4.6	0.141
ACT _{u20} , n (%) ⁺	114 (74.5)	59/94	46 (78.0)	68 (72.3)	0.568
EXA _{his} , events [¶]	1 (10.1)	59/94	2.0 (5.0)	0.0 (3.8)	0.321
Bude _{eq} , $\mu\text{g}\cdot\text{day}^{-1}$ [¶]	640 (465.3)	59/94	640.0 (400.0)	640.0 (306.0)	0.244
Pred _{eq} , $\text{mg}\cdot\text{day}^{-1}$ [¶]	0 (5.6)	59/94	0.00 (2.50)	0.00 (5.00)	0.069
AR, n (%) ⁺	113 (73.9)	59/94	44 (74.6)	69 (73.4)	0.999
GR, n (%) ⁺	57 (37.3)	59/94	15 (25.4)	42 (44.7)	0.017
NP, n (%) ⁺	38 (24.8)	59/94	14 (23.7)	24 (25.5)	0.850

Data are presented as mean $\pm$ SD or median (interquartile range) unless indicated otherwise. n: the number of patients among anti-IL-5/IL-5R α and anti-IL-4R α users, respectively, who had data for the corresponding variable. Age_{diag}: age at asthma diagnosis; BMI: body mass index; FEV_1 : predicted pre-bronchodilator forced expiratory volume in 1 s; $\text{FEV}_{1\text{u80}}$: patients with baseline $\text{FEV}_1 <80\%$; BEC: blood eosinophil count; BEC₁₅₀ and BEC₃₀₀: patients with baseline BEC ≥ 150 and $\geq 300 \text{ cells}\cdot\mu\text{L}^{-1}$, respectively; Sp-EOS: sputum eosinophils as a percentage; Sp-EOS_{2%}: patients with baseline Sp-EOS $\geq 2\%$; F_{ENO} : fractional exhaled nitric oxide; F_{ENOa25} : patients with baseline $F_{\text{ENO}} >25 \text{ ppb}$; ACT: asthma control test score; ACT_{u20}: patients with baseline ACT $<20\%$; EXA_{his}: recall exacerbation number during the previous year; Bude_{eq} and Pred_{eq}: budesonide and prednisolone equivalent doses, respectively; AR: allergic rhinitis; GR: gastroesophageal reflux; NP: nasal polyp. p-values were determined using: [#]: ANOVA for continuous variables; [¶]: rank sum test for non-parametric variables; ⁺: Fisher's exact test for categorical variables. p-values <0.05 are indicated in bold.

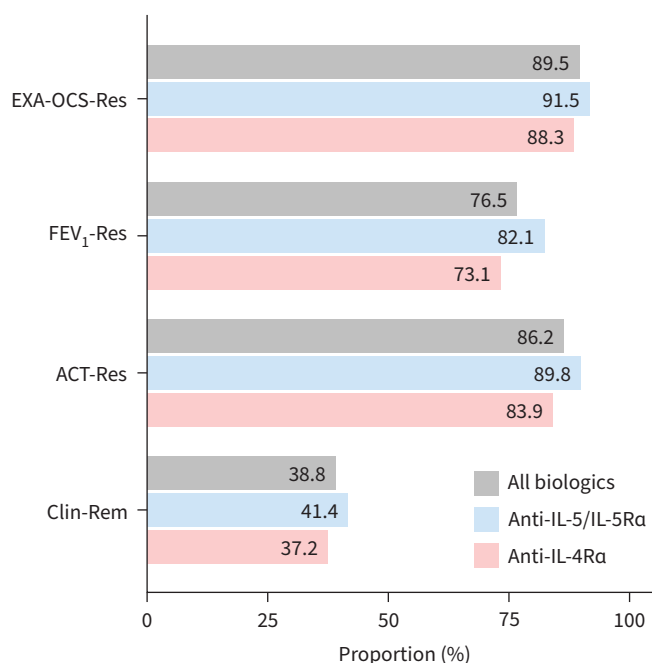


FIGURE 1 Responder rate. Bars represent the responder rate in the overall data, anti-interleukin (IL)-5/IL-5R α users, and anti-IL-4R α users for each response domain and remission. EXA-OCS-Res: responder is defined as a reduction by $\geq 50\%$ in the annual exacerbation rate, or a reduction by $\geq 50\%$ in the maintenance oral corticosteroid (mOCS) dose, or remaining without exacerbations; FEV₁-Res: FEV₁ responder is defined as having a 12-month visit FEV₁ $\geq 80\%$, or an FEV₁ increase by ≥ 100 mL and $\geq 10\%$; ACT-Res: ACT responder is defined as having a 12-month visit ACT score ≥ 20 , or an ACT score increase by ≥ 3 points; Clin-Rem: clinical remission is defined as having no mOCS use and no exacerbations during the 12-month follow-up, plus meeting the criteria for FEV₁-Res and ACT-Res.

tables 4S and 5S). Patients who met the criteria for Clin-Rem had elevated BEC levels (both absolute counts and the proportion of patients with >300 cells· μL^{-1} , all $p < 0.05$) in the overall dataset and among anti-IL-4R α users, but not among anti-IL-5/IL-5R α users. These patients also required higher doses of mOCS (in the overall dataset and among anti-IL-5/IL-5R α users). Additionally, anti-IL-4R α users who achieved Clin-Rem after 12 months of treatment were younger and had higher baseline FEV₁ and F_{ENO} levels (table 2, supplementary tables 4S and 5S).

Association with treatment response and remission

Multivariate regression analysis adjusted for age and sex showed that baseline F_{ENO} was positively correlated with EXA-OCS-Res, FEV₁-Res and ACT-Res in the overall dataset (odds ratio (OR) 1.54 (95% CI 0.92–2.64), 1.8 (1.21–2.74) and 2.15 (1.29–3.75), respectively). Meanwhile, baseline F_{ENO} was positively correlated with FEV₁-Res and ACT-Res among anti-IL-4R α users (OR 2.34 (95% CI 1.39–4.17) and 3.6 (1.73–8.84), respectively). Baseline Sp-EOS levels showed no association with any outcome in any dataset. Clin-Rem also did not show any significant association with any of the three T2-inflammation biomarkers, either in the overall data or when stratified by biologic groups (table 3).

In an analysis of data after over-sampling using the ROSE technique, baseline BEC was inversely correlated with EXA-OCS-Res in the overall dataset (OR 0.55, 95% CI 0.37–0.8) and positively correlated with EXA-OCS-Res (OR 1.67, 95% CI 1.05–2.85) and ACT-Res (OR 1.65, 95% CI 1.03–2.76) among anti-IL-4R α users. Baseline Sp-EOS was inversely correlated with ACT-Res and Clin-Rem among anti-IL-5/IL-5R α users (OR 0.24 (95% CI 0.06–0.61) and 0.42 (0.19–0.86), respectively) and positively correlated with Clin-Rem among anti-IL-4R α users (OR 1.92, 95% CI 1.19–3.26). Baseline F_{ENO} was positively correlated with EXA-OCS-Res, FEV₁-Res, ACT-Res and Clin-Rem in the overall dataset (OR 1.46 (95% CI 1.02–2.11), 2.08 (1.43–3.15), 2.45 (1.65–3.84) and 1.44 (1.03–2.04), respectively). Among anti-IL-4R α users, F_{ENO} was positively correlated with FEV₁-Res, ACT-Res and Clin-Rem (OR 1.73 (95% CI 1.11–2.79), 6.03 (2.98–14.39) and 2.25 (1.39–3.89), respectively), whereas among anti-IL-5/IL-5R α users, F_{ENO} was positively correlated only with EXA-OCS-Res (OR 1.94, 95% CI 1.05–3.89) (supplementary table 6S).

TABLE 2 Baseline characteristics stratified by response groups for each outcome domain on overall data

Variable	EXA-OCS Res		FEV ₁ -Res		ACT-Res		Clin-Rem	
	Non	Responder	Non	Responder	Non	Responder	Non	Remission
Male, n (%) ⁺	11 (68.8)	55 (40.1)*	20 (57.1)	46 (40.4)	10 (47.6)	56 (42.7)	45 (48.4)	21 (35.6)
Age, y [#]	54.4±11.4	53.8±10.2	55.5±8.2	53.6±10.9	58.8±10.9	53.0±10.0*	54.4±10.1	53.0±10.7
Age _{diag} , y [#]	42.5±24.5	42.0±18.0	39.0±18.0	42.0±21.0	50.0±21.0	42.0±20.0	40.5±19.0	44.0±20.0
BMI, kg·m ⁻² [#]	26.9±5.3	24.7±3.5	25.1±4.5	24.8±3.6	24.0±3.2	25.1±3.9	25.4±4.1	24.2±3.3
FEV ₁ , % [#]	60.8±23.9	64.3±19.1	56.2±17.8	66.4±19.4*	54.5±25.0	65.4±18.3	62.9±18.9	65.2±20.7
BEC, cells·μL ⁻¹ [¶]	533.0 (326.0)	538.0 (450.0)	338.0 (484.5)	550.0 (442.5)*	295.0 (304.0)	550.0 (430.0)*	480.0 (488.0)	567.0 (377.0)*
BEC ₁₅₀ , n (%) ⁺	15 (93.8)	122 (89.1)	26 (74.3)	107 (93.9)*	17 (81.0)	119 (90.8)	81 (87.1)	55 (93.2)
BEC ₃₀₀ , n (%) ⁺	12 (75.0)	100 (73.0)	20 (57.1)	88 (77.2)*	10 (47.6)	101 (77.1)*	62 (66.7)	49 (83.1)*
Sp-EOS, % [¶]	4.5 (13.8)	7.0 (32.0)	3.0 (21.5)	7.5 (32.0)	3.5 (34.5)	7.5 (31.2)	5.5 (25.2)	11.0 (34.5)
Sp-EOS _{2%} , n (%) ⁺	9 (64.3)	71 (64.0)	16 (59.3)	63 (65.6)	9 (56.2)	70 (64.8)	47 (63.5)	33 (66.0)
F _{ENO} , ppb [¶]	42.0 (31.0)	56.0 (69.5)	35.0 (72.5)	56.0 (61.5)*	36.5 (35.8)	56.0 (70.5)*	45.5 (71.2)	58.0 (58.5)
ACT, points [#]	15.8 (4.9)	16.1 (4.9)	15.3 (4.5)	16.6 (4.8)	15.0 (3.7)	16.3 (5.0)	15.6 (4.7)	16.9 (5.0)
EXA _{his} , events [¶]	0.0 (1.0)	1.0 (5.0)*	0.0 (5.5)	1.0 (3.0)	4.0 (13.0)	0.0 (3.0)*	1.0 (5.0)	0.0 (3.0)
Bude _{eq} , μg·day ⁻¹ [¶]	400.0 (290.0)	640.0 (250.0)	400.0 (297.0)	640.0 (240.0)	640.0 (352.0)	640.0 (240.0)	640.0 (280.0)	640.0 (240.0)
Pred _{eq} , mg·day ⁻¹ [¶]	0.0 (0.0)	0.0 (5.0)	0.0 (3.7)	0.0 (5.0)	0.0 (7.5)	0.0 (4.4)	2.0 (5.0)	0.0 (0.0)*
AR, n (%) ⁺	11 (68.8)	102 (74.5)	29 (82.9)	81 (71.1)	15 (71.4)	97 (74.0)	69 (74.2)	44 (74.6)
GR, n (%) ⁺	7 (43.8)	50 (36.5)	16 (45.7)	39 (34.2)	9 (42.9)	47 (35.9)	39 (41.9)	18 (30.5)
NP, n (%) ⁺	4 (25.0)	34 (24.8)	8 (22.9)	29 (25.4)	3 (14.3)	35 (26.7)	23 (24.7)	15 (25.4)

Data are presented as mean±SD or median (interquartile range) unless indicated otherwise. EXA-OCS Res, FEV₁ Res, ACT Res: response based on exacerbation and oral corticosteroid use, FEV₁ and ACT, respectively; Clin-Rem: clinical remission; Age_{diag}: age at asthma diagnosis; BMI: body mass index; FEV₁: predicted pre-bronchodilator forced expiratory volume in 1 s; BEC: blood eosinophil count; BEC₁₅₀ and BEC₃₀₀: patients with baseline BEC ≥150 and ≥300 cells·μL⁻¹, respectively; Sp-EOS: sputum eosinophils as a percentage; Sp-EOS_{2%}: patients with baseline Sp-EOS ≥2%; F_{ENO}: fractional exhaled nitric oxide; ACT: asthma control test score; EXA_{his}: recall exacerbation number during the previous year; Bude_{eq} and Pred_{eq}: budesonide and prednisolone equivalent doses, respectively; AR: allergic rhinitis; GR: gastroesophageal reflux; NP: nasal polyp. p-values were determined using: [#]: ANOVA for continuous variables; [¶]: rank sum test for non-parametric variables; ⁺: Fisher's exact test for categorical variables. *: p-values <0.05.

Discriminative power

Figure 2 illustrates the AUC of the seven models adjusted for age and sex for each treatment response domain and clinical remission. The analysis was conducted on the overall dataset, anti-IL-5/IL-5Rα users and anti-IL-4Rα users. For the treatment response domains (figure 2a–i), there were no differences in AUC between the three T2-inflammation factors across EXA-OCS-Res (all datasets: figure 2a–c), FEV₁-Res for the overall dataset and among anti-IL-5/IL-5Rα users (figure 2d, f), and ACT-Res for the overall dataset and among anti-IL-4Rα users (figure 2g, i). For FEV₁-Res among anti-IL-4Rα users, the F_{ENO} model (M3) had a higher AUC compared to the BEC model (M1) (AUC: 0.75 versus 0.62). Adding BEC or Sp-EOS into M3 did not improve the model performance (figure 2f). For ACT-Res among anti-IL-5/IL-5Rα users, Sp-EOS outperformed BEC and F_{ENO} in predicting ACT-Res (AUC: 0.91, 0.4 and 0.65, respectively, with all p-values from the DeLong test <0.05). However, adding BEC or F_{ENO} to the Sp-EOS model did not increase the AUC (figure 2h). Overall, the combination of the three factors did not significantly increase the AUC compared to models using individual factors. An exception was observed among anti-IL-5/IL-5Rα users and FEV₁-Res, where the combination of three factors (M7) improved the AUC of the Sp-EOS (M2) and F_{ENO} (M3) models (AUC: 0.92 versus 0.69 and 0.72, respectively) (figure 2e). For Clin-Rem, there were no differences in AUC across all models, whether individual or combined, in any dataset (figure 2j–l).

In the ROSE-adjusted analysis, differences emerged across analyses for treatment response domains. In the overall dataset, the BEC model (M1) demonstrated a higher AUC compared to the Sp-EOS model (M2) for EXA-OCS-Res (0.75 versus 0.61, p<0.05). However, adding Sp-EOS (M4) or F_{ENO} (M5) did not enhance the AUC of the model (supplementary figure 1Sa). The F_{ENO} model showed superior performance compared to the Sp-EOS model for both FEV₁-Res (AUC: 0.73 versus 0.56, p<0.05) and ACT-Res (AUC: 0.75 versus 0.60, p<0.05). Combining BEC or Sp-EOS with F_{ENO} did not improve the model's predictive performance (supplementary figure 1Sd and g). For anti-IL-5/IL-5Rα users, similar to the pre-over-sampling analysis, the Sp-EOS model had a superior AUC for predicting ACT-Res compared to the BEC and F_{ENO} models (AUC: 0.83 versus 0.59 and 0.59, respectively). However, adding BEC or F_{ENO} to the Sp-EOS model did not enhance the predictive power (supplementary figure 1Sh). There were no differences in predictive power among the three predictors in the analysis of EXA-OCS-Res or

TABLE 3 Multivariate regression and optimal cut-off for BEC, Sp-EOS and F_{ENO} in predicting treatment response

Outcome/predictor	All biologics					Anti-IL-5/IL-5R α users					Anti-IL-4R α users				
	OR (95% CI)	p-value	Cut-off	Se	Sp	OR (95% CI)	p-value	Cut-off	Se	Sp	OR (95% CI)	p-value	Cut-off	Se	Sp
EXA-OCS-Res															
BEC	0.96 (0.55–1.58)	0.864	≤ 538	0.50	0.50	0.66 (0.18–1.6)	0.438	≥ 638	0.56	0.60	1.05 (0.55–1.92)	0.885	≤ 470	0.54	0.55
Sp-EOS	1.19 (0.68–2.16)	0.543	≥ 6	0.58	0.50	1.31 (0.43–4.21)	0.620	≥ 16	0.51	0.75	1.1 (0.56–2.23)	0.787	≥ 6	0.51	0.60
F_{ENO}	1.54 (0.92–2.64)	0.106	≥ 45	0.59	0.69	2.4 (0.89–8.19)	0.109	≥ 51	0.66	0.60	1.37 (0.72–2.64)	0.335	≥ 44	0.53	0.55
FEV₁-Res															
BEC	1.47 (1–2.2)	0.055	≥ 480	0.61	0.60	1.76 (0.89–3.94)	0.121	≥ 638	0.59	0.70	1.25 (0.78–2.03)	0.343	≥ 350	0.59	0.60
Sp-EOS	1.29 (0.83–2.02)	0.263	≥ 7	0.53	0.56	0.94 (0.38–2.17)	0.879	≤ 24	0.55	0.57	1.31 (0.77–2.31)	0.338	≥ 5	0.53	0.60
F_{ENO}	1.8 (1.21–2.74)	0.004	≥ 45	0.63	0.66	0.85 (0.4–1.74)	0.657	≤ 70	0.61	0.60	2.34 (1.39–4.17)	0.002	≥ 43	0.69	0.68
ACT-Res															
BEC	1.44 (0.89–2.3)	0.13	≥ 427	0.68	0.67	1.03 (0.33–2.81)	0.960	≤ 674	0.53	0.50	1.75 (0.96–3.26)	0.069	≥ 312	0.67	0.67
Sp-EOS	1.15 (0.67–2.02)	0.622	≥ 7	0.52	0.56	0.03 (0–0.47)	0.075	≤ 36	0.79	0.75	1.83 (0.88–4.34)	0.127	≥ 4	0.58	0.58
F_{ENO}	2.15 (1.29–3.75)	0.005	≥ 44	0.62	0.65	0.55 (0.18–1.45)	0.241	≤ 73	0.64	0.60	3.6 (1.73–8.84)	0.002	≥ 39	0.72	0.73
Clin-Rem															
BEC	1.27 (0.89–1.85)	0.194	≥ 550	0.53	0.58	1.19 (0.66–2.33)	0.580	≥ 700	0.54	0.59	1.31 (0.85–2.1)	0.236	≥ 459	0.60	0.59
Sp-EOS	1.27 (0.88–1.84)	0.210	≥ 9	0.56	0.57	0.81 (0.43–1.48)	0.490	≤ 19	0.52	0.48	1.57 (0.98–2.58)	0.065	≥ 7	0.55	0.61
F_{ENO}	1.38 (0.98–1.97)	0.071	≥ 56	0.59	0.59	0.71 (0.4–1.24)	0.239	≤ 63	0.58	0.55	1.95 (1.23–3.28)	0.007	≥ 52	0.66	0.66
p-values <0.05 are indicated in bold. BEC: blood eosinophil count; Sp-EOS: sputum eosinophils as a percentage; F_{ENO} : fractional exhaled nitric oxide; OR (95% CI): odds ratios and 95% confidence intervals adjusted for age and sex for a 1-unit increase in the log-transformed predictor; cut-off: optimal cut point of raw values of the predictor estimated by the sensitivity–specificity equality criterion; Se and Sp: corresponding sensitivity and specificity of the identified cut-off; IL: interleukin; EXA-OCS-Res, FEV ₁ -Res, ACT-Res: response based on exacerbation and oral corticosteroid use, predicted pre-bronchodilator forced expiratory volume in 1 s (FEV ₁) and asthma control test score (ACT), respectively; Clin-Rem: clinical remission.															

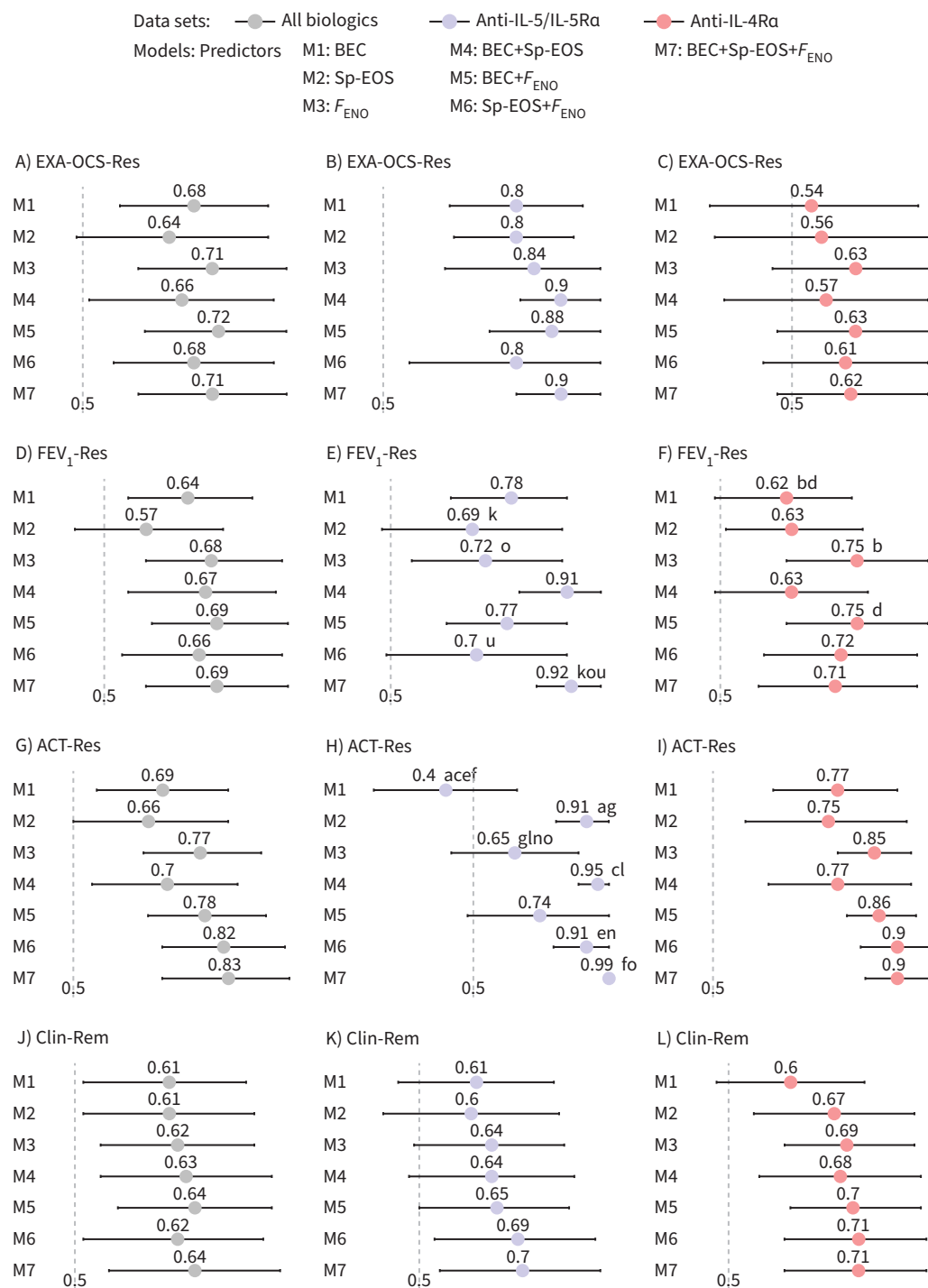


FIGURE 2 Area under the curve (AUC) and 95% confidence interval of the models predicting each response outcome. Datasets: overall data, anti-interleukin (IL)-5/IL-5Ra users and anti-IL-4Ra users. Model 1 (M1): outcome—BEC+covariates; Model 2 (M2): outcome—Sp-EOS+covariates; Model 3 (M3): outcome— F_{ENO} +covariates; Model 4 (M4): outcome—BEC+Sp-EOS+covariates; Model 5 (M5): outcome—BEC+ F_{ENO} +covariates; Model 6 (M6): outcome— F_{ENO} +Sp-EOS+covariates; Model 7 (M7): outcome—BEC+Sp-EOS+ F_{ENO} +covariates. Covariates were age and sex. Data are presented as the mean and 95% confidence intervals of the AUC of the receiver operating characteristic (ROC) curves. The vertical dashed grey line is the reference line for the AUC value of 0.5. Pairwise comparisons of AUC by DeLong test with p-value <0.05: a: M1 versus M2; b: M1 versus M3; c: M1 versus M4; d: M1 versus M5; e: M1 versus M6; f: M1 versus M7; g: M2 versus M3; h: M2 versus M4; i: M2 versus M5; j: M2 versus M6; k: M2 versus M7; l: M3 versus M4; m: M3 versus M5; n: M3 versus M6; o: M3 versus M7; p: M4 versus M5; q: M4 versus M6; r: M4 versus M7; s: M5 versus M6; t: M5 versus M7; u: M6

versus M7. EXA-OCS-Res: responder is defined as a reduction by $\geq 50\%$ in the annual exacerbation rate, or a reduction by $\geq 50\%$ in the maintenance oral corticosteroid (mOCS) dose, or remaining without exacerbations; FEV₁-Res: FEV₁ responder is defined as having a 12-month visit FEV₁ $\geq 80\%$, or an FEV₁ increase by ≥ 100 mL and $\geq 10\%$; ACT-Res: ACT responder is defined as having a 12-month visit ACT score ≥ 20 , or an ACT score increase by ≥ 3 points; Clin-Rem: clinical remission is defined as having no mOCS use and no exacerbations during the 12-month follow-up, plus meeting the criteria for FEV₁-Res and ACT-Res. BEC: blood eosinophil count; Sp-EOS: sputum eosinophils; F_{ENO} : fractional exhaled nitric oxide.

FEV₁-Res (supplementary figure 1Sb, e). For EXA-OCS-Res, combining all three factors in one model (M7) significantly increased the AUC compared to models with a single predictor (M1, M2, M3) (AUC: 0.96 *versus* 0.83, 0.76 and 0.82, respectively) (supplementary figure 1Sb). For FEV₁-Res, the model incorporating all three factors (M7, AUC=0.9) outperformed the F_{ENO} model (M2, AUC: 0.64) but was not superior to the BEC (M1) or Sp-EOS (M3) models (supplementary figure 1Se). For anti-IL-4R α users, the F_{ENO} model (M3) was superior to the BEC and Sp-EOS models for ACT-Res (AUC: 0.90 *versus* 0.77 and 0.71). However, combining other factors did not improve the performance of the F_{ENO} model (Figure 1Si). No differences in performance were observed between the seven models for EXA-OCS-Res (supplementary figure 1Sc). The F_{ENO} model (M3) outperformed the BEC model (M1) for FEV₁-Res (AUC: 0.73 *versus* 0.65). Combining BEC or Sp-EOS with F_{ENO} did not enhance the performance of the model (supplementary figure 1Sf). For the Clin-Rem outcome, there were no differences in predictive power between the BEC, Sp-EOS and F_{ENO} models in the overall datasets and among anti-IL-5/IL-5R α users (supplementary figure 1Sj, k), whereas F_{ENO} showed a higher AUC than BEC (AUC 0.76 *versus* 0.65, supplementary figure 1Si) in the anti-IL-4R α group. The model combining Sp-EOS and F_{ENO} (M6) increased the predictive power of the model with F_{ENO} alone (M3) in the anti-IL-5/IL-5R α group (AUC 0.89 *versus* 0.69, supplementary figure 1Sk). However, combining predictors did not improve the single predictor model in the anti-IL-5/IL-5R α group or across the entire dataset.

Discussion

Predicting the response to biologics and remission in SEA treatment will enhance effectiveness and cost-efficiency in personalised medicine. Previous discoveries of predictors of response were mostly based on secondary data analyses from RCTs, which selected patients for mAb therapy according to strict criteria [16–19]. However, asthma pathogenesis is highly heterogeneous, and few studies have investigated the predictors of treatment response and remission to biologics in real-life settings [12, 29–33]. Our study showed that the 1-year response rate to biologics in patients with SEA was relatively high and varied depending on outcome domains. Meanwhile, only one-third of patients with SEA fulfilled the requirements for Clin-Rem. The discriminative power of the predictors among the three T2 inflammation biomarkers also differed depending on outcome domains and mAbs used. T2 inflammation markers were less likely to predict outcomes in exacerbation and mOCS domains than in lung function and asthma control outcomes. Higher pre-treatment BEC was observed in individuals who responded to biologics, particularly among anti-IL-4R α users and for outcomes such as ACT-Res and Clin-Rem. However, when adjusted for covariates such as age and sex, this relationship no longer persisted. F_{ENO} was a predictor of treatment response in ACT and FEV₁ domains for anti-IL-4R α users. Analysis of the over-sampled data highlighted the relationship between predictors and treatment response. However, the association between T2 inflammation markers and Clin-Rem was weak in all analyses across groups, regardless of the type of biologics used. The combination of predictors did not significantly improve their predictive ability.

The concept of response to biologics treatment should be evaluated from multiple aspects [9–11]. Studies on mAb effects mostly relied on the reduction in exacerbation rate as the primary outcome [5]. However, asthma is heterogeneous, with many patients showing a response in one domain but not in others [12]. The frequency of exacerbations is directly proportional to the decline in lung function, which occurs at a faster rate in individuals aged <40 years [34]. For these individuals, rapid improvement in lung function to prevent irreversible lung remodeling should be a critical outcome. Recently, data from the International Severe Asthma Registry revealed that the rate of treatment response using the exacerbation domain was the highest (>80%), while response rates in other domains were <50%. Another real-world study reported response rates of <50% across all four response domains [35]. The current study showed the response rate to biological therapy using two domains, exacerbation and mOCS, as well as one domain (either FEV₁ or ACT), all >75%. This is because we also considered patients who had good pre-treatment conditions (no exacerbations, or high FEV₁ or ACT) and maintained these conditions throughout treatment as responders, rather than solely defining a response as an improvement in pre-treatment impairment. Given that conditions of patients with SEA often deteriorate gradually and irreversibly, maintaining any outcome

domain in a good state is clinically significant. The rates of achieving clinical remission have also been reported inconsistently. Although there has been consensus on the four criteria in the definition of Clin-Rem [13], specific thresholds for lung function and asthma control status vary between studies. Recent real-world studies have shown that remission rates in patients using biologics range from 19% to 32.1%, depending on the type of biologics [31, 33]. Our data indicate a relatively high Clin-Rem rate (ranging from 37% to 41%), suggesting that Clin-Rem is a feasible target for a substantial proportion of patients with SEA.

BEC is widely recognised as a predictor of biologics treatment efficacy. This understanding stems from *post hoc* analyses of RCTs comparing biologics to placebo across various BEC levels [15–18]. These analyses concluded that higher baseline BEC correlates with improved response. Consequently, Global Initiative for Asthma (GINA) recommends anti-IL-5/IL-5R α and anti-IL-4 α therapies for patients with high BEC (typically $>150 \text{ cells} \cdot \mu\text{L}^{-1}$) [1]. However, it remains uncertain whether this association persists in real-life patients with SEA who already present with elevated BEC before treatment. Some real-world studies have confirmed the association between higher BEC and better treatment response [12, 32] or clinical remission [31, 33] for biologic users. However, in our study, the association between BEC and treatment response was not as strong. While BEC was associated with ACT-Res and Clin-Rem in univariate regression, this association disappeared after adjusting for covariates. The discrepancy between our findings and prior studies may be attributed to several factors. First, the small sample size may have significantly impacted the estimates, especially in the presence of imbalanced outcome variables. When we analysed the over-sampled data, BEC was associated with EXA-OCS-Res and ACT-Res in anti-IL-4 α users. BEC is a skewed variable, and the correlation between BEC and eosinophilic airway inflammation is stronger at particularly high levels of BEC. Several previous studies have found a correlation between BEC and biological treatment responses, particularly when comparing groups with high BEC ($>300 \text{ cells} \cdot \mu\text{L}^{-1}$) to those with lower BEC levels [31, 32] or examining BEC doubling concentration [33]. In contrast, our analysis used log-transformed BEC as a continuous variable, which may explain the differing results.

Post hoc analyses of RCT data showed higher baseline F_{ENO} levels predicted better treatment response to dupilumab [20]. Real-life data indicated that patients with SEA with high F_{ENO} who did not respond to anti-IL-5/IL-5R α therapy achieved remission after transitioning to anti-IL-4R α [36]. In our study, F_{ENO} was associated with responses in FEV₁-Res and ACT-Res among anti-IL-4 α users, consistently observed in both original and over-sampled data. This highlights the importance of F_{ENO} as a predictor in anti-IL-4 therapy.

Sp-EOS, as a direct marker of eosinophilic airway inflammation, is less commonly used owing to its invasive nature and technical requirements. Two RCT analyses found Sp-EOS less predictive than BEC for anti-IL-5/IL-5R α treatment [37, 38]. In our study, higher Sp-EOS levels were observed in anti-IL-5/IL-5R α users with improved ACT scores, but multivariate analyses found no significant associations with treatment responses or remission, likely because of modest sample size and incomplete Sp-EOS data.

Several attempts have been made to combine potential predictors to improve predictive models for treatment response to biologics in patients with SEA [19, 39]. Combining the two criteria of BEC >150 and $F_{\text{ENO}} >25 \text{ ppb}$ could enhance the likelihood of response to treatment in patients with SEA using anti-IL-4R α [19]. However, no real-world study has evaluated the combination of all three T2 inflammation markers. In this study, combining the markers in pairs or using all three markers together did not significantly improve the predictive power compared to using only a single marker with the highest predictive power. This result only considered pre-treatment conditions and did not account for the variability of these markers during follow-up, possibly influencing the treatment response.

The findings should be interpreted within the study's strengths and limitations. This real-world study comprehensively examined multiple domains of treatment response using three T2 markers and their combinations. However, small sample sizes limited separate analyses for specific drugs among anti-IL-5/IL-5R α users. High response rates in certain domains (FEV₁, ACT) may bias prediction models, though this was addressed with the ROSE technique. The follow-up was limited to only 12 months, which may not fully capture the long-term effects of biological therapy. The predictive models employed only three markers and their combinations, without considering interactions with other confounding factors. The results should not be extended to all biological treatments because the study did not include other mAbs, such as anti-IgE or anti-TSLP. Potential bias from site differences in this multicentre cohort was minimised through standardized protocols and rigorous training.

We conclude that in this study, pre-treatment BEC and Sp-EOS do not have a clear association with the treatment response to T2-biologics in SEA patients. Pre-treatment F_{ENO} better predicts specific responses,

particularly with anti-IL-4 therapy. Combining T2 biomarkers does not significantly improve predictive power compared with the best single marker.

Provenance: Submitted article, peer reviewed.

This study is registered a www.clinicaltrials.gov as NCT05164939.

Ethics statement: The Institutional Review Board at each study site approved the study protocol and registered it on ClinicalTrials.gov (registration number NCT05164939).

Conflict of interest: W-J. Song serves as the Chief Editor of this journal. P. Bhavsar has received grants from GSK and MSD for investigator-initiated studies, as well as honoraria from GSK and AstraZeneca; and is an associate editor of this journal. I. Adcock has received grants from GSK, Sanofi, UKRI and EPSRC for investigator-initiated studies, along with honoraria from GSK and AstraZeneca. K.F. Chung has received grants from MRC, GSK, Merck, NIEHS and EPSRC for investigator-initiated studies, and honoraria from GSK, Novartis and AstraZeneca. All other authors declare no conflicts of interest.

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