

Prognostic Predictors of Bronchial Thermoplasty for Symptom Control in Severe Asthma

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Purpose: To explore the clinical biomarkers that predict therapeutic response to bronchial thermoplasty (BT) in severe asthma.

Patients and Methods: We prospectively recruited patients with severe asthma who completed three sessions of bronchial thermoplasty. Baseline demographics, Asthma Control Questionnaire-5 (ACQ5) scores, eosinophil counts, fractional exhaled nitric oxide (FeNO), spirometry, impulse oscillometry (IOS), endobronchial optical coherence tomography (EB-OCT), and BT activation counts were recorded. All subjects were followed for two years and classified as responders or non-responders according to ACQ5 improvement ≥ 0.5 points.

Results: Thirty patients were included (22 responders, 8 non-responders). Compared with non-responders, responders had lower body weight, BMI, and triglycerides, along with more negative X_5 values, higher RV/TLC ratios, greater Collagen Type III (COL3) expression, and larger airway luminal areas with thinner airway walls on EB-OCT. Receiver operating characteristic (ROC) analysis demonstrated that body weight (AUC = 0.759), BMI (AUC = 0.733), triglycerides (AUC = 0.694), X_5 (AUC = 0.938), RV/TLC (AUC = 0.756), COL3 (AUC = 0.846), and EB-OCT indices including airway luminal area from the 3rd to 6th generation (Ai3–6), 7th to 9th generation (Ai7–9), and airway wall area percentage from the 3rd to 6th generation (Aw%3–6) showed moderate-to-good discriminatory power (AUC range: 0.761–0.830). Multivariable logistic model integrating BMI, X_5 , and Ai3–6 achieved better discrimination (AUC = 0.988) in predicting response to BT.

Conclusion: More negative baseline X_5 , lower triglyceride levels, EB-OCT-derived thinner airway walls and larger luminal areas, and higher COL3 expression, but not BT activation number, may help identify asthma patients most likely to benefit from BT and serve as potential predictors of its long-term efficacy.

Keywords: severe asthma, bronchial thermoplasty, predictors, optical coherence tomography, prognosis

Introduction

Asthma, defined as an airway disease with reversible airflow limitation, is characterized by airway remodeling and chronic inflammation. Airway smooth muscle (ASM) hypertrophy, mucous gland hyperplasia, and inflammatory infiltration are primarily responsible for bronchoconstriction and asthmatic symptoms.^{1–3} Notably, severe asthma carries a high risk of recurrent acute attacks and corticosteroid-related side effects, imposing substantial socioeconomic and healthcare burdens.

Bronchial thermoplasty (BT) has emerged as a non-pharmacological treatment for severe asthma that is refractory to standard therapy.^{4,5} BT delivers thermal radiofrequency energy to airways with diameters between 3 and 10 mm, thereby attenuating bronchoconstriction by ablating ASM.⁶ Clinical studies have demonstrated that BT improves asthma-related

quality of life, reduces hospitalizations and emergency visits, as well as decreases reliever medication use.^{7,8} Nevertheless, not all patients derive clinical benefit, with response rates ranging between 50% and 75%.⁹ Identifying the potential predictors of BT treatment remains a great challenge in the clinical practice.

Several clinical and biological indicators, including FeNO, peripheral blood eosinophil counts, serum IgE levels, and ACQ scores, have been investigated as potential factors associated with the response to BT.^{10,11} However, their predictive performance has been reportedly inconsistent, and of limited value for predicting clinical outcomes.¹² Likewise, pulmonary function tests (eg, FEV₁, FVC) and high-resolution computed tomography (HRCT) have been explored for their association with treatment response, but their detection of airway remodeling and ASM burden remains suboptimal.^{13,14}

Endobronchial optical coherence tomography (EB-OCT), a novel imaging modality based on low-coherence interferometry,^{15,16} could generate high-resolution images of airway morphology that correlate well with HRCT and histopathological findings.¹⁷ Using an ultrathin probe introduced via the bronchoscopic working channel, EB-OCT enables *in vivo* visualization and quantitative assessment of moderate to small airway structures, including luminal area and wall thickness. EB-OCT could offer high resolution without radiation exposure, allow repeated and minimally invasive measurements for real-time monitoring of therapeutic efficacy.¹⁸ Based upon the EB-OCT metrics, we might explore the combination of potential clinical biomarkers to identify structural differences between BT responders and non-responders, thereby serving as a promising tool for predicting and evaluating BT outcomes.

In this context, we conducted a prospective study analyzing the clinical characteristics, pulmonary function, airway morphology, and inflammatory markers of patients with severe asthma who underwent BT treatment. This study aims to provide evidence for more precise eligibility criteria for BT, thereby optimizing patient selection and improving clinical outcomes.

Materials and Methods

Subjects

Patients with severe asthma, who met the GINA guideline definition and received three sessions of BT treatment, were enrolled in the First Affiliated Hospital of Guangzhou Medical University from 2017 to 2022.¹⁹ Inclusion criteria were: (1) diagnosis of severe asthma according to GINA guidelines, with all cases retrospectively re-reviewed at the time of final analysis for consistency with the GINA 2025 definition; (2) completion of all three BT sessions; and (3) availability of two-year follow-up data. Exclusion criteria included: (1) coexisting chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, or interstitial lung disease; (2) asthma-COPD overlap (ACO); (3) active respiratory infection within 4 weeks before enrollment; and (4) inability to perform pulmonary function tests. All participants were recruited while clinically stable. Each patient underwent lung function tests (bronchodilator test, IOS, plethysmography), induced sputum analysis, endobronchial mucosal biopsy and EB-OCT measurement. The demographics, medical history, ACQ5 scores, FeNO, serological profiles and total BT activations were prospectively recorded and analyzed.

This study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University. (Medical Ethics [2014] No. 51 and [2019] No. K09).

Pulmonary Function Test

Spirometry and impulse oscillometry (IOS) (Masterscreen, Jaeger, Hoechstberg, Germany) were performed in accordance with international guidelines.²⁰ Patients were instructed to withhold short-acting bronchodilators for at least 8 hours and long-acting bronchodilators for at least 24 hours before testing. Spirometry was conducted before and 15 minutes after inhalation of 400 µg salbutamol to assess bronchodilator responsiveness, yielding parameters such as pre- and post-bronchodilator FEV₁ and FEV₁/FVC.

In addition, lung-volume indices were obtained, including residual volume (RV), total lung capacity (TLC), and the RV/TLC ratio. For IOS, we recorded respiratory impedance at 5 Hz (Z_5), resonant frequency (F_{res}), airway resistance at

5 Hz (R_5) and 20 Hz (R_{20}), the difference in airway resistance (R_5 - R_{20}), reactance at 5 Hz (X_5), and the area of reactance (AX).

EB-OCT Measurement

EB-OCT imaging was performed using the LightLab OCT system (ILUMIEN OPTIS, Abbott, Westford, MA, U.S.A.). Under bronchoscopic guidance (B260F, Olympus, Tokyo, Japan), a 0.9-mm OCT catheter was advanced into the basal segments of both lower lobes — the right lower lobe bronchi (RB7–RB10) and the left lower lobe bronchi (LB7–LB10). Three-dimensional reconstructions of airway morphology were generated from the 3rd to the 9th bronchial generations. Quantitative EB-OCT metrics including airway luminal area (A_i), airway wall area (A_w), and airway wall area percentage ($A_w\% = [A_w/(A_i + A_w)] \times 100\%$) were measured and calculated.^{18,21,22}

EB-OCT imaging was performed one week prior to the first BT session, concurrent with endobronchial mucosal biopsies, to ensure baseline airway morphology assessment before any thermoplasty intervention.

Bronchial Thermoplasty Procedure

Patients underwent three bronchial thermoplasty sessions using the Alair System (Boston Scientific, Marlborough, MA, U.S.A.) at 3-week intervals. Procedures followed a standardized sequence: right lower lobe first, left lower lobe second, and both upper lobes in the final session. The total number of radiofrequency activations delivered for each patient was recorded.

Immunohistochemistry Analysis

Endobronchial mucosal biopsies were obtained one week prior to the first BT session. Immunohistochemistry (IHC) was performed to evaluate the expression of molecular biomarkers involved in airway remodeling and inflammation, including transforming growth factor- β 1 (TGF- β 1), matrix metalloproteinase-9 (MMP-9), Collagen Type III (COL3), muscarinic M3 receptor (M3), α 7-nicotinic acetylcholine receptor (α 7nAChR), acetylcholine (ACh), heat shock protein 70 (HSP70), and α -smooth muscle actin (α -SMA). Quantitative analysis was conducted using Image-Pro Plus version 6.0 (Media Cybernetics, Rockville, MD, U.S.A.), and the staining intensity was expressed as the integrated optical density (IOD) normalized to the measured tissue area (IOD/mm²).

Follow-up and BT Response Assessment

All patients underwent two-year follow-up after bronchial thermoplasty. Based on an a priori defined BT response (≥ 0.5 -point improvement in ACQ score from baseline at two years), participants were stratified into responders and non-responders.^{23,24}

Statistical Analysis

All statistical analyses were conducted using SPSS version 29.0 (IBM Corporation, Armonk, NY, U.S.A.) and R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Bar charts with error bars representing SD were generated using GraphPad Prism version 10.5.0 (GraphPad Software, San Diego, CA, U.S.A.).

The normality of continuous variables was assessed using the Shapiro–Wilk test. Between-group comparisons of continuous variables, including cross-sectional comparisons and comparisons of change values, were performed using Student's *t*-test or Welch's *t*-test for normally distributed data, whereas the Mann–Whitney *U*-test was used for non-normally distributed data. For longitudinal comparisons within the same group (baseline vs 2 years), the paired *t*-test or Wilcoxon signed-rank test was applied, as appropriate. Categorical variables were analyzed using Fisher's exact test. Data were reported as mean $\pm$ standard deviation (SD), median [interquartile range (IQR)], or *n* (%). Available-case analysis was used for variables with missing data.

Receiver operating characteristic (ROC) analyses were performed to evaluate the discriminative ability of individual parameters. The area under the curve (AUC) with 95% confidence intervals was estimated from the available-case data, and optimal cut-off values were determined by maximizing the Youden index (sensitivity + specificity – 1). To evaluate the added value of combining variables, multivariable logistic regression was performed, and model-based predicted

probabilities were subjected to ROC analysis. Because only 21 out of 30 patients (16 responders and 5 non-responders) had data on BMI, X_5 , and Ai3–6, the multivariable logistic model was treated as exploratory and restricted to these three prespecified predictors. Model optimism was assessed using leave-one-out cross-validation (LOOCV) with the same unpenalized logistic specification.

Decision curve analysis (DCA) was performed in the complete-case dataset to evaluate the clinical utility of the prediction model. In the DCA, the threshold probability (represented on the x-axis) defines the minimum predicted probability of a response to BT at which a clinician would recommend the procedure. The net benefit (represented on the y-axis) accounts for the trade-off between true-positive and false-positive classifications, weighted by the threshold probability. Two reference strategies were included for comparison: treating all patients (“Treat All”) and treating no patients (“Treat None”).

Statistical significance was defined as $P < 0.05$ (two-tailed).

Results

Clinical Outcomes and Pulmonary Function from Baseline to Two Years

This study included 30 patients with severe asthma (aged 32–68 years). Based on a prespecified improvement of ≥ 0.5 points in ACQ5 at two years, 22 patients were classified as responders and 8 as non-responders to BT. Baseline ACQ5 scores were comparable between responders (1.96 ± 0.91) and non-responders (2.43 ± 0.89 ; $P = 0.231$). At two years, responders demonstrated significantly lower ACQ5 scores than non-responders (0.53 ± 0.30 vs 2.42 ± 1.17 ; $P < 0.001$), with a greater mean improvement in ACQ5 (Δ : -1.43 ± 0.80 vs 0.00 ± 0.44 ; $P < 0.001$). In addition, the annual exacerbation rate did not differ significantly between groups at baseline (4.20 ± 3.74 vs 8.38 ± 10.27 ; $P = 0.607$), whereas responders had significantly fewer exacerbations at two years (0.30 ± 0.66 vs 5.88 ± 8.82 ; $P = 0.006$), supporting the clinical relevance of the ACQ5-based response classification ([Table S1](#)).

Regarding pulmonary function, although baseline spirometry was available for all 30 patients, longitudinal analysis was restricted to 28 patients with paired baseline and two-year data, as two responders had missing spirometric records at two years. At baseline, no significant differences were observed between responders and non-responders in pre-bronchodilator or post-bronchodilator spirometric parameters (all $P > 0.05$). Over the two-year follow-up, both groups showed relatively stable lung function overall; however, the change in post-bronchodilator FEV₁ (% predicted) was significantly more favorable in responders than in non-responders (Δ : $+5.00$ [1.73, 11.22] vs -17.10 [–24.09, –3.04]; $P = 0.046$). No other significant between-group differences were observed in the longitudinal changes of spirometric parameters (all $P > 0.05$) ([Table S2](#)).

Baseline Clinical Characteristics

The responder and non-responder groups were comparable in sex distribution, smoking history, age at asthma onset, disease duration, asthma phenotype, hematologic indices (including peripheral blood eosinophil percentage, serum C-reactive protein [CRP], and albumin levels), and FeNO (all $P > 0.05$). The total number of BT activations also did not differ significantly between groups ($P = 0.532$). Of note, non-responders had significantly higher weight ($P = 0.009$), body mass index (BMI) ($P = 0.036$), and serum triglyceride levels ($P = 0.015$) ([Table 1](#)). The detailed demographic and clinical characteristics are provided in [Table S3](#).

Spirometric, IOS, and Lung-Volume Parameters at Baseline

The BT responders exhibited significantly greater negative X_5 values (-0.18 ± 0.09 vs -0.06 ± 0.04 ; $P = 0.011$) and a higher RV/TLC ratio ($44.64 \pm 9.81\%$ vs $35.20 \pm 9.11\%$; $P = 0.042$), compared with non-responders ([Table 2](#)). However, spirometric parameters, including pre- and post-bronchodilator FEV₁, FEV₁/FVC, and MMEF%pred at baseline, did not differ significantly between responders and non-responders (all $P > 0.05$). The IOS parameters (Fres, Z_5 , R_5 , R_{20} , $R_5 - R_{20}$, AX) and lung-volume indices (FRC, TLC) were comparable between the two groups (all $P > 0.05$) ([Table S4](#)).

Table 1 Baseline Clinical Characteristics of Severe Asthmatic Patients Treated with BT

Parameter	Responders (n = 22)	Non-Responders (n = 8)	P value
Women, no. (%)	15 (68)	3 (38)	0.143
Age (years)	50.77±12.17	42.00±15.54	0.171
Weight (kg)	60.89±9.54	73.66±14.65	0.009
BMI (kg/m ²)	23.59±3.03	26.43±3.37	0.036
Eosinophil percentage (%)	2.99±3.51	3.43±3.01	0.467
Triglycerides (mmol/L)	1.16±0.35	1.47±0.52	0.015
FeNO (ppb)	35.60±31.73	44.71±26.16	0.544
Total number of activations	210.00±39.24	200.25±29.57	0.532

Notes: P values were calculated using independent-samples t-test for continuous variables and χ^2 /Fisher's exact test for categorical variables. Data are presented as mean $\pm$ SD or n (%). Data in boldface indicate statistical significance ($P < 0.05$).

Abbreviations: BT, bronchial thermoplasty; BMI, body mass index; FeNO, fractional exhaled nitric oxide.

Table 2 Comparison of Spirometry, IOS, and Lung Volumes in BT Treated Severe Asthma Patients

Parameter	Responders (n = 22)	Non-Responders (n = 8)	P value
Pre-bronchodilator FEV ₁ (L)	1.87±0.94	2.54±0.83	0.089
Pre-bronchodilator FEV ₁ (% pred)	67.94±23.27	76.39±15.30	0.351
Pre-bronchodilator FEV ₁ /FVC (%)	62.75±14.22	67.86±6.87	0.342
Z ₅ (kPa/L/s)	0.53±0.22	0.37±0.15	0.154
X ₅ (kPa/L/s)	-0.18±0.09	-0.06±0.04	0.011
RV (L)	2.45±0.79	1.96±0.47	0.141
RV/TLC (%)	44.64±9.81	35.20±9.11	0.042

Notes: P values were calculated using independent-samples t-test for continuous variables and χ^2 /Fisher's exact test for categorical variables. Data are presented as mean $\pm$ SD or n (%). Data in boldface indicate statistical significance ($P < 0.05$).

Abbreviations: BT, bronchial thermoplasty; IOS, impulse oscillometry; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Z₅, respiratory impedance at 5 Hz; X₅, reactance at 5 Hz; RV, residual volume; TLC, total lung capacity.

EB-OCT Measurements of Airway Morphology

At baseline, BT responders had larger luminal areas of moderate to small airways compared with non-responders: Ai3–6 (10.86 ± 4.81 vs 6.15 ± 2.04 mm²; $P = 0.013$), and Ai7–9 (3.55 ± 1.62 vs 1.93 ± 0.74 mm²; $P = 0.011$). While the moderate airway, but not small airway, wall thickness was significantly lower in the responders than in non-responders: Aw%3–6 ($29.88 \pm 7.08\%$ vs $35.82 \pm 6.54\%$; $P = 0.048$) (Table 3) (Figure 1).

Quantitative Analysis of Airway Mucosal Immunohistochemical Markers

The expression of COL3 was significantly higher in BT responders than in non-responders, as determined by immunohistochemical analysis (0.30 ± 0.26 vs 0.26 ± 0.03 IOD/mm², $P = 0.020$) (Figure 2A). However, no marked differences were observed between responders and non-responders in terms of TGF- β , MMP-9, M3, α 7nAChR, ACh, HSP70, or α -SMA expression (all $P > 0.05$) (Figures 2B–D and S1A–D).

Table 3 Airway Morphological Abnormalities Assessed by EB-OCT in Bronchial Thermoplasty Treated Severe Asthma Patients

Parameter	Responders (n = 22)	Non-Responders (n = 8)	P value
Ai3–6 (mm ²)	10.86±4.81	6.15±2.04	0.013
Ai7–9 (mm ²)	3.55±1.62	1.93±0.74	0.011
Aw%3–6 (%)	29.88±7.08	35.82±6.54	0.048
Aw%7–9 (%)	46.21±9.47	53.10±5.62	0.061
Pi-10 (mm)	0.28±0.04	0.27±0.04	0.492

Notes: P values were calculated using independent-samples t-test for continuous variables. Data are presented as mean ± SD. Data in boldface indicate statistical significance ($P < 0.05$).

Abbreviations: EB-OCT, endobronchial optical coherence tomography; Ai3–6, average airway internal area from third to sixth generation of bronchi; Ai7–9, average airway internal area from seventh to ninth generation of bronchi; Aw%3–6, average airway wall area percentage from third to sixth generation of bronchi; Aw%7–9, average airway wall area percentage from seventh to ninth generation of bronchi; Pi-10, square root of wall area for a theoretical airway with internal perimeter of 10 mm.

Predictive Performance of Clinical Parameters for BT Treatment

The predictive performance of clinical, structural, and functional parameters in distinguishing responders from non-responders to BT was evaluated using ROC analysis (Figure 3 and Table S5). Body weight (AUC = 0.759, 95% CI 0.500–0.975), BMI (AUC = 0.733, 95% CI 0.495–0.950), and triglycerides (AUC = 0.694, 95% CI 0.451–0.925) showed moderate discriminative ability, whereas COL3 displayed good discriminatory power (AUC = 0.846, 95% CI 0.577–1.000). EB-OCT parameters Ai3–6 (AUC = 0.795, 95% CI 0.608–0.950), Ai7–9 (AUC = 0.830, 95% CI 0.642–0.962), and Aw%3–6 (AUC = 0.761, 95% CI 0.576–0.917), as well as lung functional indices X_5 (AUC = 0.938, 95% CI 0.799–1.000) and RV/TLC (AUC = 0.756, 95% CI 0.531–0.938), showed moderate-to-good discriminatory ability, with X_5 showing excellent discrimination for predicting BT treatment response. To further evaluate the integrated predictive capacity of BT response, an exploratory multivariable logistic regression model was constructed in the 21 patients with complete BMI, X_5 , and Ai3–6 data, yielding an apparent AUC of 0.988 (Figure 3C).

In the multivariable model, the odds ratios were 0.929 (95% CI 0.502–1.720) for BMI, 2.84×10^{-19} (95% CI 1.19×10^{-48} to 6.77×10^{10}) for X_5 , and 1.960 (95% CI 0.599–6.414) for Ai3–6. The extremely wide confidence interval for X_5 indicated model instability related to quasi-complete separation in this small complete-case subset. LOOCV using the same unpenalized logistic specification yielded a cross-validated AUC of 0.750. Analysis of standardized regression coefficients showed that X_5 contributed 52.3% of the model's predictive capacity, followed by Ai3–6 (44.2%) and BMI (3.5%). Complete logistic regression results are provided in Table S6.

Clinical Utility of the Multivariable Model

To further explore the potential clinical utility of the combined model, DCA was performed in the complete-case dataset (Figure 4). In the apparent-data analysis, the combined model (BMI + X_5 + Ai3–6) provided a greater net benefit than both the “Treat All” and “Treat None” strategies across a broad range of threshold probabilities (approximately 5–98%). Compared with the individual predictors, the combined model generally showed a favorable net benefit profile across several threshold ranges.

Discussion

To our knowledge, this study is the first to employ a combination of EB-OCT, IOS, and systemic metabolic markers to identify predictive factors for the long-term efficacy of BT on severe asthma. Our findings revealed that lower BMI and triglyceride levels, more negative X_5 values, as well as wider luminal caliber and thinner airway walls were associated with a favorable response to BT. Notably, the ROC model combining BMI, X_5 , and Ai3–6 showed a high apparent discrimination (AUC = 0.988) for predicting BT response, suggesting that these parameters might be useful for risk

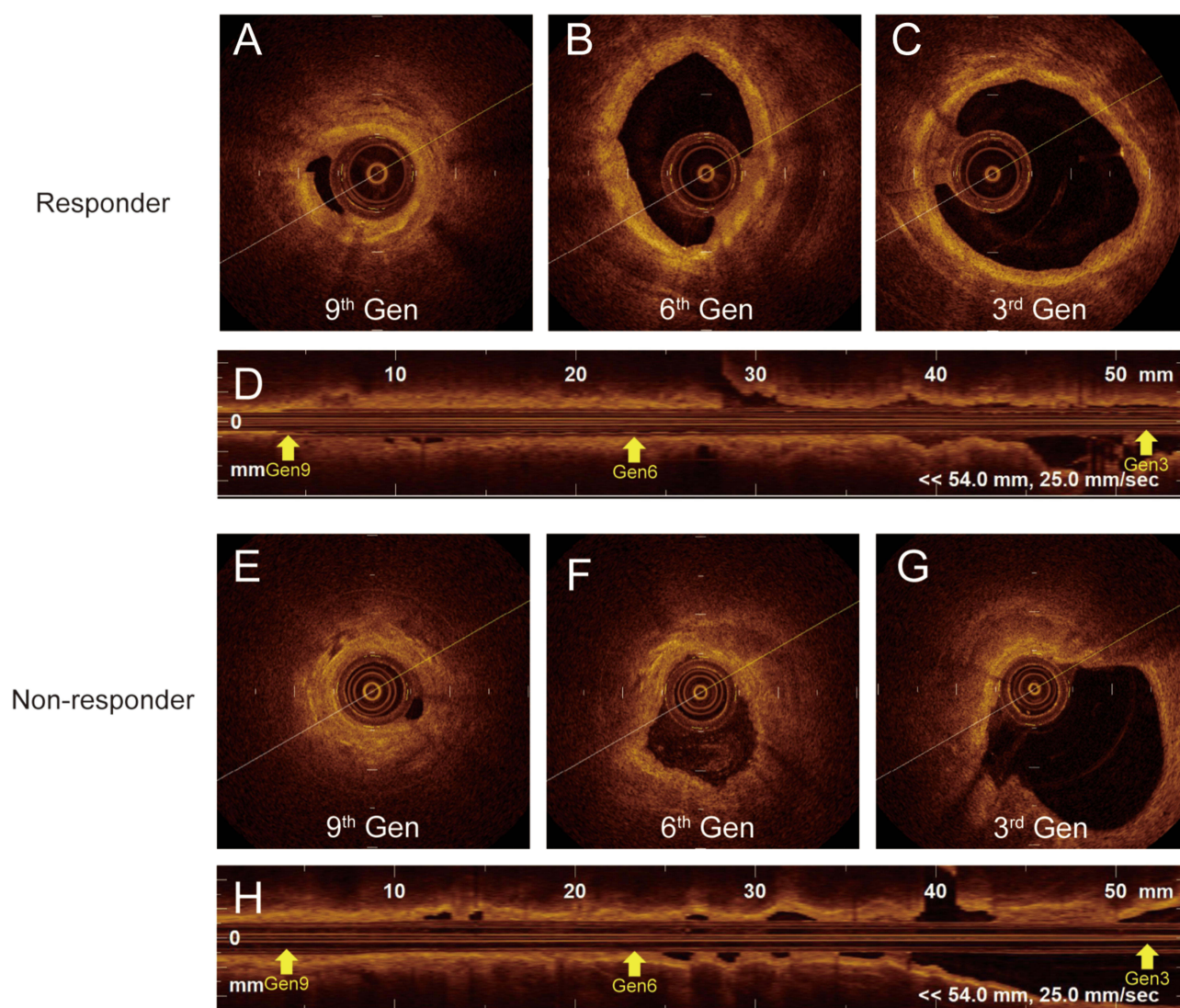


Figure 1 Representative cross-sectional and longitudinal endobronchial optical coherence tomography (EB-OCT) images illustrating airway morphology differences between a bronchial thermoplasty (BT) responder and non-responder. (A–C) Cross-sectional images and (D) a longitudinal pullback image from a representative BT responder. (E–G) Cross-sectional images and (H) a longitudinal pullback image from a representative BT non-responder. In the cross-sectional images, the central concentric rings represent the EB-OCT imaging catheter, and the thin diagonal yellow dashed lines indicate the orientation and radial scanning axes. In the longitudinal images, yellow arrows indicate the specific longitudinal positions corresponding to the 3rd, 6th, and 9th airway generations shown in the cross-sections.

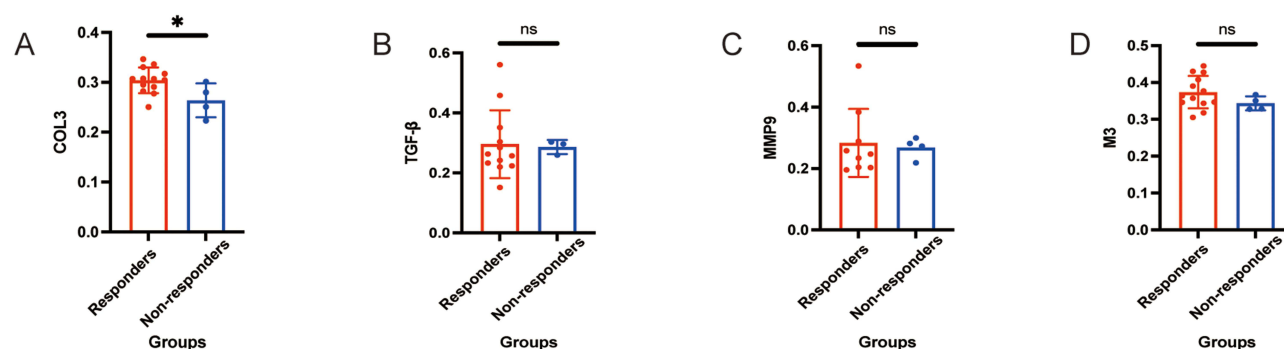


Figure 2 Quantitative analysis of airway mucosal immunohistochemical markers in responders and non-responders to bronchial thermoplasty (BT). (A) Collagen Type III (COL3), (B) Transforming growth factor-β1 (TGF-β), (C) Matrix metalloproteinase-9 (MMP-9), (D) Muscarinic M3 receptor (M3). Data are presented as mean ± SD. *P < 0.05; ns, not significant.

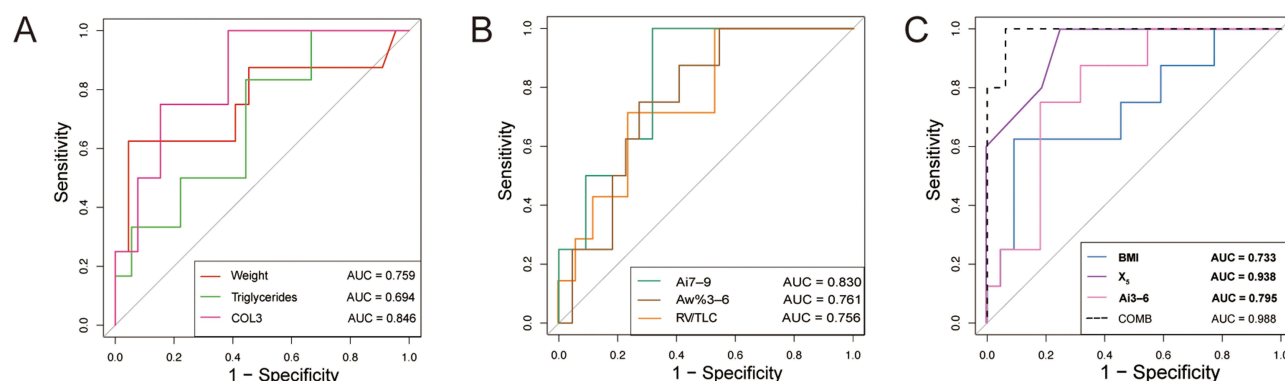


Figure 3 Receiver operating characteristic (ROC) curves showing the discriminative ability of multimodal parameters in distinguishing responders and non-responders to bronchial thermoplasty (BT). **(A)** Clinical and biochemical predictors: weight, triglycerides, and Collagen Type III (COL3). **(B)** Endobronchial optical coherence tomography (EB-OCT) parameters: airway internal area from 7th to 9th generation (Ai7-9), airway wall area percentage from 3rd to 6th generation (Aw%3-6), and residual volume to total lung capacity ratio (RV/TLC). **(C)** Functional and integrated predictors: body mass index (BMI), reactance at 5 Hz (X₅), airway internal area from 3rd to 6th generation (Ai3-6), and the combined model (COMB = BMI + X₅ + Ai3-6).

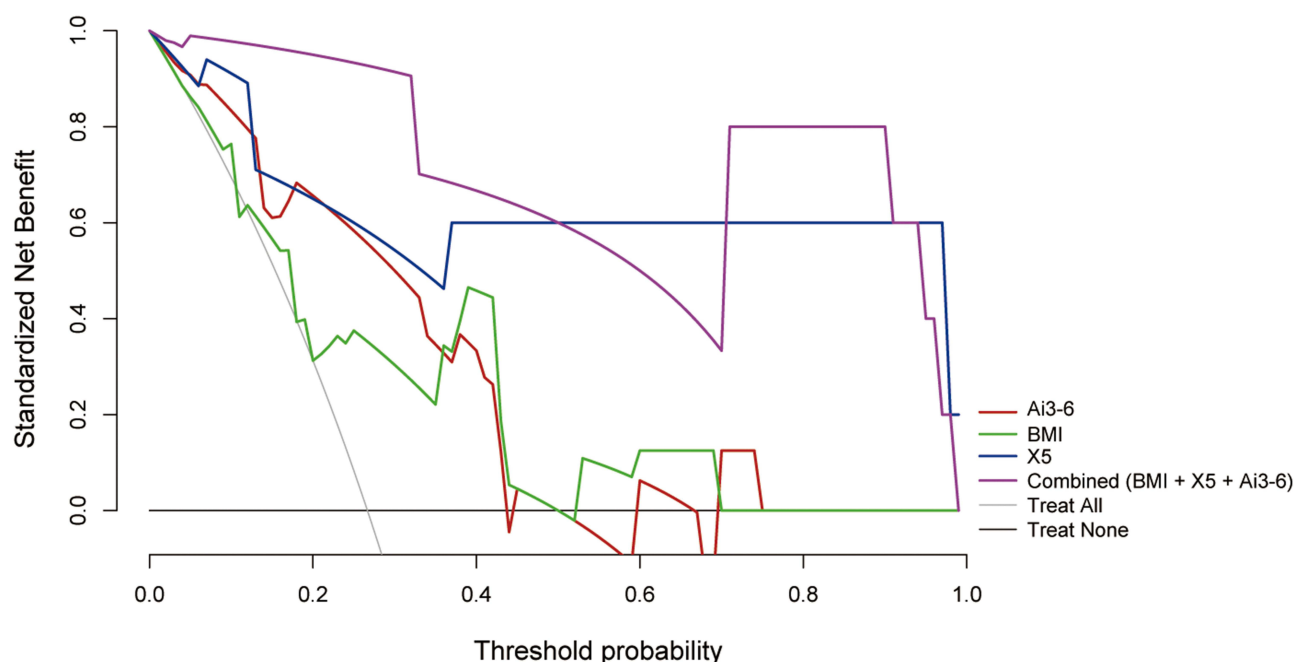


Figure 4 Decision curve analysis (DCA) evaluating the clinical utility of the combined prediction model (body mass index [BMI] + reactance at 5 Hz [X₅] + airway internal area from 3rd to 6th generation [Ai3-6]) compared with individual predictors (BMI, X₅, and Ai3-6) and two reference strategies across a range of threshold probabilities. The x-axis represents the threshold probability, defined as the minimum predicted probability of bronchial thermoplasty (BT) response at which a clinician would recommend the procedure. The y-axis represents the net benefit. The "Treat All" line represents the strategy of recommending BT for all patients, and the "Treat None" line (net benefit = 0) represents the strategy of recommending BT for no patients.

stratification, although the model requires further validation. Currently, one of the greatest challenges in clinical practice remains the identification of patients who would derive the most benefit from BT.¹² Previous studies have suggested that higher activation counts were associated with better BT treatment efficacy.^{24,25} However, our findings revealed no significant differences in activation counts between responders and non-responders. This discrepancy might be attributable to individualized BT procedures tailored to the patient's airway anatomy, with specific consideration of airway length. These findings highlight the limitations of relying solely on procedural metrics and underscore the urgent need for advanced diagnostic tools and predictive biomarkers to improve the precision of BT candidate selection.

Central to our predictive modeling was the prespecified definition of clinical response at two years after BT. We selected this long-term milestone for several reasons. First, the sustained therapeutic effects of BT, particularly those related to airway remodeling, are generally expected to consolidate over 12 to 24 months.²⁶ Second, short-term clinical assessments (eg, at 6 months) may be confounded by transient periprocedural airway inflammation or edema, as well as the temporary intensification of corticosteroid treatment required by the BT protocol. A two-year follow-up therefore provides a more stable and objective evaluation of sustained clinical benefit, particularly regarding the annualized exacerbation rate and lung function stabilization. Importantly, responders not only showed greater improvement in ACQ5 scores at two years but also had a markedly lower acute exacerbation frequency than non-responders, supporting the clinical relevance of our ACQ5-based response classification. In the paired-data subset, responders showed a more favorable longitudinal change in post-bronchodilator FEV₁ (% predicted) than non-responders over two years ($P = 0.046$), which was directionally consistent with the clinical outcome analysis. However, because no significant between-group differences were observed for other spirometric indices and this analysis was limited to a small subset ($n = 28$), this finding should be considered exploratory and interpreted cautiously.

EB-OCT provides high-resolution assessment of airway structure and remodeling and may therefore be useful for predicting BT outcomes.^{18,27} Airway remodeling in severe asthma is characterized by increased smooth muscle mass, subepithelial fibrosis, and luminal narrowing, all of which contribute to chronic airflow obstruction and limitation.^{28,29} Because BT primarily targets ASM, we also examined whether fixed airflow obstruction was present in our cohort. Post-bronchodilator FEV₁/FVC < 0.70 was observed in 57.9% (11/19) of responders and 33.3% (2/6) of non-responders with available data ($P = 0.378$), indicating that airway remodeling was present in a substantial proportion of treated patients. However, responders had larger airway luminal areas and lower airway wall area percentages at baseline than non-responders. In light of the fact that BT targets ASM, this finding could be considered unexpected. One possible explanation is that responders had a remodeling pattern in which ASM-related dysfunction was relatively more prominent than marked subepithelial fibrosis. In such patients, the principal target of BT may remain more amenable to thermal intervention. In contrast, narrower lumens and thicker walls in non-responders may reflect more advanced fibrotic remodeling that is less reversible by BT. This may also be explained by the fact that wider airways allow more complete catheter-to-wall contact and more uniform radiofrequency energy delivery, thereby improving the effectiveness of ASM ablation.²⁵ In addition, because EB-OCT-derived Aw% reflects the overall airway wall rather than its individual components, a thinner wall in responders does not necessarily indicate less ASM, but may instead reflect differences in wall composition that are more favorable for BT response. These interpretations remain hypothetical and require validation in larger cohorts with more detailed assessment of airway wall components. Previous studies have shown that a favorable clinical response to BT is associated with a reduction in airway wall thickness after treatment,^{13,30,31} and our findings extend this observation by suggesting that the degree of baseline airway morphology may also hold predictive significance.

Complementing EB-OCT's structural assessments, IOS evaluates small airway mechanics, which are critical in severe asthma. Unlike spirometry, IOS captures subtle changes in airway elasticity and resistance without forced maneuvers. IOS provides real-time, non-invasive assessments during tidal breathing and may serve as a clinically valuable tool for patients with severe symptoms who have a compromised ability to perform spirometric tests.^{32,33} The heterogeneity of airway remodeling in asthma, encompassing both structural and functional alterations, might partly explain the variability in treatment responses.³⁴ In this study, BT responders exhibited lower baseline X₅ values than non-responders. A more negative X₅, generally associated with reduced airway compliance and increased small airway resistance,³⁵ might reflect a smooth-muscle-dominant phenotype characterized by elevated peripheral tone and airway wall thickening in responders, which is in line with the therapeutic mechanism of BT treatment.^{36–38} Although the procedure anatomically targets the central airways, reductions in proximal smooth-muscle tone may improve distal mechanics through airway interdependence, thereby reducing air trapping and enhancing ventilation.³⁹ In contrast, non-responders may represent an inflammation-dominant phenotype in which airway dysfunction arises primarily from edema and mucus obstruction.^{40,41} These features impair airflow but do not involve smooth-muscle-mediated stiffness and are therefore less responsive to the mechanical and thermal effects of the treatment.^{5,42}

Obesity could significantly influence the response to asthma therapy. Elevated triglycerides generate reactive oxygen species (ROS),⁴³ activating fibroblasts and promoting collagen production.^{44,45} In the current study, lower triglyceride levels, BMI and body weight in BT responders may reflect a more favorable metabolic profile, although we did not directly measure oxidative stress or metabolic remodeling pathways in this study. Overweight asthmatic patients might exhibit diminished efficacy of BT due to systemic inflammation driven by adipose-derived cytokines (eg, TNF- α , IL-6) and adipokines (eg, leptin),^{46,47} which could exacerbate airway smooth muscle hypertrophy and remodeling.⁴⁸ Moreover, obesity-related mechanical constraints, such as increased chest wall resistance and reduced lung compliance,^{49–53} might further hinder uniform heat distribution and smooth muscle ablation during BT. In sum, these findings underscore the close interaction between systemic metabolic status and airway pathology in asthmatic patients, suggesting that metabolic disturbances (overweight or obesity) might serve as risk factors affecting the therapeutic outcomes of BT, which should be considered in patient evaluation.

As a major extracellular matrix component, COL3 reflects subepithelial fibrosis and airway wall remodeling,^{54,55} contributing to structural alterations and airflow limitation in severe asthma.⁵⁶ The higher COL3 expression observed in responders was unexpected, given that greater collagen deposition is often associated with more advanced airway remodeling. This might be attributed to the fact that higher COL3 expression reflects a remodeling pattern that remains biologically active and potentially modifiable, rather than fixed end-stage fibrosis. In this context, COL3 may be more prominent in an earlier or more dynamic phase of matrix remodeling,^{57,58} whereas lower COL3 expression in non-responders may reflect a more mature and structurally rigid remodeling pattern. This interpretation is also broadly compatible with our EB-OCT findings, in which responders showed thinner airway walls at baseline. However, these mechanistic inferences remain speculative and require further validation through detailed assessment of collagen subtypes, cross-linking markers, and longitudinal tissue sampling.

EB-OCT in combination with IOS parameters could provide deep insights into airway remodeling and small airway mechanics. While the clinical laboratory indices, such as BMI, body weight, and serum triglyceride, collectively represent broader metabolic dysregulation, we developed the combined model by integrating BMI (metabolic status), X_5 (lung function) and Ai3–6 (airway structure) for precise prediction of BT efficacy (AUC = 0.988). This integrated approach shows strong potential for guiding individualized patient selection and advancing precision-oriented management of severe asthma.

Regarding the relative contribution of individual predictors within the combined model, analysis of standardized regression coefficients showed that X_5 contributed 52.3% of the model's predictive capacity, followed by Ai3–6 (44.2%) and BMI (3.5%). Although the combined model showed higher apparent discrimination than X_5 alone (AUC 0.988 vs 0.938), this apparent gain was not retained after internal validation (LOOCV AUC 0.750 for the combined model vs 0.762 for the X_5 -only model). In addition, the likelihood ratio test comparing the full model with the X_5 -only model did not reach statistical significance ($P = 0.104$), suggesting that the added variables did not significantly improve model fit. The DCA suggested a generally favorable apparent net benefit profile for the combined model across several threshold ranges, but this finding should also be interpreted cautiously because it was derived from the same development dataset. Taken together, these results suggest that X_5 was the strongest individual predictor in the current model, whereas the incremental value of Ai3–6 and BMI requires further confirmation in larger, externally validated cohorts.

This study has several limitations that warrant consideration. First, this was a single-center study with a modest sample size, which may limit the precision of estimates and the generalizability of the findings. Second, EB-OCT and histopathology quantified airway wall morphology but did not include separate measurement of the airway smooth-muscle layer, a key structural determinant of BT efficacy.⁵⁹ Third, standardized intermediate ACQ assessments at 6, 12, and 18 months were not available, and data on oral corticosteroid dosing, hospitalizations, and emergency department visits were not uniformly collected. These missing data limited a more comprehensive, multidimensional evaluation of treatment response over time. Fourth, the multivariable logistic regression model was developed in a small complete-case subset, which may limit its stability and generalizability. In this study, ROC analysis was primarily used to identify a limited set of candidate predictors for combined evaluation of BT response, rather than to establish definitive clinical decision thresholds. Accordingly, the combined model and its proposed decision thresholds should be regarded as exploratory and require validation in larger, multicenter cohorts.

Conclusion

By integrating EB-OCT, IOS, and metabolic assessment, we developed a combined model (Ai3–6, X₅, BMI) that may provide a useful framework for future individualized patient assessment in bronchial thermoplasty. However, this model should be regarded as exploratory and requires validation in larger, independent cohorts before routine clinical use.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no potential conflicts of interest in this work.

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