Original Article

Mucus Plug Score Predicts Clinical and Pulmonary Function Response to Biologic Therapy in Patients With Severe Asthma

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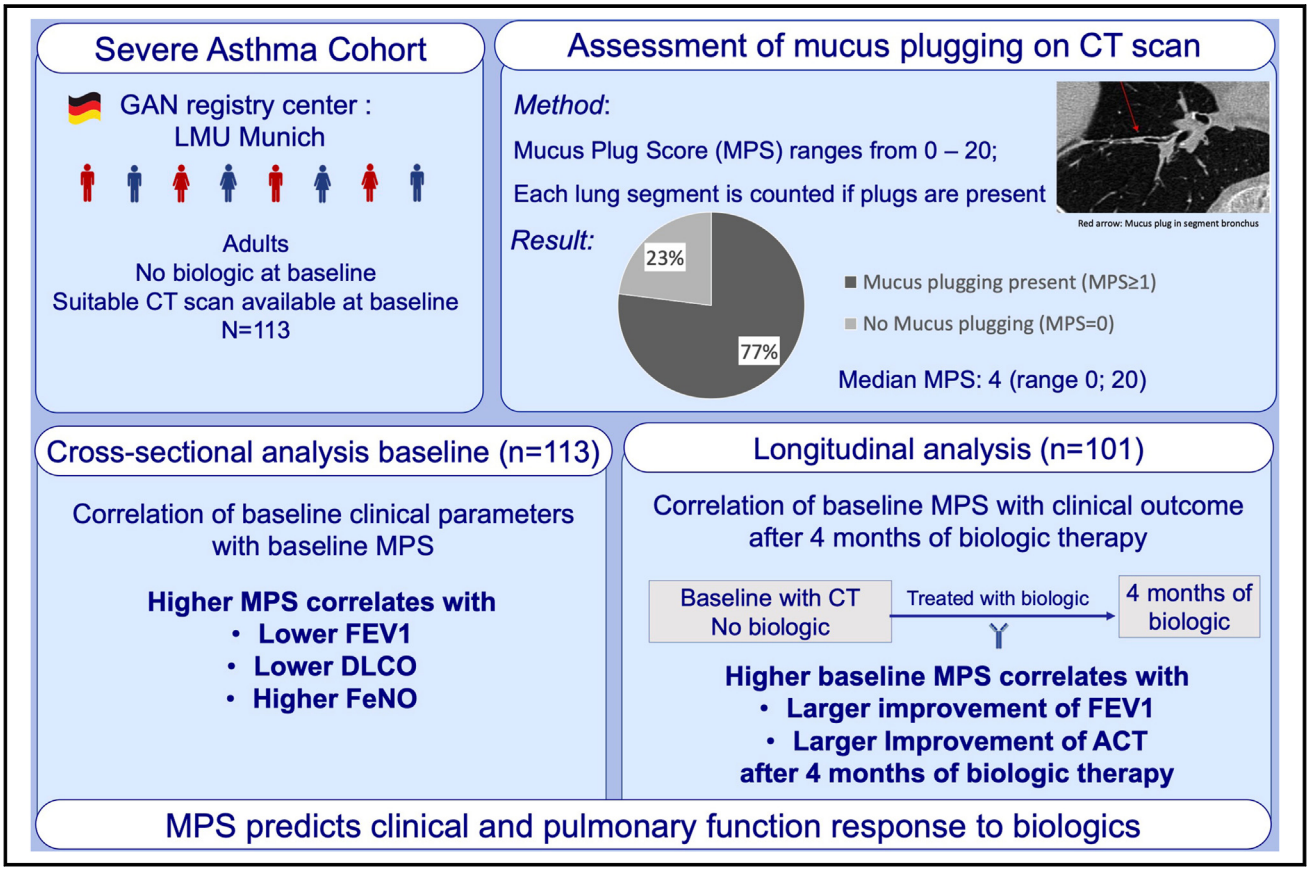
What is already known about this topic? Mucus plugging contributes to morbidity and obstruction in asthma. Recent studies suggest that biologic therapy may reduce mucus plugs in patients with severe asthma.

What does this article add to our knowledge? We found that patients with a higher mucus plug score showed a larger clinical and pulmonary function improvement in biologic treatment.

How does this study impact current management guidelines? Our study highlights the importance of mucus plugging as a feature in severe asthma and suggests it may help predict the response to biological therapies.

VISUAL SUMMARY



Abbreviations used
ACT- Asthma Control Test
BARS- Biologics Asthma Response Score
BEC- Blood eosinophil count
CT- Computed tomography
GAN- German Asthma Net
MP- Mucus plug
MPS- Mucus plug score
OCS- oral corticosteroid
TSLP- Thymic stromal lymphopoietin

BACKGROUND: Mucus plugging has been identified as an important feature of severe asthma contributing to airway obstruction and disease severity. Recently, improvement in mucus plugging has been found on treatment with several biologic therapies.
OBJECTIVES: To analyze associations of baseline characteristic with the mucus plugging score (MPS) and to determine whether the MPS at baseline predicts the clinical and functional response to biologic treatment in patients with severe asthma.
METHODS: We retrospectively analyzed biologic-naive patients with a suitable computed tomography scan available at baseline. We calculated the MPS and analyzed correlations with baseline parameters and improvements in biomarkers, pulmonary function, and clinical parameters after 4 months of biologic therapy.
RESULTS: We included 113 patients in the baseline cohort, 101 patients of whom had sufficient data after 4 months of biologic therapy for the follow-up analysis. Computed tomography showed mucus plugging in 77% of patients (median MPS, 4). Multivariate regression analysis showed a correlation of MPS with lower FEV_1 ($\rho = -0.24$; $P = .009$) and diffusing capacity for carbon monoxide ($\rho = -0.26$; $P = .01$), and higher FeNO ($\rho = .36$; $P = .0003$) at baseline. Patients received treatment with anti-IgE (8.8%), anti-IL-5 (27.4%), anti-IL-5R (37.2%), anti-IL-4R (25.7%), and anti-thymic stromal lymphopoietin (0.9%) in clinical routine. Baseline MPS correlated with improvements in FEV_1 ($\beta = 0.72$; $P = .01$) and Asthma Control Test ($\beta = 0.24$; $P = .001$) in multivariate regression analysis.
CONCLUSION: Our study suggests that a higher MPS correlates with worse pulmonary function at baseline but also predicts a larger clinical and pulmonary function response to biologic therapies in severe asthma. **(J Allergy Clin Immunol Pract 2025;13:1110-22)**

Key words: *Asthma; Mucus plugging; Mucus plug score; Biologic therapy; Antibody; FEV_1; Pulmonary function; Diffusion capacity; FeNO; Response*

INTRODUCTION

Mucus plugging, or mucus impaction of the bronchi, has been identified as an important feature of severe asthma contributing to disease severity.[1,2] It is an important factor for persisting airway obstruction and for mortality in acute asthma attacks.[3] Autopsy studies showed that mucus plugging is a major contributing cause of fatal asthma.[4] Airway mucus plugging is also associated with reduced ventilation in the same bronchopulmonary segment, which suggests that it may be an important cause of ventilation defects in asthma.[5] Patients with MPs exhibit significantly worse airflow obstruction and greater type 2 inflammation associated with more frequent severe exacerbations.[1,2] Mucus plugging in severe asthma is driven by type 2 inflammation. Goblet cells, stimulated by IL-13, produce increased amounts of mucus. Infiltration and degranulation of eosinophils in the airways lead to the formation of disulfide bridges through eosinophil peroxidase, resulting in highly viscous mucus that can affect and obliterate the bronchi.[1]

Biologic therapy may have a role in decreasing mucus plugs (MPs) by blocking underlying type 2 inflammation. Recently, anti-thymic stromal lymphopoietin (TSLP) treatment has been shown to reduce mucus plugging, and patients with an initial higher MP score (MPS) had greater improvement in lung function.[6] Also, for anti-IL-5R, rapid clearance of mucus plugging in allergic bronchopulmonary aspergillosis[7] and in severe eosinophilic asthma[8] was reported in case series. Likewise, for anti-IL-4R, several case reports and a small randomized controlled trial described an effect on mucus plugging.[9,10]

These studies suggest that the presence of mucus plugging may be associated with a response to biologic therapy. Deplugging bronchi by targeting type 2 inflammation might enable lung function improvements not amenable to inhaled therapies, especially bronchodilators. Therefore, we aimed to investigate associations of MPS in biologic-naive patients with severe asthma with baseline characteristics and to assess whether a higher MPS predicts a larger clinical and pulmonary function response to biologic treatment.

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TABLE I. Multivariate regression analysis for mucus plugging score and baseline characteristics (ρ and *P*)

Parameter	ρ	*P*	*P* adjusted
FEV_1 (% predicted)	−0.24	.009*	.01*
FVC (% predicted)	−0.20	.04*	.09
FEV_1/FVC	0.24	.01*	.09
PEF (% predicted)	0.08	.41	.46
Airway resistance (% predicted)	0.09	.37	.49
Residual volume (% predicted)	0.17	.08	.50
Total lung capacity (% predicted)	0.02	.86	.61
Diffusion capacity for carbon monoxide (% predicted)	−0.26	.01*	.02*
Mid-expiratory flow at 25% of FVC (% predicted)	0.16	.11	.08
Asthma Control Test	−0.03	.74	.27
FeNO (parts per billion)	0.36	.0003*	.01*
IgE, kU/L	0.17	.08	.90
Blood eosinophil count, μL	0.18	.06	.31

Adjustments were made for oral corticosteroid/ICS dosage and age, sex, and body mass index for non-pulmonary function parameters in a multivariate regression analysis (*P* adjusted).
*Indicates statistical significance ($P < .05$).

METHODS

Inclusion criteria

For this retrospective study, we analyzed the center-specific cohort (LMU University Hospital) of patients enrolled in the German Asthma Net (GAN) severe asthma registry from 2017 until January 2023 and selected patients who were biologic-naive and had an appropriate routine thoracic computed tomography (CT) scan performed within 12 months before the start of biologic therapy. The inclusion criterion for enrollment in the GAN registry was physician-diagnosed severe asthma (ie, necessitating step V treatment or being uncontrolled with step IV treatment according to the definition by the Global Initiative for Asthma).[11] Before inclusion in the registry, all patients gave written informed consent. The registry operates in compliance with the Declaration of Helsinki's principles and was approved by the University of Mainz's Ethics Committee as well as our local institutional review board (21-0436). For the follow-up analysis, we included only patients with clinical outcome data available 4 months after the initiation of biologic therapy.

Computed tomography protocol

Because of the retrospective real-world design of our study, available CT scans had been acquired with different protocols. Scans with a slice thickness of 0.6 to 3.0 mm, each without a gap, a hard reconstruction kernel, and available multiplanar reconstructions in axial, coronal, and sagittal orientations, were included in the analysis. The CTs were performed unenhanced or after intravenous contrast medium administration in the pulmonary arterial, arterial, or venous phase. The Computed Tomography Dose Index was 0.23 to 16.19 mGy and the tube current varied between 15 and 352 mAs.

We excluded 17 CT examinations from the analysis owing to a slice thickness of greater than 3 mm (n = 12), breathing artifacts (n = 2), or total atelectasis of one lobe (n = 1).

Computed tomography analysis

Thoracic CT scans were retrospectively analyzed by a radiologist with more than 10 years of experience in thoracic imaging, and who was blinded to any clinical information other than that the patients had asthma. The images were viewed on a picture archiving and communication system (Visage Client Version 7.1.18, Visage Imaging GmbH, Berlin, Germany) using lung window settings (level, −600 Hounsfield units; width, 1,500 Hounsfield units). We used axial and, when necessary, sagittal and coronal reconstructions for the analysis. Each bronchopulmonary segment was evaluated for the presence (score = 1) or absence (score = 0) of MPs according to a CT mucus scoring system described by Dunican et al[1], resulting in a possible total sum score of 0 to 20 for each patient. Briefly, MPs were defined as complete bronchial occlusion. Depending on their orientation to the image plane, they appeared as tubular densities with or without branching, or as oval or rounded opacities on sequential slices, which ran in continuity with ventilated bronchi. Because of the small bronchus diameter in this area, which makes mucus plugging difficult to assess, a 2-cm zone at the costal and diaphragmatic pleura was excluded from analysis.

Choice of biologic treatment

Experienced pulmonologists prescribed biologic treatment in the routine clinical care setting of a severe asthma center in accordance with German health care standards and each drug's licensing specifications.[12] Briefly, omalizumab (anti-IgE) is licensed for severe allergic asthma with sensitization to a perennial allergen and dosed according to total IgE levels between 150 mg subcutaneously (SC) every 4 weeks and 600 mg every 2 weeks. The indication for mepolizumab (anti-IL-5) is severe eosinophilic asthma characterized by a blood eosinophil count (BEC) of greater than 150/μL, at a dose of 100 mg SC every 4 weeks. Reslizumab (anti-I-L5) is for severe eosinophilic asthma characterized by BEC greater than 450/μL, with a dose of 3 mg/kg intravenously every 4 weeks, and benralizumab (anti-IL-5R) is for severe eosinophilic asthma characterized by BEC greater than 300/μL or greater than 150/μL with the use of oral corticosteroids (OCS) at a dose of 30 mg SC every 4 weeks three times and then every 8 weeks. Dupilumab is for severe type 2 asthma with increased FeNO of 25 parts per billion or greater, or BEC 150/μL or greater at a dose of 200 or 300 mg SC (in case of OCS dependency) every 2 weeks, and tezepelumab (anti-TSLP) is for severe asthma, at 210 mg SC every 4 weeks.

Functional and clinical assessment

We assessed clinical, pulmonary function, and laboratory parameters at baseline before the initiation of biologic therapy (up to 4 weeks earlier) and at 4 months (±1.5 months) after initiation of the biologic. We used the Global Lung Initiative (GLI) calculators[13] to calculate the percent predicted and z-scores with race-neutral equations for spirometry (FEV_1, FVC, FEV_1/FVC, and mid-expiratory flow at 25% of FVC),[14] recent static lung volume GLI equations for residual volume, total lung capacity,[15] and diffusion capacity for carbon monoxide (DLCO) GLI equations.[16] As for airway resistance and PEF, no such recent standards are available, so we used percent predicted data based on the older reference equations.[17,18]

We analyzed Asthma Control Test (ACT) scores, the number of exacerbations necessitating systemic corticosteroid therapy of at least 20 mg prednisolone equivalent for at least 3 consecutive days in the past 12 months, OCS and ICS dosage, spirometric and plethysmographic pulmonary function parameters, FeNO, and laboratory measurements of serum IgE levels and BECs. In the follow-up, exacerbations that occurred under biologic therapy were extrapolated to calculate an annualized exacerbation rate also at the 4-month time point. To evaluate the response to biologic treatment, we calculated the Biologics Asthma Response Score (BARS),[19] a

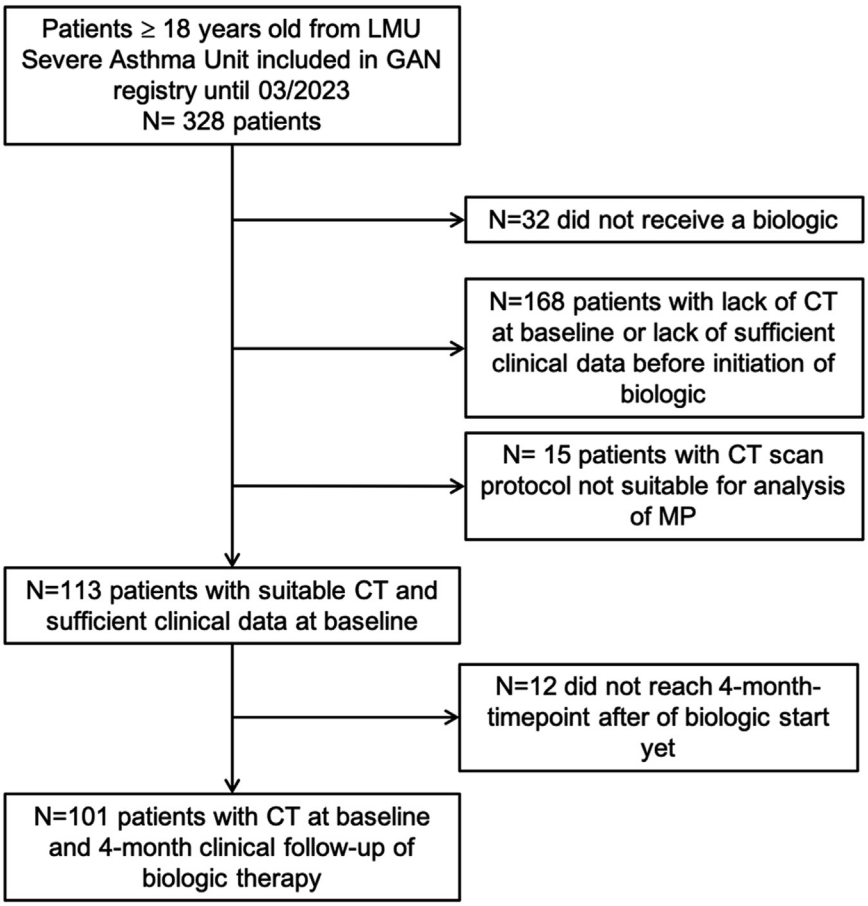


FIGURE 1. Study overview. *CT*, computed tomography; *GAN*, German Asthma Net; *LMU*, Ludwig-Maximilians University.

composite score that uses the change in exacerbations, OCS therapy, and asthma control.

Statistics

We report descriptive statistics as absolute and relative frequencies for categorical variables, means with SDs for parametric variables, and medians (interquartile ranges) for nonparametric variables. All patients were categorized into those with zero mucus plugging, low mucus plugging (score of 1-3), medium mucus plugging (score of 4-11), and high mucus plugging (score of over 11), which corresponds to the quartiles of overall distribution. We compared categorical variables among these groups using χ^2 test, and numerical variables using ANOVA. To assess the correlations among baseline lung function test parameters, baseline asthma control score and baseline laboratory parameters, and mucus plugging, we used Spearman correlation and multivariate linear regression analysis. In these regression analyses, we adjusted for OCS and ICS dosage for all outcomes. and for age, body mass index, and sex in non-pulmonary function parameters.

We used receiver operating characteristic curves to determine optimal cutoffs for outcome parameters to predict the presence of mucus plugging. Results are presented alongside values for the area under the curve (AUC), sensitivity, and specificity.

To assess changes between baseline and the 4-month follow-up, we calculated the absolute difference in parameters. We used multivariate linear regression analysis to assess the influence of mucus plugging on the change in these parameters. We adjusted all regression analyses with the value of the baseline parameter, the change in OCS dose, the ICS dose, and the mode of action of the biologic. All non-pulmonary function parameters were additionally adjusted for age, body mass index, and sex.

Data analysis was performed using R (Version 4.0.0) and RStudio (Version 1.4; Posit, Boston, MA). We applied a threshold of α less than 0.05 for significance in all analyses. For multiple regression analysis, we adjusted *P* values for multiple testing (Table I). In all other analyses, *P* values are unadjusted and should be regarded as exploratory.

RESULTS

Baseline characteristics and mucus plugging

We included 113 patients with suitable CT imagery and sufficient data at baseline. Of those, 101 had 4 months' data under biologic treatment for the follow-up analysis (Figure 1). Patients' mean age was 57 years; 57.5% were female, 58.5% had adult-onset asthma, and 36% had an allergic, 26.5% nonallergic, and 37.2% mixed phenotype (Table II). At the statistical mean value, lung function showed moderate obstruction at baseline (FEV_1/FVC in 65.6%; FEV_1 67.9% predicted; z-score, −1.93), and DLCO was slightly impaired (81.8% predicted; z-score, −1.35) (Table II).

TABLE II. Baseline characteristics

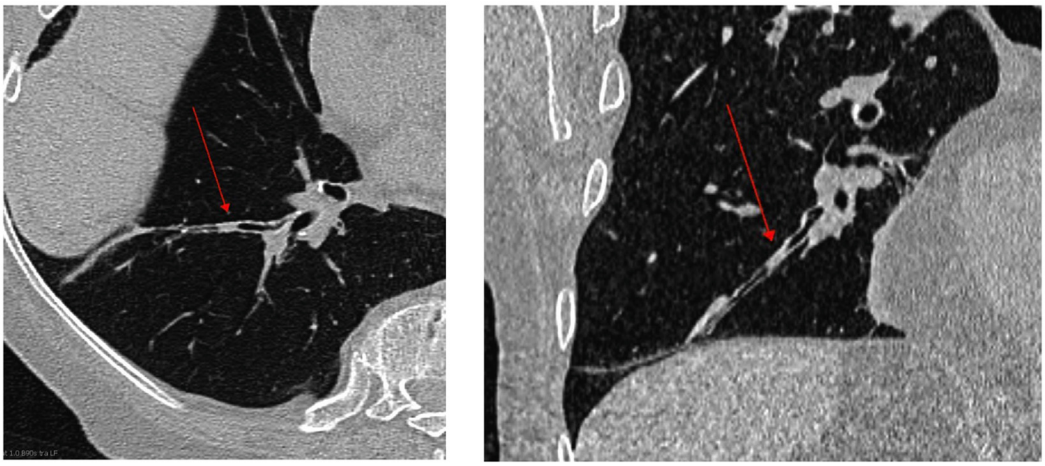
Characteristic		Total cohort (n = 113)	Follow-up cohort (n = 101)
Age, y	Mean (SD)	57.0 (14.5)	57.4 (14.6)
Female	n (%)	65 (57.5)	58 (57.4)
Body mass index, kg/m^2	Mean (SD)	26.8 (6.5)	27.0 (6.7)
Asthma phenotype	n (%)		
Allergic		41 (36.3)	37 (36.6)
Nonallergic		30 (26.5)	28 (27.7)
Mixed		42 (37.2)	36 (35.6)
Age at onset	n (%)		
Early onset (<18 y)		18 (15.9)	16 (15.8)
Adult onset (>18 y)		66 (58.4)	59 (58.4)
Unknown		29 (25.7)	27 (26.7)
Comorbidities			
Atopic dermatitis	n (%)	6 (5.3)	5 (5.0)
Allergic rhinitis	n (%)	55 (48.7)	48 (47.5)
Chronic rhinosinusitis with nasal polyps	n (%)	41 (36.3)	37 (36.6)
Chronic rhinosinusitis sNP	n (%)	18 (15.9)	16 (15.8)
Chronic obstructive pulmonary disease	n (%)	11 (9.7)	10 (9.9)
Bronchiectasis	n (%)	9 (8.0)	8 (7.9)
ABPA	n (%)	3 (2.7)	3 (3.0)
EGPA	n (%)	7 (6.2)	7 (6.9)
Smoking status			
Former	n (%)	48 (42.5)	56 (55.4)
Current	n (%)	3 (2.7)	3 (3.0)
Never	n (%)	62 (54.9)	42 (41.6)
Pack-years	Mean (SD)	22 (24)	22 (23.6)
Asthma Control Test	Median (IQR)	13 (10.0-17.0); n = 95	13 (10.0-17.7); n = 86
Exacerbations past 12 mo			
	Mean (SD)	4.2 (4.3)	4.4 (4.4)
	Median (IQR)	3 (1.3,6.0)	3 (2.0,6.0)
Pulmonary function test parameter			
FEV_1 (% predicted)	Mean (SD)	67.5 (21.3)	67.7 (21.3)
FEV_1 (z-score)	Mean (SD)	−1.93 (1.22)	−1.92 (1.23)
FVC (% predicted)	Mean (SD)	79.5 (16.1)	79.8 (16.0)
FVC (z-score)	Mean (SD)	−1.29 (1.01)	−1.28 (1.01)
FEV_1/FVC × 100	Mean (SD)	65.6 (14.4)	65.0 (14.5)
FEV_1/FVC (% predicted)	Mean (SD)	83.0 (16.0)	83.1 (16.1)
FEV_1/FVC (z-score)	Mean (SD)	−1.59 (1.41)	1.58 (1.42)
PEF (% predicted)	Mean (SD)	71.7 (24.0)	70.3 (23.5)
Mid-expiratory flow at 25% of FVC (% predicted)	Mean (SD)	66.7 (49.5)	66.8 (50.5)
Airway resistance (% predicted)	Mean (SD)	141.7 (81.3)	145.0 (83.8)
Residual volume (% predicted)	Mean (SD)	146.1 (47.9)	148.2 (48.4)
Residual volume (*z*-score)	Mean (SD)	1.33 (1.21)	1.38 (1.18)
Total lung capacity (% predicted)	Mean (SD)	98.5 (15.1)	99.6 (14.9)
Total lung capacity (z-score)	Mean (SD)	−0.16 (1.19)	0.07 (1.17)
Diffusion capacity for carbon monoxide (% predicted)	Mean (SD)	81.8 (19.8); n = 91	82.3 (18.5); n = 83
Diffusion capacity for carbon monoxide (*z*-score)	Mean (SD)	−1.35 (1.57)	−1.30 (1.48)
Biomarkers			
Blood eosinophil count, μL	Median (IQR)	290 (170.0-582.5); n = 112	310 (170.0-602.5); n = 100
Blood eosinophil count in OCS-free patients, μL	Median (IQR)	340 (215-675); n = 65	
Total IgE, kU/L	Median (IQR)	127 (48.0-447.0); n = 105	115 (39.7, 389.2); n = 34
FeNO (parts per billion)	Median (IQR)	43 (20.0-64.0); n = 101	42 (18.0, 61.5) (n = 83)
Therapy at baseline			
ICS: yes	n (%)	113 (100)	101 (100)
ICS dose (beclometasone equivalent), μg	Mean (SD)	1,621.0 (794.9)	1,592.8 (814.9)

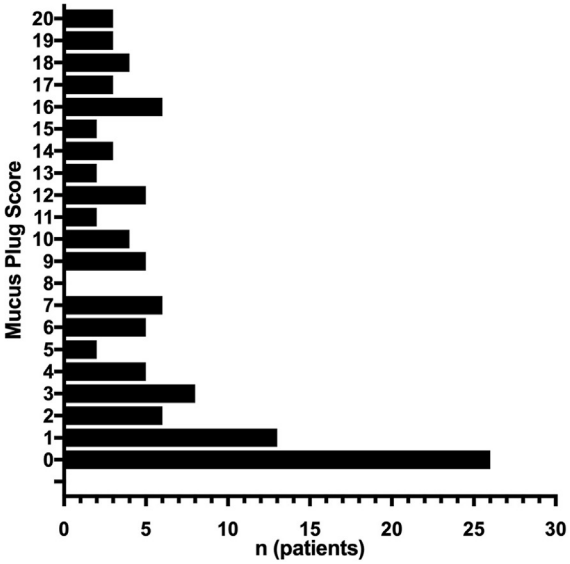
(continued)

TABLE II. *(Continued)*

Characteristic		Total cohort (n = 113)	Follow-up cohort (n = 101)
Long-acting β-agonist: yes	n (%)	104 (92.0)	92 (91.1)
Long-acting muscarinic antagonist: yes	n (%)	94 (83.2)	83 (82.2)
LTRA: yes	n (%)	43 (37.2)	40 (39.6)
OCS maintenance: yes	n (%)	47 (41.6%)	42 (41.6)
OCS maintenance dose prednisolone equivalent, mg/d	Median (IQR)	10 (5.0-15.0)	10 (5.0-15.8)
Biological therapy started after baseline			
Dupilumab	n (%)	29 (25.7)	25 (24.8)
Omalizumab	n (%)	10 (8.8)	8 (7.9)
Benralizumab	n (%)	42 (37.2)	38 (37.6)
Mepolizumab	n (%)	30 (26.5)	28 (27.7)
Reslizumab	n (%)	1 (0.9)	1 (1.0)
Tezepelumab	n (%)	1 (0.9)	0

ABPA, Allergic broncho-pulmonary aspergillosis; *EGPA*, eosinophilic granulomatosis with poliangiitis; *IQR*, interquartile range; *LTRA*, leucotriene receptor antagonist; *OCS*, oral corticosteroid; *sNP*, sine nasal polyps.





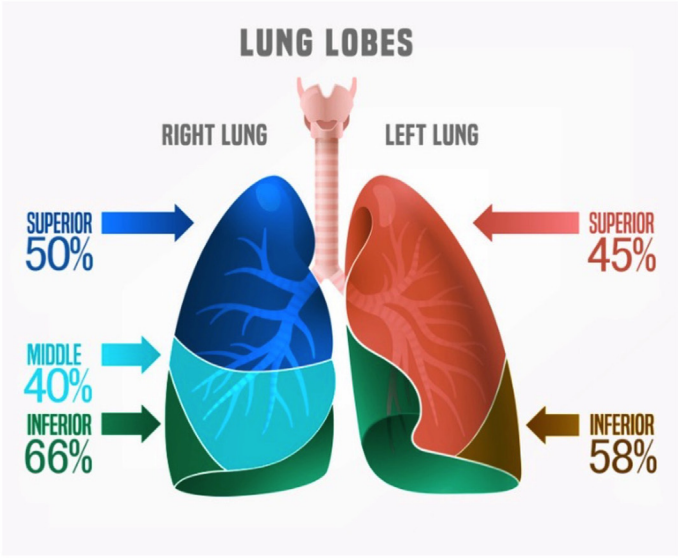


FIGURE 2. Mucus plugging at baseline in total cohort (n = 113). (*Upper*) Example of computed tomography scan with mucus plugging in axial (*left*) and coronal (*right*) reconstruction. *Red arrow* indicates plug in segment bronchus S10R. (*Lower left*) Frequency histogram of mucus plug score (MPS). An MPS of 0 signifies no segment with mucus plugging, and 20 signifies mucus plugging in all lung segments. (*Lower right*) Prevalence (percentage of patients) of mucus plugs in different lung lobes.

TABLE III. Baseline characteristics of total cohort (n = 113) according to mucus plugging score quartile

Characteristic		Zero mucus plugging (n = 26)	Low mucus plugging (n = 27)	Medium mucus plugging (n = 29)	High mucus plugging (n = 31)	*P*	
Age, y	Mean (SD)	53.3 (14.6)	55.0 (15.5)	60.8 (14.4)	58.3 (13.5)	.23	
Female	n (%)	19 (73.1%)	15 (55.6%)	19 (65.5%)	12 (38.7%)	.05	*
Body mass index, kg/m^2	Mean (SD)	28.4 (7.02)	28.9 (7.42)	24.7 (5.04)	25.3 (5.76)	.03	*
Phenotype	n (%)						
Allergic		9 (34.6)	11 (40.7)	10 (34.5)	11 (35.5)		
Nonallergic		6 (23.1)	7 (25.9)	11 (37.9)	6 (19.4)		
Mixed		11 (42.3)	9 (33.3)	8 (27.6)	14 (45.2)	.67	
Age at onset of asthma	n (%)						
Early onset		6 (23.1)	5 (18.5)	4 (13.8)	3 (9.7)		
Adult onset		11 (42.3)	14 (51.9)	16 (55.2)	25 (80.6)		
Unknown		9 (34.6)	8 (29.6)	9 (31.0)	3 (9.7)	.24	
Smoking status							
Former	n (%)	9 (34.6)	11 (40.7)	15 (51.7)	13 (41.9)	.84	
Current	n (%)	1 (3.8)	0	1 (3.4)	1 (3.2)		
Never	n (%)	16 (61.5)	16 (59.3)	13 (44.8)	17 (54.8)		
Pack-years in current or former smokers	Mean (SD)	14.2 (11.4)	15.4 (10.4)	29.3 (29.3)	24.4 (29.9)	.33	
Asthma Control Test	Median (IQR)	12 (11.0-14.0)	13 (9.0, 17.0)	13 (10.0-19.0)	13 (9.0-16.0)	.73	
Exacerbations in past 12 mo							
	Mean (SD)	5.2 (5.6)	3.5 (3.4)	5.1 (4.9)	3.4 (2.7)	.21	
	Median (IQR)	3.0 (1.0-8.0)	3.0 (2.0-3.5)	4.0 (3.0-6.0)	3.0 (1.5-4.5)	.38	
Pulmonary function test parameter							
FEV_1 (% predicted)	Mean (SD)	74.2 (23.0)	72.0 (19.3)	64.1 (20.5)	61.2 (20.8)	.06	
FEV_1 (z-score)	Mean (SD)	−1.60 (1.42)	−1.70 (1.14)	−2.07 (1.10)	−2.30 (1.17)	.11	
FVC (% predicted)	Mean (SD)	81.9 (14.3)	83.3 (14.2)	79.7 (16.9)	74.2 (17.6)	.15	
FVC (z-score)	Mean (SD)	−1.19 (0.94)	−1.06 (0.87)	−1.25 (1.02)	−1.64 (1.12)	.14	
FEV_1/FVC	Mean (SD)	68.4 (20.0)	68.9 (13.2)	62.4 (12.7)	63.3 (10.6)	.21	
PEF (% predicted)†	Mean (SD)	72.0 (24.1)	74.7 (19.8)	71.1 (24.8)	69.3 (27.3)	.86	
Mid-expiratory flow at 25% of FVC (% predicted)	Mean (SD)	89.2 (77.8)	64.3 (38.2)	57.3 (32.3)	57.8 (35.1)	.07	
Mid-expiratory flow at 25% of FVC (*z*-score)	Mean (SD)	−0.77 (1.54)	−1.21 (1.26)	−1.28 (1.07)	−1.25 (1.13)	.44	
Airway resistance (% predicted)†	Mean (SD)	137.3 (83.6)	127.0 (50.6)	158.0 (108.0)	142.0 (71.5)	.56	
Residual volume (% predicted)	Mean (SD)	141.1 (62.1)	143.2 (43.8)	153.2 (50.0)	146.1 (35.6)	.80	
Residual volume (*z*-score)	Mean (SD)	1.07 (1.36)	1.26 (1.20)	1.52 (1.22)	1.42 (1.06)	.54	
Total lung capacity (% predicted)	Mean (SD)	99.7 (18.0)	99.8 (14.9)	105.0 (16.2)	98.3 (13.9)	.41	
Total lung capacity (*z*-score)	Mean (SD)	−0.34 (1.40)	−0.13 (1.12)	0.17 (1.21)	−0.34 (1.04)	.30	
Diffusion capacity for carbon monoxide (% predicted)	Mean (SD)	89.2 (14.0)	86.0 (22.3)	79.7 (19.9)	73.9 (19.4)	.04	*
Diffusion capacity for carbon monoxide (z-scores)	Mean (SD)	−0.81 (0.97)	−1.12 (1.82)	−1.51 (1.72)	−1.86 (1.50)	.13	
Biomarkers							
Blood eosinophil count, μL	Median (IQR)	215 (122.0-290.0)	230 (170.0-372.0)	400 (260.0-580.0)	420 (165.0-790.0)	.08	
IgE, kU/L	Median (IQR)	84 (45.8-268.0)	92 (39.0-275.0)	145 (665-497.0)	168 (56.0-490.0)	.48	
FeNO (parts per billion)	Median (IQR)	12.5 (12.0-42.2)	25 (1.95-49.5)	45 (30.5-72.5)	60 (24.0-86.0)	.004	*

Therapy at baseline						
ICS: yes	n (%)	26 (100)	27 (100)	29 (100)	31 (100)	.34
ICS dose (beclometasone equivalent), μg	Mean (SD)	1,719 (748)	1,739 (696)	1,337 (751)	1,702 (918)	.17
Long-acting β-agonist: yes	n (%)	24 (92.3)	25 (92.6)	26 (89.7)	29 (93.5)	.72
Long-acting muscarinic antagonist: yes	n (%)	22 (84.6)	22 (81.5)	25 (86.2)	25 (80.6)	.98
LTRA yes	n (%)	11 (42.3)	15 (55.6)	10 (34.5)	7 (22.6)	.08
OCS therapy at baseline: yes	n (%)	9 (34.6)	8 (29.6)	15 (51.7)	15 (48.4)	.86
Type of biologic therapy started after baseline						
Dupilumab	n (%)	6 (23.1)	9 (33.3)	9 (31.0)	5 (16.1)	.42
Omalizumab	n (%)	5 (19.2)	2 (7.4)	0	3 (9.7)	.08
Benralizumab	n (%)	6 (23.1)	9 (33.3)	8 (27.6)	19 (61.3)	.01 *
Mepolizumab	n (%)	7 (26.9)	7 (25.9)	12 (41.4)	4 (12.9)	.10
Reslizumab	n (%)	1 (3.8)	0	0	0	.23
Tezepelumab	n (%)	1 (3.8)	0	0	0	.23

OCS, oral corticosteroids.
P values by ANOVA or Kruskal-Wallis test.
*Significant *P*-level <.05.

The CT analysis revealed that 77% of patients exhibited mucus plugging. An example of MP is shown in Figure 2. The median score was 4 before biologic therapy was initiated. The frequency histogram showed the higher prevalence of the lowest MPS from 1 to 3, but medium and high scores were equally present: three patients reached the maximum score of 20 points (Figure 2). Regarding the distribution of MPs across different lung lobes, the lower lung lobes were affected more frequently. However, up to 50% also exhibited mucus plugging in the upper lung lobes (Figure 2).

According to the quartile distribution, we grouped the cohorts into no MPS (0), low MPS (1-3), medium MPS (4-11), and high MPS (12-20). There were no significant differences in age, smoking status, or OCS use among quartile groups (Table III). However, patients in the highest MPS quartile were more frequently male (61.3%) compared with the other quartiles (34.5%, 44.4%, and 26.9%), and patients with no or a low MPS had a higher body mass index (28.4 and 28.9 kg/m^2, respectively) than the higher MPS quartiles (24.7 and 25.3 kg/m^2, respectively). Additionally, type 2 biomarkers increased from the lowest to the highest MPS quartile: FeNO increased significantly ($P = .004$), and BEC numerically ($P = .08$) (Table III). Interestingly, patients with a higher MPS at baseline later received benralizumab more frequently (61.3%) (Table II). Lung function parameters did not show significant differences among the four MPS groups using ANOVA, except that DLCO percent predicted was reduced in the high MPS quartile (Table III).

Multiple regression analysis showed that the baseline MPS correlated significantly with other baseline parameters including lower FEV_1 (ρ −0.24; adjusted $P = .01$), lower diffusion capacity (ρ −0.26; adjusted $P = .02$), and higher FeNO (ρ 0.36; adjusted $P = .01$) (Table I). In contrast, we found no significant correlation for the ACT, exacerbations in the past 12 months, or bronchodilator responsiveness (in milliliters) at baseline with MPS. Additionally, there was no significant correlation of the MPS with BEC in the total cohort. Because OCS use decreases BEC, we also performed an analysis restricted to patients without maintenance OCS at baseline (n = 65) (Table II). Here, median BEC was higher than in the total cohort (340/μL) and correlated significantly with the MPS (Spearman $r = 0.39$; $P = .002$).

In receiver operating characteristic curve analysis, FeNO showed high specificity for MP at a cutoff of 49.5 parts per billion, but lower sensitivity (AUC = 0.70, sensitivity = 0.47, and specificity = 0.91). The most sensitive marker was diffusion capacity (AUC = 0.59, sensitivity = 0.91, and specificity = 0.26) at a cutoff of 63.5 percent predicted (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Associations between baseline MPS and improvements in outcome parameters under biologic therapies

After 4 months of biologic therapy, asthma outcome parameters improved significantly with increased ACT scores (+5; 95% CI, 2-6), reduced frequency (−10%), dose (−5.7 mg, SD, 15.6 mg) of OCS maintenance therapy, and reduced annualized exacerbations (−3/y; 95% CI, −3 to −2). The composite BARS that ranges from 0 to 2 was 1.33 at median, corresponding to a response to the biologic (Table IV). Likewise, pulmonary function parameters improved significantly, including increases in FEV_1, FVC, FEV_1/FVC, PEF, and DLCO and reductions in resistance (Table IV). Biomarkers BEC and FeNO were

TABLE IV. Outcome parameters at baseline and after 4 mo of biologic treatment

Parameter		Follow-up cohort baseline (n = 101)	4-mo biologic treatment (n = 101)	% predicted change in PFT	*P* (baseline vs follow-up)	Test
Asthma Control Test	Median (IQR); n = 86 baseline	13.0 (10.0-17.7)				
	Median (IQR); n = 70 baseline plus follow-up	13.0 (10.0-17.8)	18.5 (15.3, 22.0)		<.0001	*
Oral corticosteroids: yes	n (%)	42 (41.6)	32 (31.6)		<.0001	‡
Prednisolone equivalent dose (in those with oral corticosteroids at baseline), mg/d	Mean (SD)	12.1 (15.5)	6.4 (6.8)		<.0001	†
Annualized exacerbations, y	Median (IQR)	3.0 (2.0-6.0)	0		<.0001	*
Biologics Asthma Response Score	Median (IQR)	—	1.33 (1.0-2.0)			
Pulmonary function parameters						
FEV_1 (% predicted)	Mean (SD)	67.7 (21.2)	74.1 (22.4)	6.4	.004	†
FEV_1 *z*-scores	Mean (SD)	−1.92 (1.23)	−1.53 (1.30)		.003	†
FVC (% predicted)	Mean (SD)	79.8 (16.0)	84.7 (17.7)	4.9	.002	†
FVC (*z*-scores)	Mean (SD)	−1.28 (1.01)	−0.96 (1.12)		.003	†
FEV_1/FVC	Mean (SD)	65.0 (14.5)	84.4 (14.6)		<.001	†
PEF (% predicted)	Mean (SD)	70.3 (23.5)	77.2 (25.3)	6.9	<.001	†
Airway resistance (% predicted)	Mean (SD)	145.0 (83.8)	133.0 (83.0)		.02	†
Residual volume (% predicted)	Mean (SD)	148.2 (48.4)	141.1 (54.9)	−7.2	.07	†
Residual volume *z*-scores	Mean (SD)	1.38 (1.18)	1.17 (1.35)		.06	†
Total lung capacity (% predicted)	Mean (SD)	99.6 (14.9)	100.6 (16.5)	1.0	.49	†
Total lung capacity *z*-scores	Mean (SD)	−0.07 (1.17)	0.01 (1.29)		.55	†
Diffusion capacity for carbon monoxide (% predicted)	Mean (SD); n = 83 baseline	82.3 (18.5)				
	n = 13 baseline plus follow-up	73.4 (16.5)	80.1 (22.5)	6.7	.04	†
Biomarkers						
Blood eosinophil count, μL	Median (IQR); n = 100 baseline	310 (170-603)				
	n = 88 baseline plus follow-up	305 (170.0-560.0)	40 (0-160.0)		<.0001	*
FeNO (parts per billion)	Median (IQR); n = 91 baseline	42 (18, 62)				
	n = 67 baseline plus follow-up	43 (22.5-61.5)	31 (17.0-48.0)		.01	*
IgE, kU/L	Median (IQR); n = 96 baseline	115 (40-389)				
	n = 32 baseline plus follow-up	176.5 (66.3-552.3)	140.5 (50-275)		0.12	*

IQR, Interquartile range; *PFT*, pulmonary function test.
P was determined by paired *t* test or Wilcoxon test, as appropriate.
*P by paired Wilcoxon rank test.
†P by paired *t* test.
‡P by χ^2 test.

significantly reduced under biologic therapies (Table IV), as expected. Effects varied depending on the mechanism of action of each drug (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Spearman correlation analysis showed that MPS at baseline correlated inversely with the change in OCS maintenance therapy after 4 months of biologic treatment (Spearman $r = -0.23$; $P = .019$), whereas the change in the exacerbation rate alone did not show a significant correlation (Spearman $r = -0.07$; $P = .51$). Also, there was a significant correlation with improvement in ACT scores and pulmonary function parameters (Δ FEV_1 % predicted, Δ FVC % predicted, and Δ FEV/FVC) as well as the combined

TABLE V. Multivariate regression analysis with baseline mucus plugging score as independent variable and follow-up outcome parameters as dependent variables

Parameter	β	SE	*t*	*P* adjusted
FEV_1 (% predicted)	0.72	0.26	2.75	.01*
FVC (% predicted)	0.46	0.24	1.95	.05
FEV_1/FVC	0.33	0.17	1.95	.05
PEF (% predicted) (n = 99)	0.30	0.30	0.99	.32
Airway resistance (% predicted). (n = 100)	−0.92	0.86	−1.08	.28
Residual volume (% predicted)	−0.04	0.41	−0.10	.92
Total lung capacity (% predicted).	0.28	0.16	1.73	.09
Diffusion capacity for carbon monoxide (% predicted) (n = 13)	0.14	0.61	0.22	.84
Mid-expiratory flow at 25% of FVC (% predicted) (n = 92)	0.33	0.46	0.71	.48
Asthma Control Test (n = 70)	0.24	0.07	3.42	.001*
FeNO (parts per billion) (n = 67)	−0.26	0.72	−0.37	.71
IgE, kU/L (n = 32)	11.37	24.24	0.47	.65
Blood eosinophil count, μL (n = 100)	8.72	5.16	1.69	.10

n = 101 unless otherwise specified.
*P adjusted < .05.

clinical response measured by BARS (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

Multivariate regression analysis showed that baseline MPS was significantly correlated with improvements in FEV_1 (β = 0.72; P = .01) and ACT scores (β = 0.24; P = .001) under biologic therapy (Table V and Figure 3).

DISCUSSION

We found that a higher MPS at baseline correlates with lower FEV_1 and diffusion capacity and higher FeNO at baseline, and with larger improvements in pulmonary function (FEV_1, FVC, and FEV_1/FVC) and clinical response parameters (ACT and BARS) after 4 months of biologic therapy.

At baseline, MPs in 77% of the patient cohort surpassed prevalence rates reported previously. For instance, Dunican et al[1] reported a prevalence of 58% (with 10% of patients receiving OCS), whereas Chan et al[2] found a prevalence of 53% (with 13 of 126 patients receiving OCS), both in cohorts composed of patients with differing severities of asthma. The higher prevalence in our study might be attributed to the inclusion of patients exclusively with severe asthma, a more clinically compromised cohort, as indicated, for example, by the necessity for OCS maintenance therapy in 40.7% of patients in the study.

Consistent with recent literature,[1,2] we detected mucus plugging more frequently in the lower lobes than in the upper lobes, possibly owing to the influence of gravity or nonuniform ventilation with more air entering the lower lobes, carrying more particles that might trigger asthma inflammation such as allergens, viruses, and air pollution.

The observed association between MPS and reduced FEV_1 at baseline is consistent with the concept that mucus plugging causes bronchial obstruction, impeding airflow. Moreover, the occlusion of bronchi by mucus may compromise gas exchange within the alveolar spaces, as evidenced by findings from gas MRI studies,[5] ultimately contributing to a reduction in diffusion capacity. It may be surprising that patients with a low MPS and lower inflammation markers had similar treatments but higher body mass index than patients with a high MPS. However, sex-specific differences might also have a role because these were more frequently female.

The lack of a positive bronchodilator response is a frequent finding in severe asthma.[20] Nevertheless, patients with severe eosinophilic asthma but no relevant bronchodilator response benefit from anti-IL-5/R treatment,[21] and mucus plugging and deplugging might be a mechanism behind this observation. Also, an increase in MPS over 3 years was associated with worsening of lung function in an observational study.[22] In the current study, there was a notable increase in FEV_1 after biologic treatment, with larger improvements in patients with a higher baseline MPS. Consequently, we posit that biologic agents may reduce MPs, a phenomenon documented in limited cohorts.[6,8,9] We also observed significant improvement in diffusion capacity, consistent with improvement in ventilation defects on xenon-MRI shown in some studies.[23] Yet our analysis was limited by the small fraction of patients who had DLCO measurements available at 4 months.

Consistent with previous studies, we found an association between type 2 inflammation, especially FeNO, and mucus plugging. FeNO represents IL-13–mediated inflammation, a cytokine driving mucus secretion by promoting goblet cell hyperplasia. Interestingly, in a previous analysis, BEC, which represents the other type 2 biomarker involved in MP formation,[1] showed no significant correlation with mucus plugging. However the profound suppression of BEC by OCS has to be considered as a relevant confounder.[24] Thus, in an analysis restricted to patients without OCS maintenance therapy, there was a correlation between MPS and BEC, which underlines the importance of type 2 pathways in the pathophysiology of airway obstruction by mucus plugging. A causal role for type 2 inflammation in mucus production and plug formation has been demonstrated, although other factors may also be important in this process. Thus, mucus plugging is not independent of type 2 inflammation biomarkers, but rather represents an important link between type 2 inflammation and lung function at baseline and a response to biologics that can be assessed in routine clinical practice. Because there are multiple reasons for persistent airflow obstruction after bronchodilation (eg, comorbid chronic obstructive pulmonary disease), and type 2 biomarkers may be

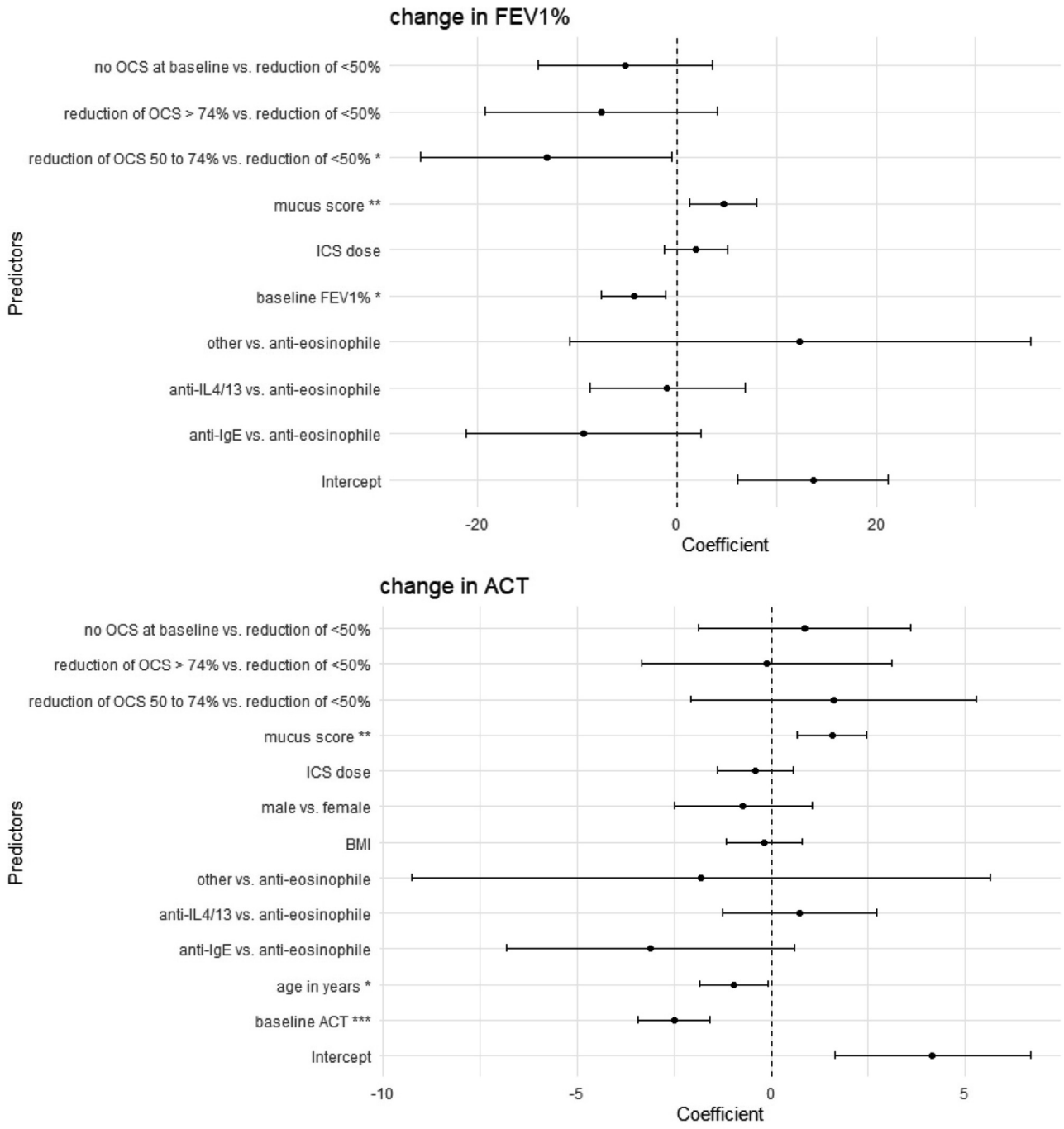


FIGURE 3. Forest plot with scaled numbers as visualization of multivariate regression analysis of factors that might correlate with changes in FEV_1/Asthma Control Test (ACT) under biologic therapy. The mucus plug score at baseline correlates significantly with changes in FEV_1 and ACT after 4 months. *BMI*, body mass index; *OCS*, oral corticosteroid.

more variable than mucus plugging and can be masked by corticosteroid treatments, assessing mucus plugging may help to predict response to biologics and specifically lung function response better than using type 2 biomarkers alone.

Our study had several limitations. Although most patients with severe asthma in our center had a thoracic CT scan at any point as part of clinical routine evaluation, a potential selection bias may have existed because we could include only patients who had undergone high-resolution CT scan in timely proximity to baseline measurements before the start of the biologic. Because of the retrospective nature of the study, some parameters have substantial amounts of missing data (eg, the partial absence of DLCO or biomarker measurements in the follow-up). Moreover, there was an uneven distribution of biologic therapies. Tezepelumab was underrepresented because it was licensed only at the end of the study period, and reslizumab is

rarely used in practice owing to intravenous administration. Also, only a small subset of patients received omalizumab (n = 10), and a notable proportion of these exhibited no MPs at baseline (n = 5), which limits the transferability of results to the allergic phenotype of severe asthma and anti-IgE therapy. Conversely, most patients in the high-MPS group received benralizumab, and results under the biologic are mainly attributable to benralizumab, mepolizumab, and dupilumab. The choice of biologic was made by the treating physician in routine clinical treatment and apart from licensing criteria and predictors of response.[12] This choice was also influenced by the order of availability of the biologics. Omalizumab, mepolizumab, and benralizumab were available for the whole time frame of the study, whereas dupilumab became available later, and tezepelumab only recently.

Different biologics target various aspects of type 2 inflammation,[25] which may be associated with varying effects on mucus plugging. For example, it is perceivable that broader substances such as anti-IL-4R or anti-TSLP that also act on IL-13 signaling might have the greatest effect. However, in our study we did not compare different biologics because of the small group sizes. Additionally, in this pragmatic retrospective analysis we included CT scans with a tolerance for slice thickness up to 3 mm even though 1 mm would be preferable. However, we used sagittal and coronal reconstructions in addition to axial ones to optimize the sensitivity for detecting small MPs. Furthermore, other parameters that can be assessed on CT scans, such as bronchiectasis,[26] bronchial wall thickening,[27] and mediastinal lymphadenopathy[28] can affect lung function and were not assessed here. In this study, MP scoring was performed by only one experienced thoracic radiologist Confirmation by a second radiologist would be desirable to assess intra-observer reliability. Moreover, our assessment of eosinophils was limited to blood eosinophils, neglecting sputum or biopsy eosinophil counts owing to the real-world study design.

With our retrospective, real-world study, we can report only associations between mucus plugging and baseline pulmonary function impairments including DLCO as well as improvements under biologic, but we cannot show causality. Regarding previous studies and clinical experience, it seems likely that mucus plugging might have a causal role, but other factors such as airway remodeling are probably also important. Because increased type 2 inflammation underlies both and is the target of biologic treatment, it is difficult to discern the influence of these different factors. Although highly significant, the correlations of baseline MPS and improvements under therapy were weak to moderate, again underlining the importance of other factors in addition to MP for the therapeutic response.

Our study highlights the importance of mucus plugging as a feature in severe asthma that is associated with stronger type 2 inflammation as well as more severe impairment of pulmonary function and diffusion capacity at baseline, but also with predicting a larger response to biologic therapies.

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TABLE E1. Biomarkers before and during biologic therapy, stratified by antibody

Biomarker		Follow-up cohort baseline	4-mo biologic treatment	Change in parameter median (95% CI)	*P* (baseline vs follow-up)
Blood eosinophil count, μL (median [interquartile range])	Benralizumab (n = 33)	290 (188-500)	0	−300 (-410 to −222)	**<.0001**
	Dupilumab (n = 24)	220 (120-330.5)	265 (132.5-465)	+25 (−24 to +260)	.1350
	Mepolizumab (n = 24)	580 (270-1,245)	60 (32.5-90)	−536.5 (−960 to −210)	**<.0001**
	Omalizumab (n = 8)	87.5 (210-355)	22.5 (65-715)	−15 (−310 to 780)	>.99
FeNO (ppb) (median [interquartile range])	Benralizumab (n = 28)	43 (25.5-64)	32 (15.5-68.5)	−4 (−31 to 7)	.32
	Dupilumab (n = 21)	44 (23.5-59)	20 (13.5-33)	-17 (-33; -4)	**.002**
	Mepolizumab (n = 12)	51.5 (36.75-77.75)	52 (33-58.5)	−3 (−43 to 18)	.56
	Omalizumab (n = 8)	17 (8-38)	20.5 (14.25-32.25)	0.5 (−13 to 11)	.96

For each parameter we considered only patients who had values at both time-points available.
P was determined by paired Wilcoxon test.
P values < .05 are in bold.

TABLE E2. Correlation of baseline mucus plug score with changes in outcome parameters after 4-mo of biologic therapies

Correlation of mucus plug score baseline with Δ (follow-up−baseline) parameter	Spearman *r*	*P* (two-tailed)	n
Biologics Asthma Response Score	0.3128	**.0012**	104
Asthma Control Test	0.4871	**<.0001**	72
Δ FEV_1 % predicted	0.3266	**.0008**	102
Δ FVC % predicted	0.2525	**.0109**	101
Δ FEV_1/FVC	0.2267	**.0226**	101
PEF % predicted	0.1046	.3003	100
Airway resistance % predicted	−0.1933	.0528	101
Residual volume % predicted	−0.01629	.8709	102
Total lung capacity % predicted	0.1558	.1179	102
Diffusion capacity for carbon monoxide % predicted	0.01333	.9656	14
Δ Mid-expiratory flow at 25% of FVC % predicted	0.1549	.1381	93
Δ FeNO (parts per billion)	−0.2013	.0972	69
Δ IgE, kU/L	−0.07848	.6591	34
Δ Blood eosinophil count, μL	−0.1349	.205	90
Δ Oral corticosteroids (% of baseline)	0.3187	**.035**	44
Δ Exacerbation rate	0.06423	.5213	102

P values < .05 are in bold."

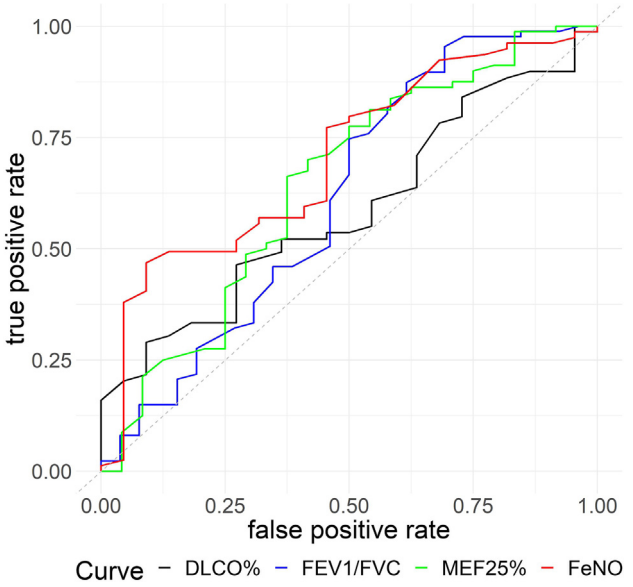

FIGURE E1. Received operating characteristic analysis. FeNO demonstrated the highest area under the curve (AUC) at 0.70, with a sensitivity of 0.47, specificity of 0.91, and cutoff of 49.5 parts per billion. Maximal expiratory flow at 25% of the pulmonary volume (MEF25%) had the second highest AUC at 0.65, with a sensitivity of 0.63, specificity of 0.66, and cutoff of 40.5%. Diffusing capacity of the lungs for carbon monoxide (DLCO) showed the highest sensitivity, with an AUC of 0.59, sensitivity of 0.91, specificity of 0.26, and cutoff of 63.5%. FEV_1/FVC had the highest specificity, with an AUC of 0.61, sensitivity of 0.36, specificity of 0.95, and cutoff of 82.07.