Exploration of Asthma & Allergy

Open Exploration

Open Access Original Article

A real-world clustering analysis reveals heterogeneous response patterns to biologic therapy in severe asthma

Shuichiro Matsumoto[1†], Yosuke Kamide[2†], Naoya Fujino[1*], Mitsuhiro Yamada[1], Yoshinao Ono[1], Seiichi Kobayashi[3], Teruyuki Sato[4], Kiyoshi Sekiya[2], Takuto Endo[1], Tsutomu Tamada[1], Tomohiro Ichikawa[1], Hiroyuki Aizawa[1], Hirohito Sano[1], Yorihiko Kyogoku[1], Takuya Saito[1], Shuichi Konno[1], Manami Suzuki[1], Koji Okutomo[3], Masami Taniguchi[2], Hisatoshi Sugiura[1]

[1]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai 980 8574, Japan
[2]Clinical Research Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Sagamihara 252 0392, Japan
[3]Department of Respiratory Medicine, Japanese Red Cross Ishinomaki Hospital, Ishinomaki 986 8522, Japan
[4]Department of Respiratory Medicine, South Miyagi Medical Center, Ogawara 989 1253, Japan

[†]These authors contributed equally to this work.
***Correspondence:** Naoya Fujino, Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aobaku, Sendai 980 8574, Japan. naoya.fujino.d2@tohoku.ac.jp
Academic Editor: Giovanni Paoletti, Humanitas University, Humanitas Research Hospital, Italy
Received: June 25, 2025 **Accepted:** August 1, 2025 **Published:** August 18, 2025

Cite this article: Matsumoto S, Kamide Y, Fujino N, Yamada M, Ono Y, Kobayashi S, et al. A real-world clustering analysis reveals heterogeneous response patterns to biologic therapy in severe asthma. Explor Asthma Allergy. 2025;3:100990. https://doi.org/10.37349/eaa.2025.100990

Abstract

Aim: Despite the revolutionary impact of biologics (Bx) on severe asthma management, predicting individual treatment responses remains challenging. We aimed to characterize the heterogeneous nature of clinical status and disease activity in patients with severe asthma after biologic therapies through a comprehensive evaluation of real-world clinical outcomes.

Methods: In this retrospective, multicenter study of 53 patients with severe asthma who received biologic therapies, hierarchical clustering analysis was performed based on three key parameters during treatment: exacerbation, maintenance oral corticosteroid (mOCS) dose, and lung function. Canonical correlation analysis and multinomial logistic regression were used to identify predictors of response patterns.

Results: Clustering analysis revealed three distinct control groups: well-controlled (n = 23), moderately controlled (n = 22), and poorly controlled (n = 8). Well-controlled patients exhibited minimal exacerbations, no oral corticosteroid (OCS) use, and optimal or stabilized lung function. Moderately controlled patients showed minimal exacerbations and no mOCS use but variable lung function improvements. Poorly controlled patients exhibited persistent exacerbations, mOCS dependence, or both with limited lung function improvement. Baseline forced expiratory volume in 1 second (FEV_1) %predicted (percent predicted FEV_1) values and blood eosinophil counts independently differentiated well-controlled from moderately controlled patients, whereas baseline mOCS use distinguished moderately controlled from poorly controlled patients.

Conclusions: Our findings reveal distinct patterns of disease control following biologic therapy in severe asthma, with baseline lung function, eosinophilic inflammation, and OCS use as key predictive factors. These results support the need for personalized treatment approaches in severe asthma management.

Keywords

Severe asthma, biologics, cluster analysis, treatment response

Introduction

Severe asthma is characterized by persistent symptoms and frequent exacerbations despite the use of high-dose inhaled corticosteroid (ICS) and long-acting bronchodilators [1, 2] and has an impact on the quality of life and healthcare costs [3, 4]. The introduction of biologic therapies has revolutionized the management of severe asthma by suppressing inflammatory pathways [5]. Biologics (Bx), including anti-immunoglobulin E (IgE), anti-interleukin (IL)-5, anti-IL-5 receptor (IL-5R), anti-IL-4R, and anti-thymic stromal lymphopoietin antibodies, have demonstrated efficacy in reducing exacerbations and improving symptom control [6].

Despite the remarkable efficacy of biologic therapies for the management of severe asthma, predicting individual treatment responses using biomarkers, including fractional exhaled nitric oxide (FeNO), remains a significant challenge [7–10]. However, the complexity of the pathobiology of severe asthma and the multifaceted nature of treatment responses have hindered the establishment of reliable and universally applicable predictors. Recent studies have highlighted the importance of considering multiple clinical and biological factors to better forecast treatment outcomes and optimize biologic therapy for individual patients [11].

Real-world studies are crucial for understanding heterogeneous responses to biologic therapies in patients with severe asthma, because clinical trial populations often do not fully represent the complexity encountered in clinical practice [12, 13]. Identifying easily measurable clinical predictors is essential for practical applications in clinical settings, potentially improving patient outcomes and optimizing resource allocation. Better prediction of treatment responses could lead to more personalized and effective management strategies, thus reducing the burden of uncontrolled asthma on both patients and healthcare systems [14].

The present study, therefore, aimed to characterize the heterogeneity of clinical status and disease activity after biologic therapies for patients with severe asthma through a comprehensive evaluation of clinical outcomes in a real-world setting. Using clustering analysis, we sought to identify distinct disease activity phenotypes and their associated clinical characteristics. Our approach integrated multiple domains of clinical status, including exacerbation rates, lung function, and oral corticosteroid (OCS) use, to provide a more nuanced understanding of the treatment response. Results of this comprehensive analysis may reveal important predictors of biological efficacy, potentially guiding more targeted and efficient use of these therapies in managing patients diagnosed with severe asthma.

Materials and methods

Study design

This retrospective, observational multicenter study analyzed data from patients diagnosed with severe asthma who underwent biologic therapy at 4 tertiary hospitals in Japan: Tohoku University Hospital (Miyagi), National Hospital Organization Sagamihara National Hospital (Kanagawa), Japanese Red Cross Ishinomaki Hospital (Miyagi), and South Miyagi Medical Center (Miyagi) (Figure 1A). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Tohoku University Hospital (IRB No. 2022-1-198). Written informed consent was obtained from all participants prior to enrollment in the study. Patient enrollment was conducted between July 2020 and July 2022. The study timeline comprised 2 main phases: baseline and follow-up (Figure 1A). The cohort entry date for each participant was defined as the date of

initiation of Bx. The baseline period was established as the first visit to the cohort entry date, during which pre-Bx clinical characteristics were assessed. For all patients, baseline measurements (including FeNO and spirometry) were obtained immediately before initiation of their current biologic therapy, regardless of prior biologic exposure history. This approach ensured standardized baseline assessments for both biologic-naïve patients and those switching from previous biologic treatments. Pre-Bx exacerbations were evaluated for 12 months preceding the cohort entry date. This period was designated as the pre-Bx exacerbation assessment period. The follow-up period began on the cohort entry date and extended for at least 12 months. Patients were required to have received the current biologic agent for a minimum of 12 consecutive months to be eligible for the study analysis. The post-Bx exacerbation assessment period was defined as the 12 months before patient enrollment, which coincided with the end of the follow-up period.

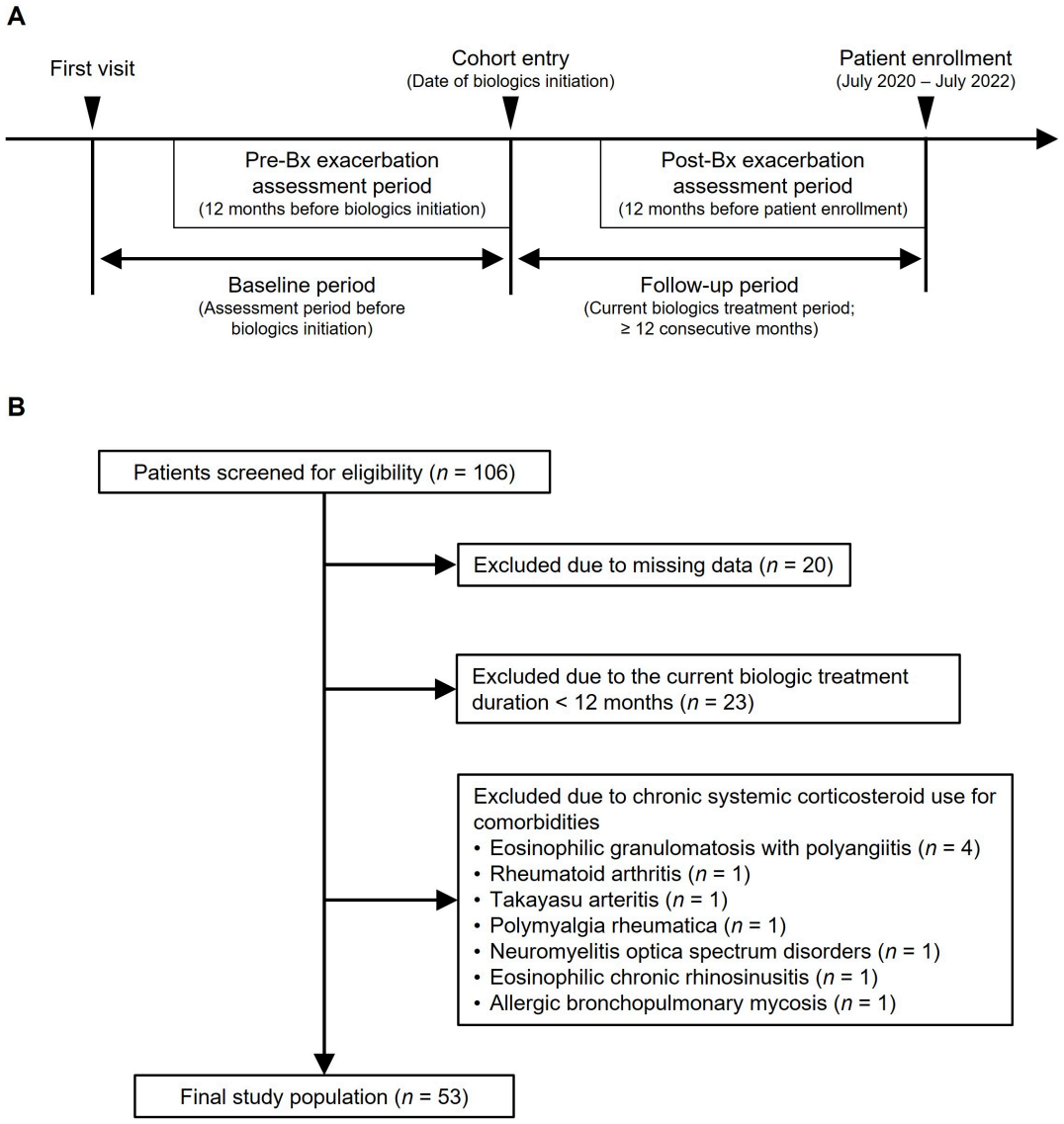

Figure 1. Overview of study timeline and patient selection process. (**A**) Study design and timeline of the clinical research study. The study period consisted of two main phases: a baseline period before Bx initiation and a follow-up period after Bx initiation. The pre-Bx exacerbation assessment period was defined as 12 months before Bx initiation. The post-Bx exacerbation assessment period was defined as 12 months before patient enrollment. (**B**) Patient selection flowchart. Of 106 patients initially screened for eligibility, 53 patients were included in the final study population. Bx: biologics

Patients

Asthma was diagnosed by respiratory physicians in accordance with the Japanese guidelines or the Global Initiative for Asthma (GINA) guidelines, while severe asthma was defined according to the GINA guidelines. Eligible patients were ≥ 18 years of age, had been undergoing biologic therapy for ≥ 1 year, and had

baseline assessments conducted at enrollment and upon initiation of the first biologic therapy. Biologic agents included in the present study were omalizumab, mepolizumab, benralizumab, and dupilumab, the choice of which was at the discretion of the attending physician. Patients who switched Bx upon enrollment were included, provided that the current biologic used at enrollment had been administered for ≥ 1 year. Patients with insufficient data for analysis were excluded to ensure the integrity and completeness of the dataset. Additionally, individuals with a current biologic treatment duration of less than 12 months were excluded. Patients with comorbidities requiring chronic systemic corticosteroid use were also excluded to avoid potential confounding effects on asthma-related outcomes. Non-steroidal anti-inflammatory drug-exacerbated respiratory disease, allergic bronchopulmonary mycosis, and eosinophilic granulomatosis with polyangiitis were also excluded due to their distinct pathophysiology, which could obscure the core features of severe asthma.

Data collection and evaluation

The following patient characteristics were analyzed: sex; age; body mass index (BMI); and baseline treatments, including Bx, duration of asthma, and comorbid diseases. Additionally, the following parameters were evaluated during the baseline period: peripheral blood eosinophil count (BEC); serum IgE, FeNO; pulmonary function test (PFT) results [forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, percent predicted FEV_1 (FEV_1 %predicted)]; and daily maintenance OCS (mOCS), expressed as prednisone equivalents (mg per day). The post-bronchodilator values for the PFT were collected. The highest BEC and FeNO levels were recorded during the baseline period. Serum IgE levels were determined on the date nearest the cohort entry date. Specific IgE positivity for ≥ 1 aero-allergen(s) was required to confirm the presence of atopy. Data regarding exacerbation history, including the frequency and severity of exacerbations in the 12 months preceding biologic initiation or the enrollment, were also collected.

Statistics

Statistical analyses were performed using Prism version 10.4.1 (GraphPad Inc., San Diego, CA, USA), JMP Pro version 17.0.0 (SAS Institute, Cary, NC, USA), or Python version 3.12. Data are expressed as median with interquartile range (IQR) for continuous variables, and numbers with percentages for categorical variables unless otherwise indicated. Changes from pre-Bx to post-Bx were analyzed using the Wilcoxon matched-pairs signed-rank test for non-normally distributed continuous variables, paired *t*-test for normally distributed continuous variables, and McNemar's test or Fisher's exact test for categorical variables. Changes in lung function categories were visualized using a Sankey diagram created in Python version 3.12, and analyzed using Markov chain analysis, with a chi-squared test for statistical significance using the "scipy.stats" package on Python. JMP was used for hierarchical clustering analysis to identify distinct disease activity groups. Canonical correlation analysis was used to evaluate relationships between clinical variables and disease activity groups, and analysis of covariance (ANCOVA) was used to assess the relationship between pre-Bx and post-Bx outcomes. Differences in clinical outcomes across groups identified through the clustering analysis were assessed using the Kruskal-Wallis test, followed by Dunn's multiple comparison test for continuous variables and negative binomial regression, followed by Dunnett's multiple comparison test for exacerbation frequencies. Multinomial logistic regression analysis was performed to identify predictors of post-Bx control status. Odds ratios were calculated as exp(β), where β represents the regression coefficient for each variable. Covariates for the multinomial logistic regression model were selected based on clinical relevance, previous literature, and statistical considerations. We initially included variables with $p < 0.10$ in univariable analyses. Additionally, we incorporated variables deemed important for group discrimination based on canonical correlation analysis, even if they did not meet the $p < 0.10$ threshold in univariable comparisons. To address multicollinearity, we employed variance inflation factor analysis. For highly correlated variables, we selected representative variables to include in the model, avoiding the simultaneous inclusion of strongly correlated predictors. We then performed backward stepwise selection to retain variables with $p < 0.05$ in the final multivariable model,

balancing statistical significance with clinical relevance. Receiver operating characteristic (ROC) curves were constructed using GraphPad Prism by plotting sensitivity versus (vs.) 1-specificity across all thresholds, with optimal cutoff values determined via the Youden index to maximize diagnostic accuracy. Differences with p-value < 0.05 were considered to be statistically significant in all analyses.

Results

Clinical outcomes and biomarker changes after biologic therapy in patients diagnosed with severe asthma

Data from 106 patients with severe asthma were initially screened for eligibility during the enrollment period (Figure 1). The final study population consisted of 53 patients, all of whom had severe asthma classified as GINA step 4 or 5 prior to initiating biologic therapy. The clinical characteristics of the study population at baseline are summarized in Table 1. A comprehensive analysis comparing clinical parameters pre-Bx vs. post-Bx was used to determine the clinical impact of biologic therapies on patients diagnosed with severe asthma. The median duration of overall biologic use was 42.0 months (range: 12.9–138.5 months). For the currently administered biologic agent, the median duration of use was 34.5 months (range: 12.9–138.5 months). Findings revealed significant improvements in multiple clinical outcomes following biologic treatment. The annual exacerbation frequency decreased significantly from a median of 3.0 (IQR 2.0–6.0) pre-Bx to 0.0 (0.0–0.0) post-Bx (p < 0.0001) (Figure 2A). The proportion of patients experiencing zero exacerbations increased dramatically, whereas that of patients with frequent exacerbations decreased substantially (p < 0.0001) (Figure 2B), demonstrating the efficacy of Bx in reducing exacerbation rates. Use of mOCS was significantly reduced after biologic therapy (p < 0.001) (Figure 2C). Concurrently, the number of patients requiring mOCS decreased significantly (p < 0.05) (Figure 2D), reflecting the steroid-sparing effect of biologic therapies. Lung function parameters also demonstrated a notable improvement. Median FEV_1 %predicted values increased significantly from pre-Bx to post-Bx (Figure 2E). Markov chain analysis revealed a significant shift toward improved lung function categories after biologic therapy (p < 0.0001) (Figure 2F). The distribution of absolute change in FEV_1 (Δ FEV_1) post-Bx is illustrated in Figure 2G, with a threshold of 200 mL improvement, demonstrating the positive impact of Bx on airway obstruction. BEC decreased significantly, from a median of 590/μL (IQR 265–1,206/μL) pre-Bx to 180/μL (IQR 0–415/μL) post-Bx (p < 0.0001) (Figure 2H). Similarly, median FeNO levels were markedly reduced from 55 ppb (IQR 31–87 ppb) to 26 ppb (IQR 16–46 ppb) (p < 0.001) (Figure 2I). Serum IgE levels remained unchanged after treatment (Figure 2J).

Table 1. Patient demographic and clinical characteristics before biologic initiation

Clinical information	Total study population (n = 53)
Demographic variables	
Age, years	60.0 (50.0–71.0)
Female, n (%)	38 (71.7%)
BMI, kg/m^2	25.2 (20.4–26.9)
Age at asthma onset, years	42.0 (24.0–53.0)
Adult onset ≥ 18 years, n (%)	44 (83.0%)
Duration of disease, years	18.0 (7.0–30.0)
Duration of disease ≥ 10 years, n (%)	36 (67.9%)
Smoking status	
Never smokers, n (%)	36 (67.9%)
Previous smokers, n (%)	15 (28.3%)
Current smokers, n (%)	2 (3.8%)
Pack-years in previous and current smokers	15.0 (2.5–39.3)
Indoor pet keeping, n (%)	11 (20.8%)
History of comorbidities	
Allergic rhinitis, n (%)	28 (52.8%)

Table 1. Patient demographic and clinical characteristics before biologic initiation (*continued*)

Clinical information	Total study population (*n* = 53)
Chronic rhinosinusitis, *n* (%)	23 (43.4%)
Eosinophilic chronic rhinosinusitis, *n* (%)	11 (20.8%)
Atopic dermatitis, *n* (%)	1 (1.9%)
COPD, *n* (%)	4 (7.5%)
Obesity (BMI ≥ 30 kg/m^2), *n* (%)	3 (5.7%)
Exacerbations in 12 months before Bx initiation	
0, *n* (%)	7 (13.2%)
1, *n* (%)	4 (7.5%)
≥ 2, *n* (%)	42 (79.2%)
Medication use in the year preceding Bx initiation	
Budesonide equivalent dose, mcg	1,000 (800–1,440)
ICS/LABA, *n* (%)	28 (52.8%)
ICS/LABA/LAMA, *n* (%)	23 (43.4%)
ICS/LAMA, *n* (%)	1 (1.9%)
mOCS, *n* (%)	17 (32.1%)
mOCS, prednisolone equivalent dose, mg	5.0 (3.5–9.5)
LTRA, *n* (%)	37 (69.8%)
Theophylline, *n* (%)	12 (22.6%)
Pre-Bx lung function	
FEV_1, L	1.73 (1.37–2.20)
FEV_1, %predicted	85.6 (62.9–94.9)
FVC, L	2.51 (2.22–3.07)
FVC, %predicted	96.1 (84.6–104.6)
FEV_1/FVC	0.69 (0.58–0.78)
PAL, *n* (%)	27 (50.9%)
Type 2 inflammation markers	
Pre-Bx highest BEC, cells/μL	590 (265–1,206)
Pre-Bx BEC < 100/μL, *n* (%)	7 (13.2%)
Pre-Bx BEC ≥ 150/μL, *n* (%)	42 (79.2%)
Pre-Bx BEC ≥ 300/μL, *n* (%)	39 (73.6%)
Pre-Bx BEC ≥ 500/μL, *n* (%)	30 (56.6%)
Pre-Bx latest serum IgE, IU/mL	277 (70.8–755)
Positive SPT and/or positive specific IgE, *n* (%)	35 (66.0%)
Pre-Bx highest FeNO, ppb	53.0 (27.8–87.3)
FeNO ≥ 25 ppb, *n* (%)	32 (60.4%)

Data are presented as median (interquartile range), or *n* (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; Bx: biologics; ICS: inhaled corticosteroid; LABA: long-acting beta2 agonist; LAMA: long-acting muscarinic antagonist; mOCS: maintenance oral corticosteroid; LTRA: leukotriene receptor antagonist; FEV_1: forced expiratory volume in 1 second; FEV_1 %predicted: percent predicted FEV_1; FVC: forced vital capacity; PAL: persistent airflow limitation; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; SPT: skin prick test; IgE: immunoglobulin E

Comparative clinical profiles and treatment outcomes of anti-IgE, anti-IL-5/IL-5R, and anti-IL-4R therapies in patients with severe asthma

Among the 53 patients analyzed, 19, 15, and 19 patients currently underwent anti-IgE, anti-IL-5/IL-5R, and anti-IL-4R therapy, respectively. Of the 15 patients receiving anti-IL-5/IL-5R therapy, 2 had previously been treated with anti-IgE. Similarly, among the 19 patients receiving anti-IL-4R therapy, 5 had a history of treatment with anti-IgE alone, while 2 had previously been treated with anti-IL-5/IL-5R. Additionally, 2 of the anti-IL-4R users had a history of treatment with both anti-IgE and anti-IL-5/IL-5R Bx. Baseline characteristics of patients receiving anti-IgE, anti-IL-5/IL-5R, or anti-IL-4R therapies were compared (Table 2). It should be noted that for patients with previous biologic exposure (*n* = 9), baseline clinical parameters represent measurements obtained immediately before starting their current biologic agent, ensuring comparable baseline assessments across all study participants. Patients in the anti-IL-5/IL-5R

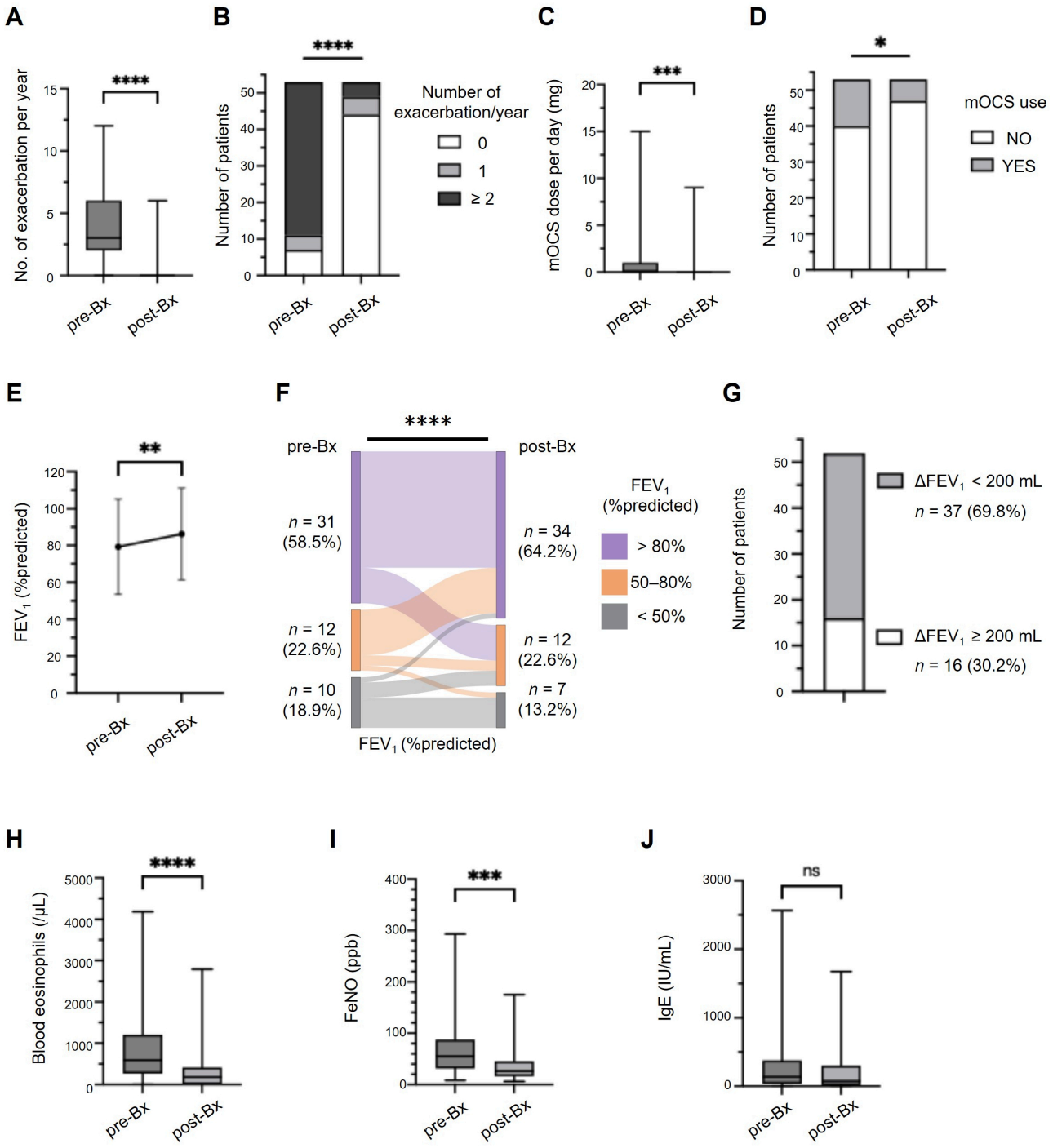

Figure 2. Clinical outcomes and biomarkers before and after Bx treatment in patients with severe asthma. (**A**–**D**) Exacerbations and maintenance oral corticosteroid (mOCS) use. (**A**) Number of exacerbations during pre- and post-biologics (Bx) periods (Wilcoxon matched-pairs signed-rank test, ****$p < 0.0001$). (**B**) Patient distribution by annual exacerbation frequency (Fisher's exact test, ****$p < 0.0001$). (**C**) mOCS dose pre- and post-Bx (Wilcoxon matched-pairs signed-rank test, ***$p < 0.001$). (**D**) Patients requiring mOCS (McNemar's test with continuity correction, *$p < 0.05$). (**E**–**G**) Lung function parameters. (**E**) Percent predicted forced expiratory volume in 1 second (FEV_1 %predicted values) pre- and post-Bx (mean ± SD; paired *t*-test, **$p < 0.01$). (**F**) Sankey diagram illustrating transitions in lung function status based on FEV_1 %predicted values (> 80%, 50–80%, and < 50% categories) pre- and post-Bx (Markov chain analysis with chi-square test, ****$p < 0.0001$). (**G**) Patient distribution by absolute change in FEV_1 (ΔFEV_1) post-Bx (threshold: 200 mL). (**H**–**J**) Type 2 inflammation biomarkers. Pre- and post-Bx levels of (**H**) blood eosinophils (/μL), (**I**) fractional exhaled nitric oxide (FeNO, ppb), and (**J**) serum immunoglobulin E (IgE, IU/mL). Wilcoxon matched-pairs signed-rank test: ****$p < 0.0001$, ***$p < 0.001$. ns: not significant; FEV_1: forced expiratory volume in 1 second. Box plots show median, interquartile range, and whiskers (minimum to maximum)

Table 2. Demographics and clinical characteristics in three classes of Bx

Current Bx	Anti-IgE therapy	Anti-IL-5/IL-5R therapy	Anti-IL-4R therapy	*p*-value
Subjects, *n*	19	15	19	
Previously treated with anti-IgE, *n*	N.A.	2	5	
Previously treated with anti-IL-5/IL-5R, *n*	0	N.A.	2	
Previously treated with both anti-IgE and anti-IL-5/IL-5R, *n*	N.A.	N.A.	2	
Demographic variables				
Age, years	56.0 (43.0–71.0)	64.0 (52.0–73.0)	60.0 (52.0–69.0)	0.2081
Female, *n* (%)	17 (89.5%)	8 (53.3%)	13 (68.4%)	0.0548
BMI, kg/m^2	20.5 (18.2–22.9)	25.8 (25.1–27.9)**	26.4 (21.4–28.4)*	**0.0025**
Age at asthma onset, years	45.0 (32.0–54.0)	42.0 (28.0–52.0)	33.0 (20.0–54.0)	0.9621
Duration of disease, year	15.3 (5.5–23.4)	23.2 (15.9–30.6)	18.1 (5.6–34.3)	0.3163
Smoking status				0.6009
Never smokers, *n* (%)	15 (78.9%)	10 (66.7%)	11 (57.9%)	
Previous smokers, *n* (%)	4 (21.1%)	4 (26.7%)	7 (36.8%)	
Current smokers, *n* (%)	0 (0.0%)	1 (6.7%)	1 (5.3%)	
Indoor pet keeping, *n* (%)	3 (15.8%)	1 (6.7%)	7 (36.8%)	0.1154
History of comorbidities				
Allergic rhinitis, *n* (%)	10 (52.6%)	6 (40.0%)	12 (63.2%)	0.4022
Chronic rhinosinusitis, *n* (%)	8 (42.1%)	7 (46.7%)	8 (42.1%)	> 0.9999
Eosinophilic chronic rhinosinusitis, *n* (%)	3 (15.8%)	5 (33.3%)	3 (15.8%)	0.5171
Atopic dermatitis, *n* (%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	> 0.9999
COPD, *n* (%)	0 (0.0%)	2 (13.3%)	2 (10.5%)	0.3121
Type 2 inflammation markers				
Pre-Bx highest BEC, cells/μL	470 (120–880)	846 (680–1,780)*	420 (90–688)††	**0.0055**
Pre-Bx highest FeNO, ppb	24.0 (12.0–48.0)	76.5 (40.5–108.8)**	55.0 (32.0–97.0)	**0.0084**
Pre-Bx latest serum IgE, IU/mL	213.0 (59.2–412.0)	357.0 (95.0–1,380.0)	277.0 (70.2–1,480.0)	0.4284
Positive SPT and/or positive specific IgE, *n* (%)	15 (78.9%)	6 (40.0%)	14 (73.7%)	**0.0448**
Exacerbation				
Pre-Bx exacerbation	3.0 (2.0–6.0)	3.0 (0.0–4.0)	4.0 (2.0–6.0)	0.4585
Post-Bx exacerbation	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.4221
Difference of exacerbation between post-Bx and pre-Bx	–3.0 (–5.0 to –2.0)	–3.0 (–4.0 to 0.0)	–3.0 (–6.0 to –2.0)	0.8149
mOCS				
Pre-Bx mOCS user, *n* (%)	2 (10.5%)	6 (40.0%)	5 (26.3%)	> 0.9999
Post-Bx mOCS user, *n* (%)	1 (5.3%)	2 (13.3%)	2 (10.5%)	
Lung function				
Pre-Bx FEV_1 %predicted	89.2 (78.7–104.5)	77.3 (46.8–94.6)	84.2 (49.3–93.1)	0.1662
Post-Bx FEV_1 %predicted	93.6 (77.8–106.6)	85.8 (69.7–103.6)	84.1 (72.2–100.0)	0.6205

Data are presented as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. Statistics: Kruscal-Wallis test and Dunn's multiple comparison test for continuous variables; Fisher's exact test for categorical data. $p < 0.05$ considered statistically significant and highlighted in bold font. $^{**}p < 0.01$, $^{*}p < 0.05$ compared with anti-IgE; $^{\dagger\dagger}p < 0.01$ compared with anti-IL-5/IL-5R. BMI: body mass index; COPD: chronic obstructive pulmonary disease; Bx: biologics; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; mOCS: maintenance oral corticosteroid; SPT: skin prick test; FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; IgE: immunoglobulin E; IL: interleukin; IL-5R: IL-5 receptor; pre-Bx exacerbation: exacerbations in 12 months before Bx initiation (/year); post-Bx exacerbation: exacerbations in 12 months before patients enrollment (/year); pre-Bx mOCS user: patients receiving mOCS in the year preceding Bx initiation; post-Bx mOCS user: patients receiving mOCS at enrollment; pre-Bx FEV_1 %predicted: FEV_1 %predicted values before biologic therapy; post-Bx FEV_1 %predicted: FEV_1 %predicted values at enrollment

group had significantly higher pre-Bx BEC compared to both the anti-IgE and anti-IL-4R groups (median: 846 vs. 470 and 420 cells/μL, respectively; $p < 0.05$ and $p < 0.01$). Additionally, FeNO levels were significantly elevated in the anti-IL-5/IL-5R group compared to the anti-IgE group (median: 76.5 vs. 24.0 ppb, $p = 0.0084$). A higher proportion of patients in the anti-IgE and anti-IL-4R groups demonstrated the positivity of skin prick test (SPT) or the presence of specific IgE compared to the anti-IL-5/IL-5R group.

The clinical outcomes before and after each biologic therapy are shown in Figure 3. All three Bx significantly reduced annual exacerbation rates compared to baseline (Figure 3A). Among patients who were receiving mOCS prior to the initiation of Bx, mOCS dose also decreased (Figure 3B). mOCS dose between before and after anti-IgE therapy was not statistically evaluated because only 2 patients underwent mOCS in this group. Reductions in mOCS dose were observed even among patients who had switched Bx (red lines, Figure 3B). FEV_1 %predicted values improved significantly only in the anti-IL-4R group (Figure 3C). We conducted a sensitivity analysis by excluding patients who had received prior biologic treatments ($n = 44$). The clinical outcomes in this subgroup were very similar to those in the full cohort, suggesting that previous biologic use did not have a major impact on the response patterns observed (Table 3).

Identification of distinct patterns of clinical status and disease activity of patients treated with biologic therapy

A hierarchical clustering analysis was used to evaluate the heterogeneity in clinical status and disease activity of patients treated with Bx, based on 3 key outcome measures during the follow-up period: exacerbation frequency; mOCS dose; and FEV_1 %predicted values. We analyzed the clinical status and disease activity irrespective of the specific biologic agent, because we sought to identify common response patterns across different type2-targeted Bx. This clustering analysis revealed that patients were classified into three distinct control groups using the following criteria: well-controlled patients ($n = 23$) experienced fewer than 3 exacerbations, required no mOCS use, and achieved post-biologic FEV_1 more than 80% predicted; moderately controlled patients ($n = 22$) experienced fewer than 3 exacerbations and required no mOCS use, but did not achieve post-biologic FEV_1 more than 80% predicted; poorly controlled patients ($n = 8$) experienced 3 or more exacerbations or required daily mOCS during biologic therapy. Among the eight subjects with the poorly controlled cluster, two met only the exacerbation criterion, five met only the mOCS criterion, and one met both criteria (Figure 4A). Individual components of the disease control status were analyzed (Figure 4B–D). Exacerbation rates varied significantly between groups, with poorly controlled patients experiencing substantially higher exacerbation rates than well-controlled and moderately controlled patients (Figure 4B). The use of mOCS was markedly higher in the poorly controlled patients, indicating a greater dependence on systemic corticosteroids for their disease control (Figure 4C). Well-controlled patients demonstrated superior lung function, while moderately and poorly controlled patients exhibited similar levels of airflow limitation, both of which were significantly lower than those of well-controlled patients (Figure 4D). An analysis of lung function transition from pre-Bx to post-Bx revealed that 26.1% of well-controlled patients ($n = 23$) improved to achieve $FEV_1 \geq 80\%$ predicted post-Bx (Figure 4E). The moderately controlled group ($n = 22$) exhibited heterogenous responses.

Canonical correlation analysis was performed to identify predictors of the 3 distinct control groups using hierarchical clustering, and to compare baseline clinical parameters. This analysis clearly separated the 3 groups: lung function, BEC, and BMI pre-Bx distinguished well-controlled from moderately controlled patients, while baseline mOCS use was important in differentiating moderately from poorly controlled patients (Figure 5A). Examination of baseline characteristics revealed that the poorly controlled group exhibited higher baseline mOCS use and lower FEV_1 %predicted values than the other groups (Table 4). FEV_1 %predicted values, mOCS use, BEC, and BMI at baseline were identified as potential predictors for group classification. Multinomial logistic regression analysis using these variables as covariates revealed that FEV_1 %predicted values and BEC were independent predictors distinguishing well-controlled from moderately controlled patients (Table 5). We excluded FVC %predicted values and FEV_1/FVC to avoid the multicollinearity between these lung function parameters and FEV_1 %predicted values. While FEV_1

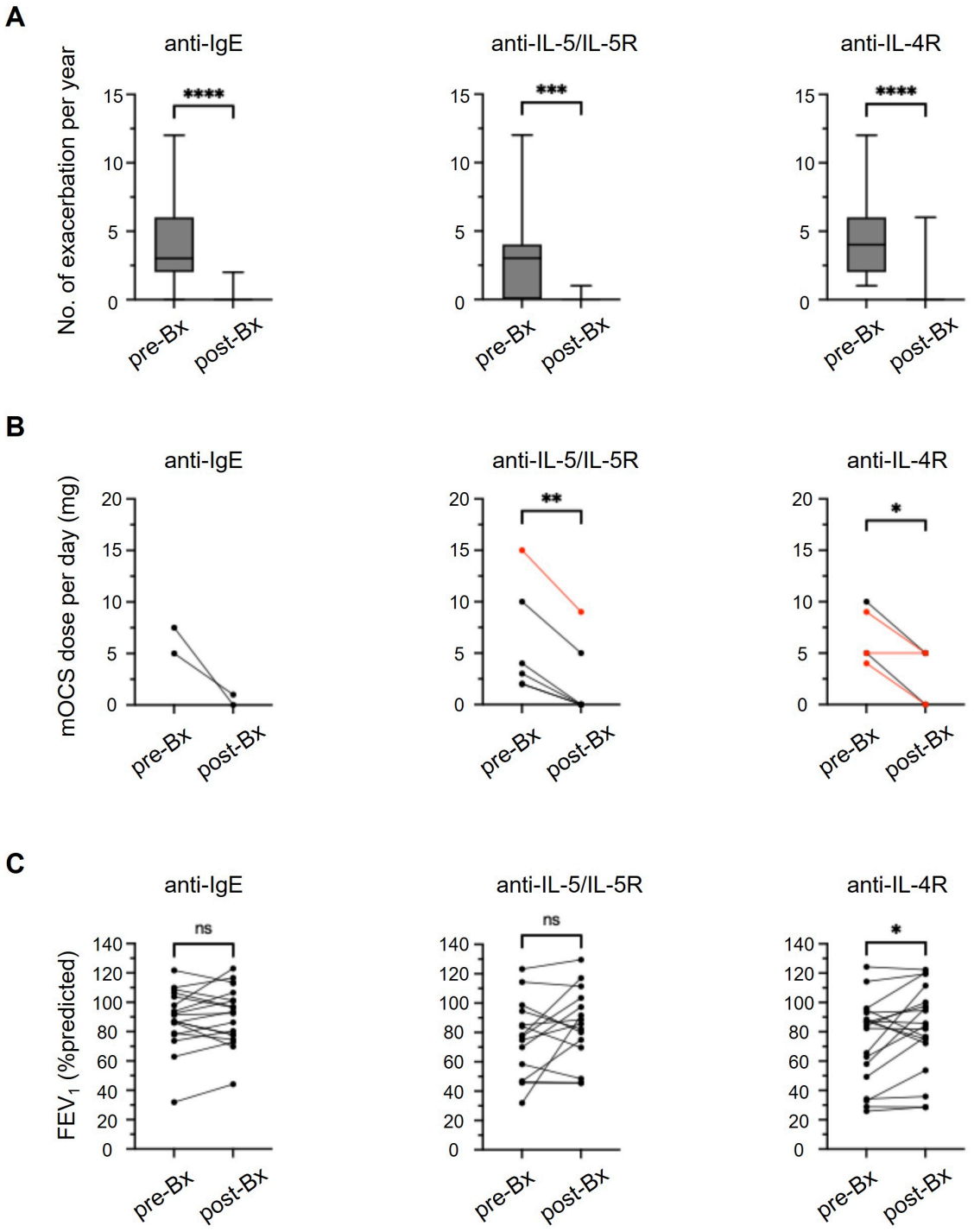

Figure 3. Clinical outcomes before and after anti-IgE, anti-IL-5/IL-5R, or anti-IL-4R therapy in patients with severe asthma. (**A**) Number of exacerbations per year during pre- and post-anti-IgE (left), anti-IL-5/IL-5R (middle), and anti-IL-4R (right) therapies (Wilcoxon matched-pairs signed-rank test, $^{****}p < 0.0001$, $^{***}p < 0.001$). (**B**) Daily maintenance oral corticosteroid (mOCS) dose in patients treated with anti-IgE (left, $n = 2$), anti-IL-5/IL-5R (middle, $n = 6$), or anti-IL-4R (right, $n = 5$) therapies (paired t-test, $^{**}p < 0.01$, $^{*}p < 0.05$). Analysis was limited to patients receiving mOCS prior to biologic therapy. mOCS dose between before and after anti-IgE therapy was not statistically tested because only 2 patients underwent mOCS in this group. Points and lines in red represent patients who had previously received Bx different from the current therapy. (**C**) FEV_1 %predicted pre- and post-treatment of anti-IgE (left), anti-IL-5/IL-5R (middle), and anti-IL-4R therapies (paired t-test, $^{*}p < 0.05$). ns: not significant; IgE: immunoglobulin E; IL: interleukin; IL-5R: IL-5 receptor; Bx: biologics; FEV_1 %predicted: percent predicted forced expiratory volume in 1 second

%predicted values demonstrated good discriminatory power (AUC = 0.73, $p = 0.0095$), BEC showed limited standalone predictive utility (AUC = 0.58, $p = 0.3460$) (Figure 5B). Using a cut-off of ≥ 90.0% FEV_1 %predicted values, well-controlled and moderately controlled patients were differentiated with a sensitivity of 59.1% and a specificity of 86.4%. ANCOVA was performed to determine the relationship between clinical outcomes and control group classification, adjusting for baseline values (Figure 5C). For

Table 3. A sensitivity analysis for biologic-naïve patients

Outcome	Full cohort (*n* = 53)	Biologic-naïve (*n* = 44)	*p*-value
Post-Bx exacerbation	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.8739
Post-Bx mOCS user, *n* (%)	6 (11.3%)	4 (9.1%)	> 0.9999
Post-Bx FEV_1 %predicted	86.3 (74.8–102.5)	86.1 (72.7–101.9)	0.7983

Data are presented as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. Statistics: Mann-Whitney test for continuous variables; Fisher's exact test for categorical data. Bx: biologics; FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; mOCS: maintenance oral corticosteroid; post-Bx exacerbation: exacerbations in 12 months before patients' enrollment (/year); post-Bx mOCS user: patients receiving mOCS at enrollment; post-Bx FEV_1 %predicted: FEV_1 %predicted values at enrollment

exacerbation frequency, there was a significant effect of group differences ($p = 0.0008$), independent of pre-Bx exacerbation rates ($p = 0.0548$). Regarding mOCS dose, both groups ($p = 0.0009$) and pre-Bx mOCS dose ($p < 0.0001$) had significant effects, showing that post-Bx mOCS use was independently influenced by both pre-Bx dose and group classification. Similarly, for FEV_1 %predicted values, ANCOVA revealed significant effects for both group differences ($p < 0.0001$) and pre-Bx FEV_1 %predicted values ($p < 0.0001$). This suggests that post-Bx lung function was affected by baseline values, but also differed independently among the 3 control groups.

Discussion

The study used hierarchical clustering to analyze clinical status and disease activity patterns after biologic therapy in 53 patients with severe asthma who were treated for at least one year. Three distinct groups were identified: well-controlled, moderately controlled, and poorly controlled. Well-controlled patients had stable disease, minimal exacerbations, no mOCS use, and optimal lung function. Moderately controlled patients had some exacerbations and no mOCS use, but less lung function improvement. Poorly controlled patients showed suboptimal disease control, frequent exacerbations, mOCS dependence or both, and limited lung function gains. Baseline BEC and FEV_1 %predicted values differentiated well and moderately controlled groups, while baseline mOCS use distinguished moderately from poorly controlled patients.

Our study confirmed the heterogeneous nature of the control status and disease activity after biologic treatment in severe asthma, underscoring the complexity of disease progression and airway remodeling due to chronic inflammation [12, 14–18]. This variability highlights the need for personalized treatment approaches [19–23]. While prior studies have focused on BEC as a predictor of response [19, 24, 25], our multifaceted approach using multiple clinical parameters provides a more comprehensive framework for patient stratification. These findings suggest that a "one-size-fits-all" approach to biologic therapy is suboptimal for severe asthma. Instead, a nuanced and personalized approach to treatment selection and management is warranted, as supported by several studies in this field [26, 27]. Pavord et al. [27] proposed a new classification system for airway diseases, emphasizing individualized treatment based on patient characteristics to improve outcomes and resource allocation. Similarly, Agustí et al. [26] further highlighted the value of precision medicine for airway diseases, arguing that decisions based on biomarkers and clinical features can enhance outcomes and reduce unnecessary interventions and costs. By implementing this personalized approach, we have the potential to significantly improve patient outcomes and optimize resource allocation in the challenging landscape of severe asthma care.

Our identification of three control groups supports previous findings of heterogeneous responses to biologic therapies in severe asthma. Our study adds nuance by showing that well-controlled patients had stable clinical status, low exacerbation rates, minimal mOCS use, and improved lung function, consistent with the "super responder" phenotype described by Portacci et al. [28]. Moderately controlled patients had fewer exacerbations and no mOCS use but showed less improvement in lung function, possibly reflecting partial responders in whom some aspects of asthma improve while others remain suboptimal [29, 30].

Poorly controlled patients showed persistent suboptimal disease control, with frequent exacerbations, mOCS dependence or both, and limited lung function improvement. This group likely has more complex pathophysiology or comorbidities that reduce response to Bx, similar to cluster 5 in the NHOM Asthma

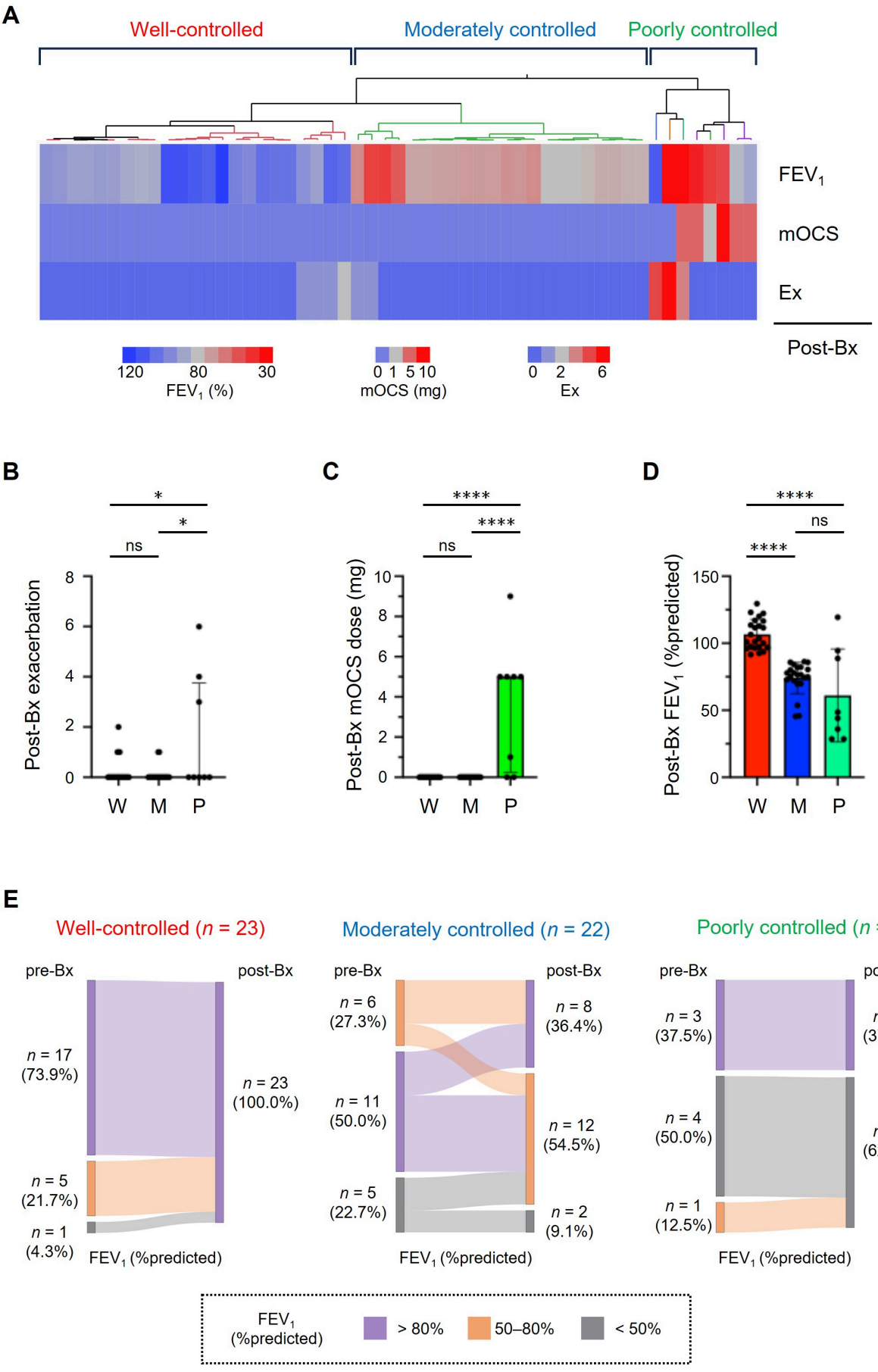

Figure 4. Hierarchical clustering analysis of clinical responses in Bx-treated patients with severe asthma. (**A**) Hierarchical clustering heatmap stratifying patients into well-controlled, moderately controlled, and poorly controlled patients based on post-biologics (Bx) treatment outcomes. Color intensity represents the magnitude of three key clinical parameters:

FEV_1 %predicted values (FEV_1; blue to red: 120% to 30%), maintenance oral corticosteroid (mOCS) dose (prednisolone equivalent, blue to red: 0 to 10 mg/day), and annual exacerbation frequency (Ex; blue to red: 0 to 6 events/year). Dendrogram shows the hierarchical relationship between patient clusters. (**B**–**D**) Post-Bx clinical characteristics across groups. Bar graphs showing (**B**) annual exacerbation frequency, (**C**) mOCS dose (prednisolone equivalent, mg per day), and (**D**) FEV_1 %predicted values post-Bx in well-controlled (W; red), moderately controlled (M; blue), and poorly controlled (P; green) patients. Data are presented as median with interquartile range. Statistical analysis was performed using negative binomial regression followed by Dunnett's multiple comparison test for annual exacerbation frequency, and by Kruskal-Wallis test followed by Dunn's multiple comparison test for mOCS dose and FEV_1 %predicted values. $^{****}p < 0.0001$, $^{***}p < 0.001$, $^{*}p < 0.05$. ns: not significant. (**E**) Sankey diagrams illustrating transitions in lung function status based on FEV_1 %predicted values (> 80%, 50–80%, and < 50% categories) pre- and post-Bx in well-controlled, moderately controlled, and poorly controlled patients. FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; FEV_1: forced expiratory volume in 1 second

Study, characterized by severe, female-dominant, T1/T2-mixed asthma [31]. Despite high use of ICS, OCS, and Bx, these patients continued to experience exacerbations and hospitalizations. Their disease likely involves both T1 and T2 inflammation and structural airway changes, making it difficult to treat with current Bx [16, 18, 32–36]. Baseline mOCS use helps distinguish these patients, highlighting that systemic inflammation and corticosteroid dependence may predict poor response to Bx. These findings support early biologic intervention before long-term OCS dependence develops [37, 38].

There are several limitations to be acknowledged. First, this investigation was conducted in a single country using a relatively small sample size, which may limit the generalizability of our findings to other populations. Although the sample size in our study may be comparable to other real-world evaluations of biologic therapies in severe asthma, the limited number of patients in certain subgroups, particularly those with poor disease control, reduces the statistical resolution for detecting subtle between-group differences. This may increase the risk of overlooking potentially meaningful associations, especially in subpopulations characterized by persistent exacerbations or systemic corticosteroid dependence. Therefore, our subgroup findings should be interpreted as exploratory and hypothesis-generating rather than conclusive. However, the multi-center nature of our study strengthened its validity and reduced potential site-specific bias. Second, it is important to note that our study period coincided with the novel coronavirus disease 2019 (i.e., "COVID-19") pandemic, which may have influenced exacerbation frequencies. Third, future prospective studies with larger and more diverse cohorts are required to validate and extend our findings. In fact, one-quarter of patients in the poorly controlled cluster had comorbid chronic obstructive pulmonary disease (COPD), which may have contributed to lower lung-function gains and poorer overall control despite biologic therapy; therefore, the impact of overlapping COPD should be interpreted cautiously when generalizing these findings. Future studies could incorporate more detailed biomarker analyses, including gene expression profiling specific to lung component cells [39] and oxidative/nitrosative stress [40, 41] to elucidate the underlying mechanisms of differential responses to biologic therapies. Fourth, we did not incorporate the asthma control test (ACT) or other standardized patient-reported outcomes, as these were not routinely documented in our retrospective dataset [42]. Thus, our assessment of asthma control relied on clinical events and spirometric parameters. We acknowledge that ACT and related scores provide valuable complementary information, and future prospective studies should include such measures to ensure a more holistic evaluation of asthma control [43]. Fifth, while BEC might help in identifying response patterns when combined with other factors, its standalone predictive value was limited. Our data show that reliable prediction of biologic response requires integrating eosinophil counts with clinical measures such as baseline FEV_1 %predicted values. Future models should therefore use combined predictors rather than single biomarkers.

In conclusion, this multicenter real-world study highlights the heterogeneity of clinical responses to type 2-targeted Bx in severe asthma and proposes three pragmatic control patterns. While the observations are internally consistent, they stem from a modest, single-nation cohort and should therefore be regarded as hypothesis-generating. Confirmation in larger, multi-ethnic populations is required before these patterns can be translated into routine decision algorithms. Nevertheless, the present findings underscore the potential value of tailoring biologic selection and monitoring to baseline lung function, eosinophilic inflammation, and OCS exposure.

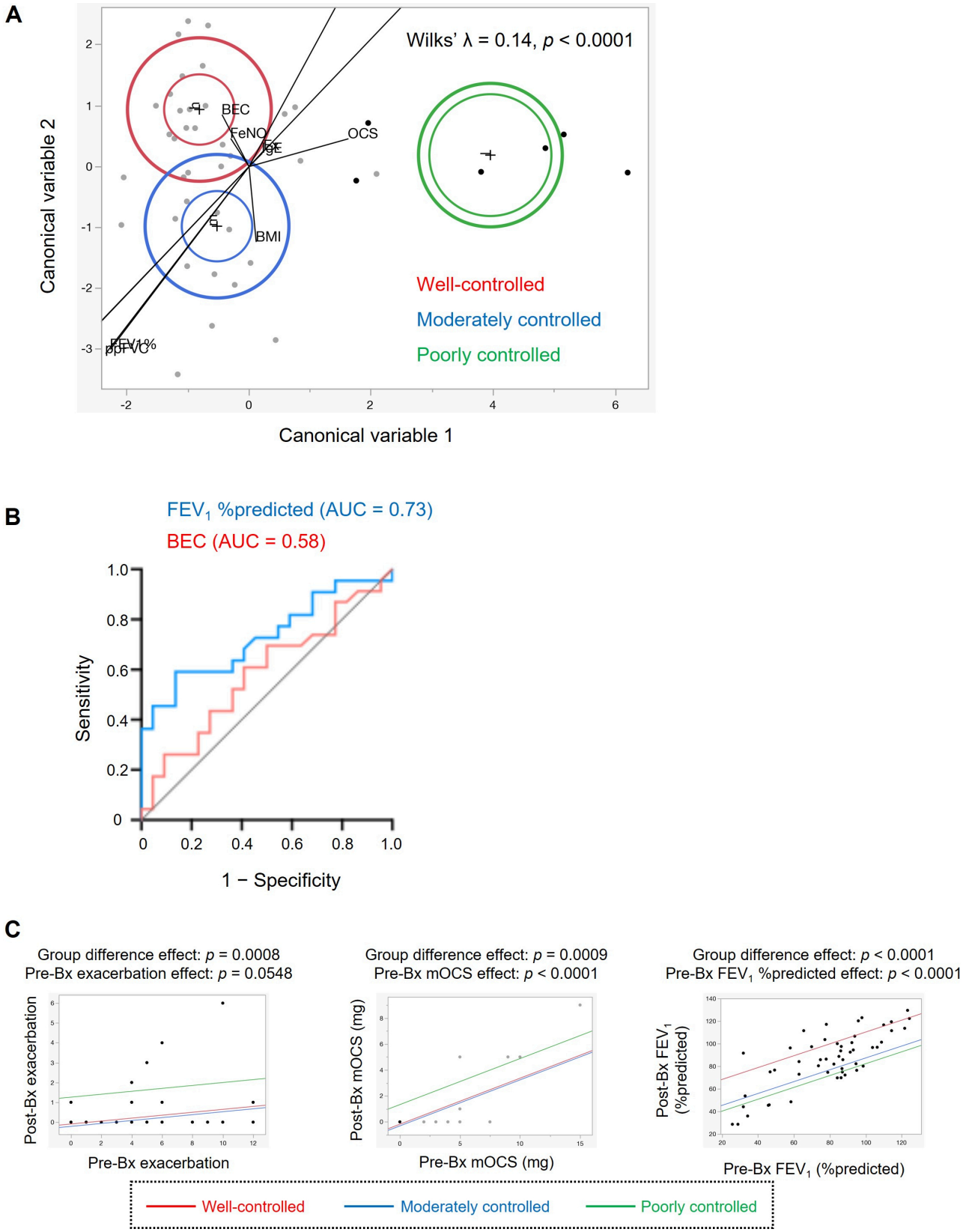

Figure 5. Canonical correlation analysis in Bx-treated patients with severe asthma. (**A**) Canonical correlation analysis of clinical parameters and treatment response. The biplot displays the relationship between clinical variables and patient clusters, with vectors indicating the direction and strength of variable correlations. Ellipses represent 95% confidence regions for well-controlled (red), moderately controlled (blue), and poorly controlled (green) patients. Variables analyzed included blood eosinophil count (BEC), fractional exhaled nitric oxide (FeNO), body mass index (BMI), oral corticosteroid (OCS), and FEV_1 %predicted values ($ppFEV_1$). Statistical significance was determined by Wilks' lambda test ($\lambda = 0.14$, $p < 0.0001$). (**B**) Receiver operating characteristic (ROC) curves comparing the predictive performance of FEV_1 %predicted (blue line) and BEC (red line). (**C**) Relationship between pre- and post-biologics (Bx) outcomes across groups stratified by hierarchical clustering analysis. Analysis of covariance (ANCOVA) was performed to evaluate exacerbation frequency (left), mOCS dose (middle), and FEV_1 %predicted values (right). Each model was adjusted for the corresponding pre-Bx values. The analysis demonstrated

independent effects of group differences (exacerbation: $p = 0.0008$; mOCS: $p = 0.0009$; FEV_1: $p < 0.0001$) with significant effects of pre-Bx values for mOCS ($p < 0.0001$) and FEV_1 ($p < 0.0001$), but not for exacerbations ($p = 0.0548$) after Bx therapy. Regression lines show predicted relationships for well-controlled (red), moderately controlled (blue), and poorly controlled (green) patients, with parallel trajectories indicating consistent group differences across pre-Bx therapy values. Black dots represent individual patient data. FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; mOCS: maintenance OCS; FEV_1: forced expiratory volume in 1 second; IgE: immunoglobulin E

Table 4. Clinical characteristics before treatment with Bx in each control group

Clinical characteristics	Well-controlled patients	Moderately controlled patients	Poorly controlled patients	*p*-value
Patient number, *n* (%)	23 (43.4%)	22 (41.5%)	8 (15.1%)	
Demographic variables				
Age, years	56.0 (48.0–71.0)	62.0 (48.3–70.5)	64.5 (53.8–71.8)	0.6414
Female, *n* (%)	19 (82.6%)	14 (63.6%)	5 (62.5%)	0.2721
BMI, kg/m^2	22.8 (20.3–25.8)	25.6 (20.4–27.2)	26.1 (20.7–30.1)	0.3972
Age at asthma onset, years	48.0 (30.0–52.0)	36.0 (15.0–54.3)	42.0 (22.5–63.5)	0.6766
Duration of disease, years	15.3 (5.5–25.3)	21.4 (12.5–35.5)	18.1 (3.8–32.3)	0.2565
Smoking status				0.3324
Never smokers, *n* (%)	18 (78.3%)	13 (59.1%)	5 (62.5%)	
Previous smokers, *n* (%)	5 (21.7%)	8 (36.4%)	2 (25.0%)	
Current smokers, *n* (%)	0 (0.0%)	1 (4.5%)	1 (12.5%)	
Indoor pet keeping, *n* (%)	5 (21.7%)	3 (13.6%)	3 (37.5%)	0.3912
History of comorbidities				
Allergic rhinitis, *n* (%)	14 (60.9%)	10 (45.5%)	4 (50.0%)	0.5711
Chronic rhinosinusitis, *n* (%)	9 (39.1%)	11 (50.0%)	3 (37.5%)	0.7499
Eosinophilic chronic rhinosinusitis, *n* (%)	3 (13.0%)	7 (31.8%)	1 (12.5%)	0.2511
Atopic dermatitis, *n* (%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0.1509
COPD, *n* (%)	0 (0.0%)	2 (9.1%)	2 (25.0%)	**0.0309**
Exacerbation				
Exacerbations in 12 months before Bx initiation (/year)	3.0 (2.0–5.0)	4.0 (1.8–6.0)	4.0 (0.5–9.0)	0.9263
Medication use in the year preceding Bx initiation				
mOCS, prednisolone equivalent dose, mg	0.0 (0.0–0.0)	0.0 (0.0–0.0)	7.0 (1.3–10.0)***†††	**0.0002**
Pre-Bx lung function				
FEV_1, %predicted	93.1 (77.9–109.1)	80.6 (59.5–87.1)‡	46.4 (29.7–91.1)*	**0.0085**
FVC, %predicted	102.4 (94.8–111.8)	91.9 (90.0–99.6)	80.6 (64.8–102.2)	**0.0186**
FEV_1/FVC	73.3 (62.9–80.8)	68.1 (59.9–72.5)	47.1 (35.7–72.8)	0.0583
Type 2 inflammation markers				
Pre-Bx highest BEC, cells/μL	650 (230–1,300)	483 (253–785)	1,048 (158–1,503)	0.5080
Pre-Bx highest FeNO, ppb	49.5 (31.3–92.3)	57.5 (34.5–96.0)	23.5 (11.8–77.3)	0.3231
Pre-Bx latest serum IgE, IU/mL	279.0 (76.4–541.0)	317.0 (134.0–870.5)	56.8 (20.4–3,096)	0.4696

Data are presented as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. Statistics: $p < 0.05$ is considered statistically significant and highlighted in bold font. $^{***}p < 0.001$, $^{*}p < 0.05$ compared with well-controlled patients, $^{\dagger\dagger\dagger}p < 0.001$ compared with moderately controlled patients, $^{\ddagger}p < 0.05$ compared with well-controlled patients. BMI: body mass index; COPD: chronic obstructive pulmonary disease; Bx: biologics; mOCS: maintenance oral corticosteroid; BEC: blood eosinophil count; FeNO: fractional exhaled nitric oxide; FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; IgE: immunoglobulin E

Table 5. Multinomial logistic regression analysis for predicting the clinical status and disease activity after biological therapy in patients with severe asthma

Pre-Bx clinical factors	Well-controlled vs. moderately controlled; adjusted OR (95% CI)	Moderately controlled vs. poorly controlled; adjusted OR (95% CI)
mOCS, prednisolone equivalent dose, mg	0.86 (0.51–1.33)	1.55 (1.17–2.32)**
FEV_1, %predicted values	1.05 (1.02–1.11)*	1.00 (0.94–1.05)
Blood eosinophil counts	1.001 (1.000–1.002)*	1.000 (0.999–1.002)

Table 5. Multinomial logistic regression analysis for predicting the clinical status and disease activity after biological therapy in patients with severe asthma (*continued*)

Pre-Bx clinical factors	Well-controlled vs. moderately controlled; adjusted OR (95% CI)	Moderately controlled vs. poorly controlled; adjusted OR (95% CI)
Body mass index	0.98 (0.82–1.16)	1.02 (0.78–1.34)

$^{*}p < 0.05$, $^{**}p < 0.01$. OR: odds ratio; Bx: biologics; mOCS: maintenance oral corticosteroid; FEV_1 %predicted: percent predicted forced expiratory volume in 1 second; vs.: versus

Abbreviations

ACT: asthma control test

ANCOVA: analysis of covariance

BEC: blood eosinophil count

BMI: body mass index

Bx: biologics

COPD: chronic obstructive pulmonary disease

FeNO: fractional exhaled nitric oxide

FEV_1 %predicted: percent predicted forced expiratory volume in 1 second

FEV_1: forced expiratory volume in 1 second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroid

IgE: immunoglobulin E

IL: interleukin

IL-5R: interleukin-5 receptor

IQR: interquartile range

LABA: long-acting beta2 agonist

LAMA: long-acting muscarinic antagonist

mOCS: maintenance oral corticosteroid

OCS: oral corticosteroid

PFT: pulmonary function test

ROC: receiver operating characteristic

SPT: skin prick test

vs.: versus

ΔFEV_1: absolute change in forced expiratory volume in 1 second

Declarations

Author contributions

SM and NF: Conceptualization, Data curation, Formal analysis, Writing—original draft, Writing—review & editing. Y Kamide: Conceptualization, Data curation, Writing—review & editing. MY: Conceptualization, Data curation, Funding acquisition, Writing—review & editing. H Sugiura: Conceptualization, Funding acquisition, Supervision, Writing—review & editing. KS: Data curation, Writing—review & editing. MT: Supervision, Writing—review & editing. YO, S Kobayashi, T Sato, TE, TT, TI, HA, H Sano, Y Kyogoku, T Saito, S Konno, MS, KO: Data curation. All authors read and approved the submitted version.

Conflicts of interest

Yosuke Kamide received lecture fees from GlaxoSmithKline and AstraZeneca. Naoya Fujino has received research funding from AstraZeneca and received lecture fees from AstraZeneca and Sanofi. Mitsuhiro Yamada has received lecture fees from GlaxoSmithKline, AstraZeneca, and Sanofi. Seiichi Kobayashi has received research funding from AstraZeneca, and lecture fees from GlaxoSmithKline and AstraZeneca. Kiyoshi Sekiya received lecture fees from Kyorin, GlaxoSmithKline, AstraZeneca, and Sanofi. Tsutomu Tamada has received lecture fees from Novartis, GlaxoSmithKline, AstraZeneca and Sanofi. Tomohiro Ichikawa has received lecture fees from GlaxoSmithKline and AstraZeneca. Takuya Saito has received lecture fees from AstraZeneca. Masami Taniguchi has received research funding from GlaxoSmithKline, and lecture fees from GlaxoSmithKline, AstraZeneca and Sanofi. The rest of the authors have no conflicts of interest.

Ethical approval

The study protocol was approved by the Institutional Review Board of Tohoku University Hospital (IRB No. 2022-1-198) and complies with the Declaration of Helsinki (2024 version).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The clinical datasets analyzed in the current study are available from the corresponding author on reasonable request. The original code for Sankey diagram has been deposited at Zenodo (http://doi.org/10.5281/zenodo.15256087).

Funding

This research was supported by AMED [JP23ek0410084] in the collection. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73. [DOI] [PubMed]
2. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 2017;377:965–76. [DOI] [PubMed]
3. Settipane RA, Kreindler JL, Chung Y, Tkacz J. Evaluating direct costs and productivity losses of patients with asthma receiving GINA 4/5 therapy in the United States. Ann Allergy Asthma Immunol. 2019; 123:564–72.e3. [DOI] [PubMed]
4. Nagase H, Adachi M, Matsunaga K, Yoshida A, Okoba T, Hayashi N, et al. Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan. Allergol Int. 2020;69: 53–60. [DOI] [PubMed]

5. Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022;386:157–71. [DOI] [PubMed]
6. Salter B, Lacy P, Mukherjee M. Biologics in Asthma: A Molecular Perspective to Precision Medicine. Front Pharmacol. 2022;12:793409. [DOI] [PubMed] [PMC]
7. Gerday S, Graff S, Moermans C, Guissard F, Paulus V, Henket M, et al. Super-responders to anti-IL-5/anti-IL-5R are characterised by high sputum eosinophil counts at baseline. Thorax. 2023;78:1138–41. [DOI] [PubMed] [PMC]
8. Hanania NA, Castro M, Bateman E, Pavord ID, Papi A, FitzGerald JM, et al. Efficacy of dupilumab in patients with moderate-to-severe asthma and persistent airflow obstruction. Ann Allergy Asthma Immunol. 2023;130:206–14.e2. [DOI] [PubMed]
9. Djukanović R, Brinkman P, Kolmert J, Gomez C, Schofield J, Brandsma J, et al.; SoMOSA study team and the U-BIOPRED study team. Biomarker Predictors of Clinical Efficacy of the Anti-IgE Biologic Omalizumab in Severe Asthma in Adults: Results of the SoMOSA Study. Am J Respir Crit Care Med. 2024;210:288–97. [DOI] [PubMed] [PMC]
10. Wechsler ME, Scelo G, Larenas-Linnemann DES, Torres-Duque CA, Maspero J, Tran TN, et al. Association Between T2-related Comorbidities and Effectiveness of Biologics in Severe Asthma. Am J Respir Crit Care Med. 2024;209:262–72. [DOI] [PubMed]
11. Scelo G, Tran TN, Le TT, Fagerås M, Dorscheid D, Busby J, et al. Exploring Definitions and Predictors of Response to Biologics for Severe Asthma. J Allergy Clin Immunol Pract. 2024;12:2347–61. [DOI] [PubMed]
12. Denton E, Hew M, Peters MJ, Upham JW, Bulathsinhala L, Tran TN, et al.; ISAR LUMINANT Working Group. Real-world biologics response and super-response in the International Severe Asthma Registry cohort. Allergy. 2024;79:2700–16. [DOI] [PubMed]
13. Park SY, Lee SK, Song WJ, Kim MH, Ban GY, Kim JH, et al. Real-World Effectiveness of Biologics in Patients With Severe Asthma: Analysis of the KoSAR. Allergy Asthma Immunol Res. 2024;16:253–66. [DOI] [PubMed] [PMC]
14. Nagase H, Suzukawa M, Oishi K, Matsunaga K. Biologics for severe asthma: The real-world evidence, effectiveness of switching, and prediction factors for the efficacy. Allergol Int. 2023;72:11–23. [DOI] [PubMed]
15. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18:716–25. [DOI] [PubMed]
16. Varricchi G, Ferri S, Pepys J, Poto R, Spadaro G, Nappi E, et al. Biologics and airway remodeling in severe asthma. Allergy. 2022;77:3538–52. [DOI] [PubMed] [PMC]
17. Siddiqui S, Bachert C, Bjermer L, Buchheit KM, Castro M, Qin Y, et al. Eosinophils and tissue remodeling: Relevance to airway disease. J Allergy Clin Immunol. 2023;152:841–57. [DOI] [PubMed]
18. Varricchi G, Brightling CE, Grainge C, Lambrecht BN, Chanez P. Airway remodelling in asthma and the epithelium: on the edge of a new era. Eur Respir J. 2024;63:2301619. [DOI] [PubMed] [PMC]
19. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C, et al. Real-World Effectiveness of Benralizumab in Severe Eosinophilic Asthma. Chest. 2021;159:496–506. [DOI] [PubMed]
20. Yamada M, Motoike IN, Kojima K, Fuse N, Hozawa A, Kuriyama S, et al. Genetic loci for lung function in Japanese adults with adjustment for exhaled nitric oxide levels as airway inflammation indicator. Commun Biol. 2021;4:1288. [DOI] [PubMed] [PMC]
21. Hansen S, Baastrup Søndergaard M, von Bülow A, Bjerrum AS, Schmid J, Rasmussen LM, et al. Clinical Response and Remission in Patients With Severe Asthma Treated With Biologic Therapies. Chest. 2024;165:253–66. [DOI] [PubMed]
22. Biener L, Mümmler C, Hinze CA, Suhling H, Korn S, Fisser C, et al. Real-World Data on Tezepelumab in Patients With Severe Asthma in Germany. J Allergy Clin Immunol Pract. 2024;12:2399–407.e5. [DOI] [PubMed]

23. Hamada Y, Thomas D, Harvey ES, Stevens S, Fricker M, Lewthwaite H, et al. Distinct trajectories of treatment response to mepolizumab toward remission in patients with severe eosinophilic asthma. Eur Respir J. 2025;65:2400782. [DOI] [PubMed]
24. Hanania NA, Wenzel S, Rosén K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. Am J Respir Crit Care Med. 2013;187:804–11. [DOI] [PubMed]
25. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al.; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371:1198–207. [DOI] [PubMed]
26. Agustí A, Bafadhel M, Beasley R, Bel EH, Faner R, Gibson PG, et al. on behalf of all participants in the seminar. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J. 2017;50:1701655. [DOI] [PubMed]
27. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet. 2018;391:350–400. [DOI] [PubMed]
28. Portacci A, Dragonieri S, Carpagnano GE. Super-Responders to Biologic Treatment in Type 2-High Severe Asthma: Passing Fad or a Meaningful Phenotype? J Allergy Clin Immunol Pract. 2023;11:1417–20. [DOI] [PubMed]
29. Mukherjee M, Forero DF, Tran S, Boulay ME, Bertrand M, Bhalla A, et al. Suboptimal treatment response to anti-IL-5 monoclonal antibodies in severe eosinophilic asthmatics with airway autoimmune phenomena. Eur Respir J. 2020;56:2000117. [DOI] [PubMed]
30. Abdo M, Watz H, Veith V, Kirsten AM, Biller H, Pedersen F, et al. Small airway dysfunction as predictor and marker for clinical response to biological therapy in severe eosinophilic asthma: a longitudinal observational study. Respir Res. 2020;21:278. [DOI] [PubMed] [PMC]
31. Suzukawa M, Ohta K, Fukutomi Y, Hashimoto H, Endo T, Abe M, et al. Classifications of moderate to severe asthma phenotypes in Japan and analysis of serum biomarkers: A Nationwide Cohort Study in Japan (NHOM Asthma Study). Allergol Int. 2023;72:63–74. [DOI] [PubMed]
32. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell. 2021;184:1469–85. [DOI] [PubMed]
33. Saito T, Ichikawa T, Numakura T, Yamada M, Koarai A, Fujino N, et al. PGC-1α regulates airway epithelial barrier dysfunction induced by house dust mite. Respir Res. 2021;22:63. [DOI] [PubMed] [PMC]
34. Itakura K, Fujino N, Kamide Y, Saito I, Yamada M, Okutomo K, et al. Decreased expression of airway epithelial Axl is associated with eosinophilic inflammation in severe asthma. Allergol Int. 2022;71:383–94. [DOI] [PubMed]
35. Gauthier M, Kale SL, Oriss TB, Gorry M, Ramonell RP, Dalton K, et al. CCL5 is a potential bridge between type 1 and type 2 inflammation in asthma. J Allergy Clin Immunol. 2023;152:94–106.e12. [DOI] [PubMed] [PMC]
36. Fahy JV, Jackson ND, Sajuthi SP, Pruesse E, Moore CM, Everman JL, et al. Type 1 Immune Responses Related to Viral Infection Influence Corticosteroid Response in Asthma. Am J Respir Crit Care Med. 2025;211:194–204. [DOI] [PubMed] [PMC]
37. Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Rogliani P, Chetta A. Oral Corticosteroids Dependence and Biologic Drugs in Severe Asthma: Myths or Facts? A Systematic Review of Real-World Evidence. Int J Mol Sci. 2021;22:7132. [DOI] [PubMed] [PMC]
38. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. Lancet Respir Med. 2022;10:47–58. [DOI] [PubMed]

39. Fujino N, Ota C, Takahashi T, Suzuki T, Suzuki S, Yamada M, et al. Gene expression profiles of alveolar type II cells of chronic obstructive pulmonary disease: a case-control study. BMJ Open. 2012;2: e001553. [DOI] [PubMed] [PMC]
40. Kyogoku Y, Sugiura H, Ichikawa T, Numakura T, Koarai A, Yamada M, et al. Nitrosative stress in patients with asthma-chronic obstructive pulmonary disease overlap. J Allergy Clin Immunol. 2019; 144:972–83.e14. [DOI] [PubMed]
41. Matsunaga T, Sano H, Takita K, Morita M, Yamanaka S, Ichikawa T, et al. Supersulphides provide airway protection in viral and chronic lung diseases. Nat Commun. 2023;14:4476. [DOI] [PubMed] [PMC]
42. Wu TD, Diamant Z, Hanania NA. An Update on Patient-Reported Outcomes in Asthma. Chest. 2024; 165:1049–57. [DOI] [PubMed]
43. Hyland ME, Jones RC, Lanario JW, Masoli M. The construction and validation of the Severe Asthma Questionnaire. Eur Respir J. 2018;52:1800618. [DOI] [PubMed] [PMC]