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Original Article

Early Biomarker Trajectories After Biologic Initiation as Predictors of Remission in Severe Asthma

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ABSTRACT

Background: Severe asthma remains difficult to control in a substantial proportion of patients despite biologic therapy, and clinicians lack validated early indicators of long-term remission. Objective biomarker trajectories may provide earlier prognostic information than symptom response alone. Objective: To determine whether early changes in blood eosinophils, fractional exhaled nitric oxide, and asthma symptom scores during the first 12 weeks after biologic initiation predict 12-month clinical remission in adults with severe asthma. Methods: This retrospective cohort study included 102 adults with severe asthma who initiated first-line biologic therapy between January 2021 and December 2022 at a tertiary care hospital in the Islamabad-Rawalpindi region, with follow-up reviewed through December 2023. Early biomarker and symptom trajectories were assessed at weeks 4, 8, and 12. Clinical remission at 12 months was defined as no exacerbations, no maintenance oral corticosteroid use, and controlled symptoms. Multivariable logistic regression adjusted for age, sex, baseline biomarker values, biologic type, and baseline oral corticosteroid use. Results: Clinical remission was achieved by 38 patients (37.3%). Week 8 FeNO reduction was the strongest independent predictor of remission (aOR 1.92 per 10% reduction, 95% CI 1.41–2.61, p<0.001), followed by week 4 eosinophil reduction (aOR 1.41 per 10% reduction, 95% CI 1.18–1.68, p=0.002). Week 8 symptom-score improvement did not remain independently significant after biomarker adjustment (p=0.21). The combined biomarker model showed good discrimination (c-statistic 0.84, 95% CI 0.76–0.92). Conclusion: Early FeNO and eosinophil reductions were independently associated with 12-month remission after biologic initiation in severe asthma. These findings support early biomarker-based prognostic assessment but require prospective validation before use in treatment-switching decisions. Keywords: asthma; biological products; biomarkers; eosinophils; fractional exhaled nitric oxide; remission induction; retrospective studies.

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INTRODUCTION

Severe asthma remains a clinically challenging disease phenotype characterized by persistent symptoms, recurrent exacerbations, impaired functional status, and frequent exposure to systemic corticosteroids despite optimized high-dose inhaled therapy. The introduction of biologic therapies has substantially changed the management of severe asthma, particularly for patients with type 2 inflammatory features such as elevated blood eosinophils, increased fractional exhaled nitric oxide, allergic sensitization, or oral corticosteroid-dependent disease. However, response to biologic therapy is heterogeneous, and clinicians often face uncertainty during the early post-initiation period regarding whether a patient is likely to achieve sustained clinical benefit. In routine practice, biologic response is commonly reassessed after several months of therapy, but this delay may prolong exposure to ineffective treatment, increase cumulative morbidity, maintain corticosteroid burden, and defer timely optimization of care. Therefore, identifying early post-treatment signals that can predict later remission has become an important clinical and research priority in severe asthma management (1, 2).

The biological rationale for early response monitoring is based on the mechanistic effects of currently available biologics. Anti-interleukin-5 and anti-interleukin-5 receptor therapies primarily target eosinophilic inflammation, anti-interleukin-4/interleukin-13 pathway inhibition suppresses type 2 inflammatory signalling and nitric oxide production, while anti-IgE therapy modulates allergic inflammatory activity. These targeted effects suggest that objective biomarkers may change earlier than composite clinical endpoints such as exacerbation prevention, withdrawal of maintenance oral corticosteroids, and sustained symptom control. Blood eosinophil count is an accessible systemic marker of eosinophilic inflammation and remains widely used in severe asthma phenotyping and treatment selection. Fractional exhaled nitric oxide reflects type 2 airway inflammation and may provide complementary information about airway inflammatory activity that is not fully captured by peripheral eosinophil counts. Symptom scores, although clinically essential, may be influenced by multiple non-inflammatory factors, including obesity, mood, sleep disturbance, dysfunctional breathing, comorbidity burden, and patient perception of disease severity (3–6).

Previous studies have demonstrated that baseline biomarkers can help identify patients more likely to respond to specific biologic therapies. Elevated FeNO and blood eosinophilia have been associated with exacerbation risk, type 2 inflammatory activity, and biologic treatment response in moderate-to-severe and severe asthma populations. However, baseline prediction alone is insufficient for day-to-day clinical decision-making after treatment initiation. Clinicians need to determine whether early changes after biologic exposure provide prognostic information beyond pretreatment phenotype. A patient who demonstrates a marked FeNO reduction or rapid eosinophil suppression within the first few weeks of therapy may have a different probability of achieving long-term remission than a patient whose inflammatory biomarkers remain persistently elevated. Despite this clinical relevance, most available studies have evaluated baseline predictors, single biomarkers, or individual biologic classes rather than comparing serial biomarker trajectories within the same real-world cohort (7–10).

Clinical remission is increasingly recognized as a meaningful therapeutic target in severe asthma because it reflects a more stringent outcome than partial response or short-term symptom improvement alone. A remission-based endpoint combines sustained absence of exacerbations, elimination of maintenance oral corticosteroid use, and achievement of controlled symptoms. This composite approach better reflects the long-term goals of biologic therapy, but it also creates uncertainty regarding which early treatment signals are most informative. Early symptom improvement may be clinically reassuring, but it may not independently capture suppression of airway inflammation. Conversely, objective biomarker trajectories may indicate early target engagement before full clinical stabilization becomes apparent. Direct comparison of early FeNO, eosinophil, and symptom-score trajectories is therefore necessary to determine whether biomarker-guided monitoring can improve early prognostic stratification in biologic-treated severe asthma (11–14).

This question is particularly important in real-world practice, where biologic selection, treatment access, follow-up intensity, adherence, comorbidity burden, and documentation quality may differ from controlled trial settings. Although biologics have demonstrated substantial clinical benefit in severe asthma, limited evidence exists on whether changes in FeNO, blood eosinophils, and symptom scores during the first 4 to 12 weeks independently predict 12-month clinical remission within the same patient population. Establishing such associations could support earlier and more structured reassessment by helping clinicians identify likely responders and patients who may require adherence review, phenotype reassessment, comorbidity optimization, or consideration of alternative treatment strategies. However, because retrospective data can establish prognostic association but not prove the benefit of biomarker-guided switching, any proposed clinical application requires prospective validation before implementation as a treatment algorithm (15, 16).

Therefore, this retrospective cohort study was conducted to determine whether early biomarker trajectories after biologic initiation predict 12-month clinical remission among adults with severe

asthma. The population comprised adults with severe asthma initiating first-line biologic therapy; the exposure of interest was early change in blood eosinophil count, FeNO, and asthma symptom score during the first 12 weeks after biologic initiation; the comparator was patients with smaller or absent early biomarker improvement; and the primary outcome was clinical remission at 12 months. The primary objective was to assess whether early reductions in FeNO and blood eosinophils independently predicted 12-month clinical remission after adjustment for demographic factors, baseline biomarker values, biologic type, and baseline oral corticosteroid use. The secondary objective was to compare the relative predictive contribution of biomarker and symptom trajectories to identify an early monitoring profile that may support clinically meaningful prognostic assessment in severe asthma.

MATERIALS AND METHODS

This study was designed as a retrospective cohort study using routinely collected data from electronic health records and the respiratory medicine database of a tertiary care hospital serving the Islamabad-Rawalpindi metropolitan region of Pakistan. The study included adults with severe asthma who initiated first-line biologic therapy between January 2021 and December 2022. Follow-up records were reviewed through December 2023 to allow complete ascertainment of 12-month clinical outcomes after biologic initiation. This distinction between biologic initiation period and follow-up review period was maintained throughout the analysis to ensure consistency between cohort entry and outcome assessment. The retrospective cohort design was appropriate because biomarker exposure status, treatment details, and clinical outcomes had already been documented as part of routine severe asthma care before the research analysis was conducted.

The source population consisted of patients aged 18 years or older with physician-confirmed severe asthma managed in the hospital's severe asthma clinic. Severe asthma was verified from clinical records documenting persistent uncontrolled disease despite optimized high-dose inhaled corticosteroid-based therapy and specialist assessment consistent with severe asthma criteria. Diagnostic confirmation was supported by documented reversible airflow obstruction or airway hyperresponsiveness in the medical record. Patients were eligible if they initiated a first-line biologic during the defined inclusion period and had available baseline assessment immediately before the first biologic dose, follow-up biomarker and symptom-score measurements at weeks 4, 8, and 12, and complete 12-month outcome data. Eligible biologic agents included anti-IgE, anti-interleukin-5/interleukin-5 receptor, and anti-interleukin-4/interleukin-13 pathway therapies prescribed according to the treating physician's clinical assessment, patient phenotype, and local treatment availability.

Patients were excluded if they were current smokers or had a smoking history exceeding 10 pack-years, had active malignancy, were pregnant during the follow-up period, received concomitant systemic immunosuppressive therapy other than oral corticosteroids prescribed for asthma, had incomplete required biomarker or symptom-score measurements at baseline or follow-up, or had missing 12-month outcome data. These criteria were applied to reduce confounding from non-asthma inflammatory states and to preserve the validity of trajectory-based analysis. Consecutive potentially eligible records were screened to minimize selection bias. Of 157 screened patients, 102 met the final eligibility criteria and were included in the analytical cohort. Reasons for exclusion were documented during screening, including incomplete biomarker data, missing 12-month follow-up, and other eligibility exclusions, to allow transparent reporting of cohort assembly in the final manuscript flow diagram.

Data were extracted independently by two trained respiratory research fellows using a structured extraction proforma developed before analysis. The proforma was pilot tested on 10 randomly selected records to ensure consistency, completeness, and reproducibility of extraction procedures. Extracted variables included age, sex, body mass index, biologic agent, biologic administration record, baseline oral corticosteroid dependence, inhaled corticosteroid dose category, nasal polyposis, allergic rhinitis, baseline blood eosinophil count, baseline FeNO, baseline asthma symptom score, and repeat biomarker

and symptom-score values at weeks 4, 8, and 12. Blood eosinophil count was recorded in cells/μL from complete blood count reports, and FeNO was recorded in parts per billion from clinic-based respiratory assessments. Biologic exposure and treatment continuation were verified using hospital administration records and clinic documentation where available.

The primary exposure variables were early trajectories of blood eosinophil count, FeNO, and asthma symptom score during the first 12 weeks after biologic initiation. For each biomarker, both absolute change and percentage change from baseline were calculated at weeks 4, 8, and 12. Percentage change was calculated using the formula: baseline value minus follow-up value, divided by baseline value, multiplied by 100. The primary candidate predictors were percentage reduction in blood eosinophils and percentage reduction in FeNO at clinically relevant early follow-up points. Symptom-score improvement was evaluated as a clinical trajectory variable, but interpretation accounted for the subjective nature of patient-reported symptom control. Where asthma control was documented using ACQ, ACQ values were retained for longitudinal analysis. Where ACT was used, ACT-based control status was used for remission classification according to accepted control thresholds. ACT and ACQ values were not treated as directly interchangeable unless the same instrument was available across serial time points for the same patient; this approach was used to avoid bias from unvalidated conversion between symptom instruments.

The primary outcome was clinical remission at 12 months after biologic initiation. Clinical remission was operationally defined as meeting all three criteria during the 12-month follow-up assessment period: no exacerbation requiring systemic corticosteroids during the 12 months after biologic initiation, no maintenance oral corticosteroid use at the 12-month assessment, and controlled asthma symptoms at 12 months, defined as ACT ≥20 or ACQ <1.5 according to the instrument documented in the record. An exacerbation was defined as acute worsening of asthma requiring systemic corticosteroids for at least three days or a clearly documented equivalent physician-treated exacerbation. Oral corticosteroid status was verified from physician notes and medication records where available. Remission status was independently adjudicated by two reviewers blinded to early biomarker trajectories, with disagreement resolved by a senior pulmonologist.

Several procedures were used to reduce bias and improve internal validity. Consecutive sampling was used to reduce selection bias. Standardized extraction forms and predefined operational definitions were used to reduce information bias. Outcome adjudicators were blinded to early biomarker trajectories to reduce classification bias.

Baseline variables were extracted before final outcome classification. Because the study objective depended on complete serial trajectory assessment, patients missing required biomarker or outcome data were excluded from the primary analysis rather than imputed. This complete-case approach was selected to preserve internal consistency of repeated biomarker comparisons, but the number and reasons for exclusions were retained for transparent reporting. Baseline characteristics of included patients and excluded patients should be compared in supplementary analysis where source data permit, particularly to assess whether patients with complete biomarker follow-up differed systematically from those excluded for incomplete records.

The sample size rationale was based on detecting a moderate association between early biomarker change and later remission using a two-sided alpha of 0.05 and 80% power. A minimum sample of 84 patients was considered necessary, and a target of approximately 100 patients was set to maintain adequate precision after eligibility screening. The final analytical cohort included 102 patients, of whom 38 achieved 12-month clinical remission. Because the number of remission events was modest, multivariable modelling was planned and interpreted with attention to parsimony, events per model parameter, and clinical plausibility of covariate inclusion.

Statistical analysis was performed using SPSS version 26.0. Continuous variables were summarized as mean with standard deviation when approximately normally distributed and as median with

interquartile range when distributional assumptions were not met. Categorical variables were summarized as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test and visual inspection of histograms. Baseline characteristics were compared between patients who achieved 12-month remission and those who did not using independent-samples t tests or Mann-Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. Baseline comparisons were planned to include age, sex, body mass index, baseline eosinophil count, baseline FeNO, asthma symptom score, oral corticosteroid dependence, nasal polyposis, allergic rhinitis, and biologic type.

Early biomarker trajectories were compared between remission and non-remission groups using repeated-measures analysis of variance to assess time effects, group effects, and group-by-time interaction effects. Between-group differences at individual follow-up points were reported with mean differences, 95% confidence intervals, and p-values where appropriate.

Multivariable logistic regression was used to estimate the independent association between early biomarker changes and 12-month clinical remission. Adjusted odds ratios with 95% confidence intervals were calculated for percentage reduction in FeNO, percentage reduction in blood eosinophils, and symptom-score improvement at clinically relevant early time points. The primary adjusted model included age, sex, baseline biomarker values, biologic type, and baseline oral corticosteroid use. Biologic type was included as a categorical covariate, and baseline biomarker values were retained to distinguish treatment-emergent change from pretreatment inflammatory burden.

Before final model interpretation, collinearity among predictors was assessed using variance inflation factors and correlation matrices. Because several biomarkers and time points were examined, findings were interpreted according to effect size, confidence interval width, biological plausibility, and consistency across analyses rather than p-values alone. Receiver operating characteristic curve analysis was used to evaluate the discriminatory performance of individual early predictors and combined biomarker models for 12-month remission.

Model performance was summarized using the c-statistic with 95% confidence interval. Where clinically interpretable thresholds were identified, sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index were reported. Calibration was assessed using observed-versus-predicted agreement and calibration statistics where applicable. Internal validation using resampling methods was considered to evaluate optimism in model performance. Statistical significance was set at $p \leq 0.05$ for primary analyses.

Ethical approval was obtained before data extraction, and the requirement for individual informed consent was waived because the study used retrospective, de-identified clinical records without direct patient contact or intervention. Patient confidentiality was maintained by replacing medical record numbers with unique study identifiers before analysis. Extracted data were stored in a password-protected database accessible only to the study team. Data cleaning decisions, eligibility screening, variable coding, outcome adjudication, and statistical syntax were documented to improve auditability and reproducibility. The study was conducted in accordance with ethical principles for human observational research. No external funding was received, and no conflicts of interest were declared.

RESULTS

A total of 157 patients with severe asthma who initiated biologic therapy during the eligibility period were screened. After applying the predefined eligibility criteria, 102 patients were included in the final analysis, representing 65.0% of the screened population. Fifty-five patients were excluded, mainly because of incomplete biomarker data at required follow-up points or missing 12-month outcome data. The final analytical cohort included only patients with complete baseline, week 4, week 8, week 12, and 12-month follow-up data.

Table 1. Cohort Screening and Eligibility Flow

Screening Category	n	%
Patients screened from severe asthma database	157	100.0
Excluded from analysis	55	35.0
Incomplete biomarker data at required time points	31	19.7
Missing 12-month follow-up data	14	8.9
Other predefined eligibility exclusions	10	6.4
Final analytical cohort	102	65.0

The mean age of the included patients was 47.3 ± 11.8 years, and 62 patients were female, accounting for 60.8% of the cohort. The mean body mass index was 28.4 ± 5.2 kg/m². Baseline inflammatory burden was high, with a mean blood eosinophil count of 510 ± 290 cells/μL and mean FeNO of 62 ± 28 ppb. Baseline asthma control was poor, as reflected by a mean ACQ score of 2.9 ± 0.9. Oral corticosteroid dependence was present in 47 patients, representing 46.1% of the cohort. Dupilumab was the most frequently prescribed biologic, used in 44 patients, followed by benralizumab in 31, mepolizumab in 19, and omalizumab in 8 patients.

Table 2. Baseline Demographic and Clinical Characteristics of the Study Cohort

Characteristic	Value, N=102
Age, mean ± SD, years	47.3 ± 11.8
Female sex, n (%)	62 (60.8)
Male sex, n (%)	40 (39.2)
Body mass index, mean ± SD, kg/m²	28.4 ± 5.2
Baseline blood eosinophils, mean ± SD, cells/μL	510 ± 290
Baseline FeNO, mean ± SD, ppb	62 ± 28
Baseline ACQ score, mean ± SD	2.9 ± 0.9
Oral corticosteroid dependent at baseline, n (%)	47 (46.1)
Nasal polyposis, n (%)	31 (30.4)
Allergic rhinitis, n (%)	58 (56.9)
Dupilumab, n (%)	44 (43.1)
Benralizumab, n (%)	31 (30.4)
Mepolizumab, n (%)	19 (18.6)
Omalizumab, n (%)	8 (7.8)

Abbreviations: ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; SD, standard deviation.

Early biomarker trajectories showed progressive improvement during the first 12 weeks after biologic initiation. Mean blood eosinophil reduction increased from 54 ± 22% at week 4 to 62 ± 21% at week 8 and 68 ± 19% at week 12. FeNO reduction also increased over time, from 38 ± 24% at week 4 to 45 ± 23% at week 8 and 53 ± 22% at week 12. Symptom improvement followed the same direction, with mean ACQ improvement increasing from 1.0 ± 0.7 points at week 4 to 1.4 ± 0.8 points at week 8 and 1.7 ± 0.9 points at week 12.

Table 3. Early Biomarker and Symptom Trajectories During the First 12 Weeks

Variable	Week 4	Week 8	Week 12
Blood eosinophil reduction, mean ± SD, %	54 ± 22	62 ± 21	68 ± 19
FeNO reduction, mean ± SD, %	38 ± 24	45 ± 23	53 ± 22
ACQ improvement, mean ± SD, points	1.0 ± 0.7	1.4 ± 0.8	1.7 ± 0.9

Abbreviations: ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; SD, standard deviation.

At 12 months after biologic initiation, 38 patients achieved clinical remission, corresponding to a remission rate of 37.3%. The remaining 64 patients, representing 62.7% of the cohort, did not achieve remission. Among non-remitters, 28 patients continued to require oral corticosteroids, 22 experienced at least one exacerbation requiring systemic corticosteroids, and 14 had persistently uncontrolled symptoms despite absence of the other remission-failure components. These findings indicate that persistent corticosteroid requirement was the most frequent barrier to achieving remission.

Table 4. Twelve-Month Clinical Remission Status and Components of Non-Remission

Outcome	n	%
Achieved clinical remission	38	37.3
Did not achieve clinical remission	64	62.7
Required oral corticosteroids	28	27.5
Experienced ≥1 exacerbation	22	21.6
Uncontrolled symptoms only	14	13.7

Remission rates varied numerically across biologic agents, although the difference was not statistically significant. Dupilumab showed the highest remission proportion, with 20 of 44 patients achieving remission. Remission occurred in 9 of 31 patients receiving benralizumab, 6 of 19 receiving mepolizumab, and 3 of 8 receiving omalizumab. The overall comparison across biologic classes was not statistically significant, indicating that the observed differences should be interpreted cautiously and not as evidence of comparative efficacy.

Table 5. Twelve-Month Remission According to Biologic Agent

Biologic Agent	Total Treated, n	Achieved Remission, n (%)	Did Not Achieve Remission, n (%)	p-value
Dupilumab	44	20 (45.5)	24 (54.5)	
Benralizumab	31	9 (29.0)	22 (71.0)	
Mepolizumab	19	6 (31.6)	13 (68.4)	
Omalizumab	8	3 (37.5)	5 (62.5)	
Overall comparison	102	38 (37.3)	64 (62.7)	0.34

Patients who achieved remission demonstrated substantially greater early biomarker improvement than those who did not. At week 4, mean blood eosinophil reduction was 71 ± 15% among remitters compared with 42 ± 18% among non-remitters, showing a 29-percentage-point difference between groups. At week 8, mean FeNO reduction was 58 ± 20% in remitters and 29 ± 22% in non-remitters, again showing a 29-percentage-point difference. Symptom improvement was also greater among remitters, with ACQ improving by 2.2 ± 0.7 points at week 8 compared with 0.9 ± 0.6 points among non-remitters. By week 12, remitters continued to show stronger biomarker and symptom improvement, with eosinophil reduction of 83%, FeNO reduction of 72%, and ACQ improvement of 2.7 points, compared with 51%, 35%, and 1.2 points, respectively, among non-remitters.

Table 6. Early Biomarker and Symptom Differences by Twelve-Month Remission Status

Variable	Remission Group	Non-Remission Group	Mean Difference	p-value
Week 4 eosinophil reduction, mean ± SD, %	71 ± 15	42 ± 18	29 percentage points	<0.001
Week 8 FeNO reduction, mean ± SD, %	58 ± 20	29 ± 22	29 percentage points	<0.001
Week 8 ACQ improvement, mean ± SD, points	2.2 ± 0.7	0.9 ± 0.6	1.3 points	<0.001
Week 12 eosinophil reduction, %	83	51	32 percentage points	—
Week 12 FeNO reduction, %	72	35	37 percentage points	—
Week 12 ACQ improvement, points	2.7	1.2	1.5 points	—

Abbreviations: ACQ, Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; SD, standard deviation.

Note: Week 12 subgroup standard deviations were not available in the provided aggregate data; therefore, p-values for week 12 comparisons should be calculated from the raw dataset before final submission.

In multivariable logistic regression, week 8 FeNO reduction was the strongest independent predictor of 12-month clinical remission. Each additional 10% reduction in FeNO at week 8 was associated with nearly two-fold higher odds of remission after adjustment for age, sex, baseline biomarker values, biologic type, and baseline oral corticosteroid use. Week 4 blood eosinophil reduction was also independently predictive, with each additional 10% reduction associated with 41% higher odds of remission. Week 8 ACQ improvement was significant in unadjusted group comparisons but did not remain independently significant after adjustment for objective biomarker changes. Age, sex, and baseline oral corticosteroid use were not statistically significant predictors in the adjusted model. The

combined model including week 8 FeNO reduction and week 4 eosinophil reduction achieved a c-statistic of 0.84, indicating good discriminatory performance for 12-month remission.

Table 7. Multivariable Logistic Regression for Prediction of Twelve-Month Clinical Remission

Predictor	Adjusted Odds Ratio	95% CI	p-value
Week 4 eosinophil reduction, per 10% increase	1.41	1.18–1.68	0.002
Week 8 FeNO reduction, per 10% increase	1.92	1.41–2.61	<0.001
Week 8 ACQ reduction, per 0.5-point improvement	1.12	0.94–1.33	0.21
Age, per 10-year increase	0.96	0.77–1.20	0.72
Female sex vs male	1.18	0.62–2.24	0.62
Baseline oral corticosteroid use	0.63	0.35–1.13	0.12
Combined biomarker model discrimination	c-statistic 0.84	0.76–0.92	—

Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval; FeNO, fractional exhaled nitric oxide.

Model adjustment: Adjusted for age, sex, baseline biomarker values, biologic type, and baseline oral corticosteroid use.

Overall, the results show that 12-month remission was achieved in slightly more than one-third of patients with severe asthma receiving biologic therapy. Greater early reduction in objective type 2 inflammatory biomarkers, particularly FeNO at week 8 and blood eosinophils at week 4, was strongly associated with later remission. Although symptom improvement was more pronounced among remitters in unadjusted comparisons, it did not independently predict remission after accounting for biomarker trajectories. These findings suggest that early objective biomarker monitoring may provide clinically meaningful prognostic information during the first weeks after biologic initiation.

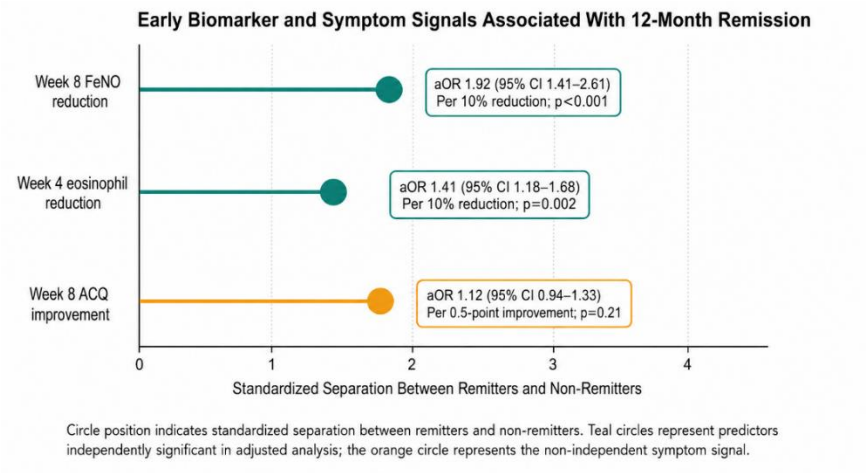

Figure 1 Early biomarker and symptom signals associated with 12-month remission.

The figure shows the degree of separation between remitters and non-remitters for the principal early response variables. Week 8 FeNO reduction and week 4 eosinophil reduction demonstrated strong separation between outcome groups and remained independently associated with 12-month remission in adjusted analysis. In contrast, although week 8 ACQ improvement showed marked between-group separation, it did not retain independent significance after adjustment for biomarker trajectories.

DISCUSSION

In this retrospective cohort of 102 adults with severe asthma initiating first-line biologic therapy, 37.3% achieved clinical remission at 12 months, defined by absence of exacerbations, absence of maintenance oral corticosteroid use, and controlled symptoms. This remission proportion is clinically plausible for a real-world severe asthma population and supports the relevance of remission as a stringent but achievable treatment target. The observed remission rate also reinforces the heterogeneity of biologic response in severe asthma, as nearly two-thirds of patients failed to meet the full remission definition

despite receiving targeted therapy. Persistent oral corticosteroid requirement was the most frequent barrier to remission, followed by exacerbation occurrence and uncontrolled symptoms, suggesting that remission failure in biologic-treated severe asthma is not driven by a single clinical domain but by overlapping inflammatory, treatment-response, and disease-control factors (17).

The principal finding of this study was that early FeNO reduction at week 8 was the strongest independent predictor of 12-month clinical remission. Each additional 10% reduction in FeNO at week 8 was associated with substantially higher odds of remission after adjustment for age, sex, baseline biomarker values, biologic type, and baseline oral corticosteroid use. This finding is biologically coherent because FeNO reflects type 2 airway inflammatory activity and is closely linked to interleukin-4 and interleukin-13 signalling within the airway epithelium. A marked decline in FeNO after biologic initiation may therefore indicate early suppression of airway type 2 inflammation, which may precede or accompany later clinical stabilization. Importantly, the present findings suggest that dynamic change in FeNO after treatment initiation may provide more clinically useful prognostic information than baseline biomarker elevation alone, although this interpretation requires prospective validation before being translated into switching algorithms (18, 19).

Early blood eosinophil reduction at week 4 also independently predicted 12-month remission, although its adjusted effect size was smaller than that observed for week 8 FeNO reduction. This supports the concept that rapid eosinophil suppression represents early target engagement, particularly among patients receiving anti-interleukin-5/interleukin-5 receptor or type 2 pathway-directed biologics. The finding that eosinophil reduction was predictive as early as week 4 is clinically important because blood eosinophil count is inexpensive, widely available, and routinely measured in severe asthma care. However, blood eosinophils reflect systemic inflammatory activity and may not fully capture airway inflammation in all patients. Therefore, the combined interpretation of FeNO and eosinophil trajectories may be more informative than reliance on either biomarker alone, particularly in patients with discordant systemic and airway inflammatory signals (20, 21).

Although week 8 ACQ improvement was greater among patients who achieved remission than among non-remitters, symptom improvement did not retain independent significance after adjustment for objective biomarker changes. This finding should not be interpreted as evidence that symptom monitoring is unimportant. Rather, it suggests that early symptom improvement alone may be less specific as a prognostic marker of 12-month remission because patient-reported asthma control can be influenced by factors beyond airway inflammation, including obesity, anxiety, depression, sleep disturbance, dysfunctional breathing, deconditioning, rhinosinusitis, and patient perception of illness. Symptoms remain essential for clinical assessment and patient-centred care, but the present findings indicate that objective biomarker trajectories may provide stronger independent prognostic value during the early biologic-treatment period (22, 23).

The numerically higher remission proportion observed among patients receiving dupilumab compared with benralizumab, mepolizumab, and omalizumab should be interpreted cautiously. The study was not powered for comparative effectiveness between biologic agents, and subgroup sizes were modest, particularly for omalizumab. In addition, biologic selection in real-world practice is influenced by baseline phenotype, biomarker profile, comorbidities, prior treatment history, drug availability, and physician judgment, creating potential confounding by indication. Therefore, the observed differences across biologic classes should be considered exploratory and should not be used to infer superiority of one biologic over another. Larger prospective comparative studies with adequate adjustment for baseline phenotype and treatment-selection factors are required to evaluate biologic-specific remission probabilities (24).

The findings have practical implications for severe asthma monitoring. A week 8 FeNO reduction and a week 4 eosinophil reduction may help identify patients more likely to achieve 12-month remission, particularly when both biomarkers show early improvement. Conversely, minimal improvement in these

biomarkers may prompt clinicians to review adherence, inhaler technique, comorbidities, phenotype accuracy, ongoing allergen or occupational exposure, and appropriateness of biologic selection. However, this study does not prove that changing or switching biologic therapy at week 8 improves outcomes. The data support early prognostic stratification, not immediate treatment-switching decisions. Any biomarker-guided escalation or switching strategy should be tested prospectively before routine clinical implementation.

This study has several strengths. It addresses a clinically relevant question in a real-world severe asthma population and evaluates remission as a meaningful composite endpoint rather than relying only on exacerbation reduction or symptom change. The use of serial biomarker measurements at clinically relevant early time points allowed assessment of post-treatment trajectories rather than baseline predictors alone. Outcome adjudication by reviewers blinded to early biomarker trajectories reduced classification bias, and adjustment for key clinical covariates strengthened the interpretation of independent associations. The combined biomarker model demonstrated good discriminatory performance, suggesting that early objective biomarker monitoring may have practical prognostic utility if validated in independent cohorts (25).

Several limitations should also be acknowledged. The retrospective design limits causal inference and creates potential for residual confounding. Patients with incomplete biomarker measurements were excluded, which may have introduced selection bias if those patients differed systematically from included patients in adherence, disease severity, access to care, or follow-up consistency. The single-centre setting may limit generalizability to other healthcare systems or populations with different biologic access, documentation practices, and treatment pathways. The modest number of remission events limited the complexity of multivariable modelling and increased the risk of model overfitting. Although adjustment was performed for important covariates, unmeasured confounding by biologic selection, adherence, comorbid disease burden, and environmental exposure may remain.

Additional limitations relate to measurement and outcome definition. Symptom assessment depended on documented clinical instruments, and ACT and ACQ are not directly interchangeable without validated conversion. The final analysis should therefore preserve instrument-specific interpretation or perform sensitivity analyses where both tools are used. Lung function was not included as a remission component, although some remission definitions incorporate spirometric stability or improvement. The study also did not include airway-specific inflammatory markers such as sputum eosinophils, periostin, IL-6, or other molecular biomarkers that may refine prediction among patients with discordant FeNO and blood eosinophil responses. Finally, although the combined model showed good discrimination, full predictive-model reporting requires calibration, internal validation, and externally validated cutoffs before clinical use (26, 27).

Future research should prospectively validate early FeNO and eosinophil trajectory thresholds in larger, multicentre cohorts. Studies should evaluate whether biomarker-guided reassessment at week 8 improves patient outcomes compared with conventional response assessment after several months of therapy. Future models should incorporate clinical variables, comorbidities, adherence measures, lung function, exacerbation history, oral corticosteroid burden, and airway-specific biomarkers to determine whether a multimodal prediction approach improves calibration and clinical usefulness. Randomized or pragmatic trials comparing standard monitoring with early biomarker-guided optimization would provide stronger evidence on whether early trajectory-based decision-making can improve remission rates, reduce corticosteroid exposure, and avoid prolonged ineffective biologic therapy.

CONCLUSION

In this retrospective cohort study of adults with severe asthma initiating biologic therapy, early objective biomarker trajectories were significantly associated with 12-month clinical remission. Greater FeNO reduction at week 8 was the strongest independent predictor of remission, while blood eosinophil

reduction at week 4 also showed independent prognostic value. Although symptom improvement was greater among patients who achieved remission, it did not remain independently predictive after adjustment for biomarker changes. These findings suggest that early FeNO and eosinophil monitoring may support clinically useful risk stratification during the first weeks of biologic therapy. However, because the study was retrospective and single-centre, prospective multicentre validation is required before early biomarker trajectories can be used to guide biologic continuation, optimization, or switching decisions.

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