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Original Article

Predictive value of quantitative CT-derived emphysema heterogeneity for outcomes following bronchoscopic lung volume reduction

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Abstract: Objective: To determine the predictive value of quantitative CT-derived emphysema heterogeneity for clinical response to bronchoscopic lung volume reduction (BLVR). Methods: This retrospective study included 150 patients who underwent bronchoscopic lung volume reduction (BLVR) between January 2023 and November 2025, of whom 82 were responders and 68 were non-responders. The primary endpoint was the BLVR outcome at 6 months post-procedure, defined as a 15% improvement in forced expiratory volume in one second (FEV1) or a 450 mL improvement in target lobe volume. Secondary endpoints included changes in Chronic Obstructive Lung Disease Assessment Test score, modified Medical Research Council dyspnea score, carbon monoxide diffusion capacity (DLCO), and 6-minute walk test (6MWT). Quantitative CT measurements such as emphysema heterogeneity index (EHI), low attenuation area percentage (LAA%), lung fissure integrity, and air trapping heterogeneity were used as baseline lung structural pmeasures. Multivariate logistic regression analysis was used to identify independent predictors of treatment response. Results: Responders exhibited significantly greater heterogeneity in emphysema: higher EHI, more significant differences in lobar destruction, and a higher proportion of heterogeneous voxels (all P<0.001). Structural parameters also differentiated responders, with responders showing more pronounced lobar volume asymmetry, higher target lobe destruction rate, and decreased vascular density (all P<0.001). Functional quantitative CT revealed markedly higher heterogeneity in air retention (P<0.001), more pronounced ventilation asymmetry (P<0.001), and larger gas retention clusters (all P<0.001) in responders. Responders also had more intact lung fissures and a lower probability of collateral ventilation (both P<0.001). Better preservation of airway morphology was observed, characterized by thinner airway walls (P<0.01), larger lumens (P<0.001), and a greater number of airways (P<0.001). Multivariate analysis showed that the EHI (OR 0.114, P<0.001), ≥90% integrity of the lung fissure (OR 0.888, P<0.001), and immediate target lobe volume reduction ≥700 mL (OR 0.106, P<0.001) were independent predictors of BLVR response. Conclusion: Quantitative CT-derived assessment of emphysema heterogeneity provides a strong and clinically significant predictor of treatment response to bronchoscopic lung volume reduction.

Keywords: Quantitative CT, emphysema heterogeneity, bronchoscopic lung volume reduction, treatment outcome, predictive value

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major health problems worldwide, and emphysema is one of its most severe phenotypes, leading to persistent destruction of alveolar structure and deterioration of airflow. For patients with heterogeneous emphysema who have undergone minimally invasive surgical lung reduction and remain symptomatic even with optimal medical therapy, bronchoscopic lung volume reduction (BLVR) has emerged as an important alternative and non-surgical method for lung volume reduction [1]. BLVR enhances respiratory mechanisms, elastic recoil, and ventilation efficiency by collapsing the most inflamed and diseased areas [2]. However, significant individual differences in clinical response to BLVR highlight the need to identify effective preoperative biomarkers to ensure maximum patient screening and optimized treatment outcome. Quantitative com-

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puted tomography (QCT) has revolutionized the assessment of structural lung disease, enabling objective measurement and quantification of emphysema burden, lobar distribution, and regional ventilation heterogeneity [3, 4]. Traditional QCT measures, such as the percentage of low-attenuation zones or the integrity of lung fissures, are often used to screen patients for BLVR, but in many cases they fail to fully describe the spatial heterogeneity of emphysematous destruction [5]. Evidence indicates that the heterogeneity of emphysematous distribution, compared to disease severity, is a key factor in defining the efficacy of lung volume reduction surgery [6-8]. Patients with highly asymmetrical lung destruction are more likely to achieve lobar collapse and improved lung function, while those with diffuse, homogeneous lesions receive only minor benefits. Despite these observations, the specific quantitative model and threshold for emphysematous heterogeneity that best predicts BLVR outcome remains unclear.

Recent innovations in quantitative image analysis have enabled more advanced characterization of emphysema topology, including voxel-based density mapping, regional gradient measurement and spatial cluster analysis [9-11]. Such new tools hold the promise for improving clinical decision-making, as they can detect subtle yet clinically important differences in disease distribution [12, 13]. Nevertheless, the predictive power of QCT-based emphysema heterogeneity for BLVR outcomes has not been evaluated in a real-world population. Investigating how structural heterogeneity translates into mechanical recruitability and post-procedural functional benefit is important for improving both the accuracy of patient selection and next-generation lung volume reduction strategies.

In this study, we assessed the predictive power of quantitative CT-based emphysema heterogeneity with respect to clinical, functional, and radiographic outcomes following bronchoscopic lung volume reduction. We aimed to identify which features of structural heterogeneity best predict treatment response, by combining advanced imaging-based metrics with standardized postBLVR outcomes. A clear understanding of these relationships may not only assist in candidate selection but also provide mechanistic insight into the pathophysiology underlying BLVR efficacy, ultimately leading to a more personalized approach to emphysema management.

Materials and methods

Case selection

This study was a retrospective analysis, including 150 patients who underwent bronchoscopic lung volume reduction (BLVR) between January 2023 and November 2025. Patients were divided into two groups (responder group and non-responder group), with the first group comprising 82 responders and the second group comprising 68 non-responders.

Inclusion criteria: (1) age of 50-75 years; (2) severe emphysema revealed on high-resolution computed tomography (HRCT); (3) baseline forced expiratory volume in one second (FEV1) of 25%-45% of predicted value; (4) heterogeneous emphysema; (5) persistent dyspnea despite standard medical therapy, with eligibility for BLVR by a multidisciplinary assessment.

Exclusion criteria: (1) presence of major comorbidities (e.g. active malignancy, uncontrolled cardiovascular disease), history of lung surgery or transplantation; (2) contraindications to bronchoscopy; (3) pregnancy, or lactation; (4) insufficient follow-up data or absence of preoperative/postoperative CT scans.

Responders were defined as those who achieved at least one of the following improvements postoperatively: an increase in FEV1 ≥15% or 100-200 ml; a decrease in residual volume (RV) ≥500 ml or 10-15%; an increase in 6-minute walk distance (6MWD) ≥25-30 meters; or an improvement of ≥4 points in the St. George's Respiratory Questionnaire (SGRQ) total score, similar to the minimal clinically important difference (MCID) [14]. Patients who did not meet these criteria were defined as non-responders. The patient selection process for this study is shown in **Figure 1**. This study was conducted under the supervision of the Institutional Review Board of Lanzhou Pulmonary Hospital, strictly adhering to patient confidentiality principles and ethical standards.

Data collection

The study included patients clinically diagnosed with COPD and emphysema who met the above-mentioned inclusion criteria. Baseline COPD severity was graded according to the Global

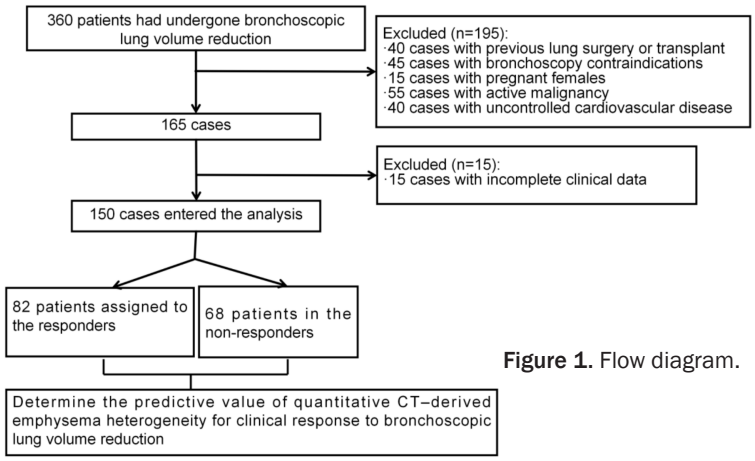

Figure 1. Flow diagram.

Initiative for Chronic Obstructive Lung Disease (GOLD) report, using post-bronchodilator FEV1 (% predicted) to classify patients into GOLD stages II, III, or IV; only patients with GOLD stage II-IV disease were included in the present analysis. The primary treatment outcome was the response to bronchoscopic lung volume reduction (BLVR), defined as a ≥15% increase in FEV1 or a target-lobe volume reduction (TLVR) of ≥450 mL at 6-month follow-up. Prior to BLVR, standard CT examinations, including high-resolution CT (HRCT) scans at both end-expiratory and end-inspiratory phases, were performed. Quantitative CT measurements included the emphysema heterogeneity index (EHI), the percentage of low-attenuation area (LAA%) in the target lobe, and indices of lobar volume asymmetry. Lung fissure integrity, collateral ventilation probability, and air-trapping parameters were also derived. Clinically, baseline and 6-month follow-up pulmonary function test results were compared, including spirometry and body plethysmography. Patient demographic data (age, sex, smoking history, and comorbidities) were collected from medical records, together with baseline symptom and health-status scores assessed by the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale.

Outcome measures

The primary outcome was BLVR response at 6 months post-procedure, defined as meeting either of the following criteria: FEV1 increase ≥15% and/or TLVR ≥450 ml. Secondary outcomes included changes from baseline to 6 months by CAT and mMRC, as well as additional functional outcomes (DLCO and 6MWT). Baseline quantitative CT metrics (EHI, target-lobe LAA, fissure completeness, and air-trapping heterogeneity) were evaluated as candidate predictors of the primary outcome, and their associations with the BLVR response were analyzed using multivariable logistic regression.

Statistical analysis

Data were analyzed using SPSS (version 26.0, IBM, Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed data were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median (interquartile range). Depending on the data distribution, independent samples t-tests or Mann-Whitney U tests were used to compare differences between responders and non-responders. Categorical variables were analyzed using Chi-square tests or Fisher's exact tests (the appropriate test method was selected as needed). Multivariate logistic regression analysis was used to identify independent predictors of BLVR response, including EHI, lung fissure integrity, and immediate TLVR. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All statistical tests were two-tailed, and $P<0.05$ was considered significant.

Results

Comparison of baseline data

There were no significant differences between responders and non-responders in age, sex distribution, body mass index (BMI), COPD duration ≥10 years, smoking status, or mMRC dyspnea score ≥3 (all $P>0.05$). There were also no significant differences in the distribution of Global Obstructive Lung Disease (GOLD) stages II/III/IV between the two groups (18/42/22 vs. 10/30/28, $P=0.155$). Responders exhibited significantly lower CAT scores than non-responders (21.34 ± 6.49 vs. 24.55 ± 6.00, $P=0.002$). A history of frequent acute exacerbations (≥2 in the previous year) was more common in non-responders (48.5% vs. 31.7%, $P=0.036$), and the proportion of hospitalizations for COPD in the previous year was also higher (38.2% vs.

Table 1. Comparison of baseline data

Variable	Responder Group (n=82)	Non-Responder Group (n=68)	t/χ^2	*P* value
Age (years), mean ± SD	65.28 ± 6.58	67.49 ± 8.38	1.804	0.073
Male sex, n (%)	49 (59.8%)	41 (60.3%)	0.004	0.947
BMI (kg/m^2), mean ± SD	23.7 ± 3.1	23.0 ± 3.4	1.26	0.21
COPD duration ≥10 years, n (%)	39 (47.6%)	38 (55.9%)	1.030	0.310
Smoking, n (%)	24 (29.3%)	21 (30.9%)	0.046	0.830
GOLD stage II/III/IV, n (%)	18/42/22	10/30/28	3.732	0.155
mMRC dyspnea score ≥3, n (%)	38 (46.3%)	39 (57.4%)	1.804	0.179
CAT score, mean ± SD	21.34 ± 6.49	24.55 ± 6.00	3.124	0.002
Frequent exacerbations (≥2 in previous year), n (%)	26 (31.7%)	33 (48.5%)	4.408	0.036
≥1 COPD-related hospitalization in previous year, n (%)	19 (23.2%)	26 (38.2%)	4.017	0.045
Long-term oxygen therapy at home, n (%)	24 (29.3%)	27 (39.7%)	1.805	0.179
Participation in pulmonary rehabilitation before BLVR, n (%)	43 (52.4%)	22 (32.4%)	6.108	0.013
Cardiovascular disease (IHD or heart failure), n (%)	34 (41.5%)	32 (47.1%)	0.472	0.492
Hypertension, n (%)	47 (57.3%)	41 (60.3%)	0.136	0.712
Diabetes mellitus, n (%)	17 (20.7%)	15 (22.1%)	0.039	0.843
Osteoporosis, n (%)	25 (30.5%)	24 (35.3%)	0.390	0.532
Depression and/or anxiety, n (%)	21 (25.6%)	21 (30.9%)	0.513	0.474

Note: COPD: chronic obstructive pulmonary disease; BLVR: bronchoscopic lung volume reduction.

23.2%, P=0.045). Responders were significantly more likely to participate in pulmonary rehabilitation before BLVR (52.4% vs. 32.4%, P= 0.013). Other comorbidities, including cardiovascular disease, hypertension, diabetes mellitus, osteoporosis, and depression/anxiety, were similarly distributed in both groups (all P> 0.05), and there was no significant difference in the number of individuals with a Charlson comorbidity index ≥3 between the two groups (**Table 1**).

Comparison of quantitative CT emphysema heterogeneity indicators

The EHI was significantly higher in responders than in non-responders (20.85 ± 4.65 vs. 13.84 ± 4.61, P<0.001). Although the LAA%, <-950 HU) was slightly higher in responders (50.21 ± 8.25 vs. 49.53 ± 6.81), the difference was not significant (P=0.591). Regarding the difference in lobar destruction, there was a significant difference between the two groups, with responders showing greater destruction (19.57 ± 6.30 vs. 13.73 ± 3.47, P<0.001). Responders also had significantly higher scores on voxel density gradient and heterogeneity voxel ratio (-13.72 ± 4.40 vs. -9.92 ± 2.72, P<0.001 and 37.05 ± 10.53 vs. 27.20 ± 7.86, P<0.001, respectively). Moreover, responders had larger hyperinflated voxel clusters (94.69 ± 18.70 vs. 78.03 ± 19.17, P<0.001) and higher lung parenchymal destruction scores (3.64 ± 0.73 vs. 3.11 ± 0.32, P<0.001) (**Table 2**).

Comparison of lung lobular structural characteristics

The target-lobe volume was significantly larger in responders (P<0.05), while the non-target lung lobe volume showed no difference between the two groups (P>0.05). Responders had a significantly higher lung lobe volume asymmetry index (P<0.001), indicating more significant interlobar imbalance. Responders also showed a significantly higher targetlobe destruction rate (P<0.001) and significantly lower parenchymal vascular density (P<0.001), reflecting a more severe parenchymal injury and vascular reduction. Geometric and mechanical parameters further distinguished the responder phenotype: responders showed significantly increased lobar sphericity (P<0.01) and a significantly higher mechanical strain index (P<0.001). Finally, responders exhibited a significantly higher air retention rate (P<0.001), consistent with more severe expiratory flow impairment (**Figure 2**).

Table 2. Comparison of quantitative CT emphysema heterogeneity indicators

Variable	Responder (n=82)	Non-responder (n=68)	t/χ^2	*P* value
Emphysema Heterogeneity Index (EHI)	20.85 ± 4.65	13.84 ± 4.61	9.244	<0.001
Target-lobe LAA% (<-950 HU)	50.21 ± 8.25	49.53 ± 6.81	0.539	0.591
Non-target lobe LAA%	28.74 ± 8.18	29.06 ± 8.02	0.240	0.811
Lobar destruction difference (%)	19.57 ± 6.30	13.73 ± 3.47	6.822	<0.001
Voxel-wise density gradient (HU/cm)	-13.72 ± 4.40	-9.92 ± 2.72	6.207	<0.001
Heterogeneous voxel proportion (%)	37.05 ± 10.53	27.20 ± 7.86	6.382	<0.001
Hyperinflated voxel cluster size (mL)	94.69 ± 18.70	78.03 ± 19.17	5.370	<0.001
Parenchymal destruction score	3.64 ± 0.73	3.11 ± 0.32	5.511	<0.001

Note: LAA: low attenuation area.

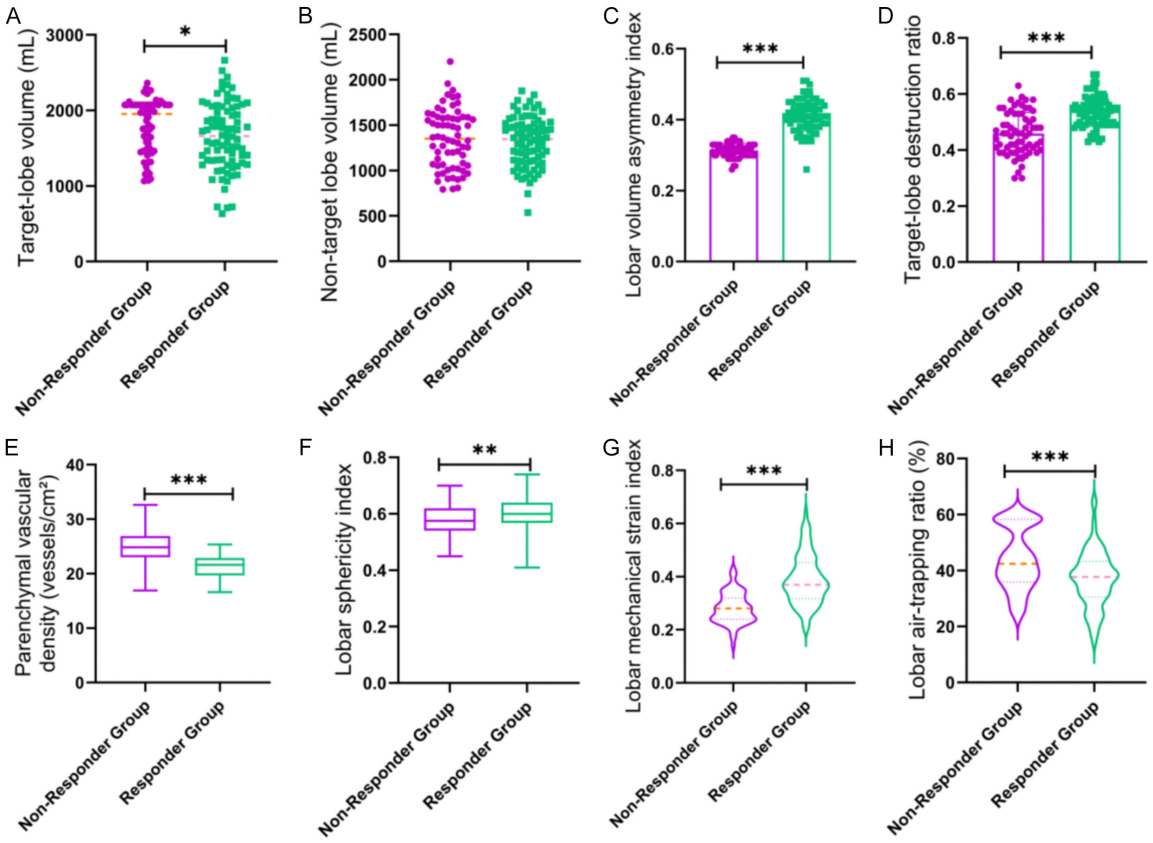

Figure 2. Comparison of lung lobular structural characteristics. A. Target-lobe volume. B. Non-target lobe volume. C. Lobar volume asymmetry index. D. Target-lobe destruction ratio. E. Parenchymal vascular density. F. Lobar sphericity index. G. Lobar mechanical strain index. H. Lobar air-trapping ratio. Compared to the responder group, *P<0.05, **P<0.01, ***P<0.001.

Comparison of heterogeneity in ventilation and air retention

The air retention heterogeneity index was significantly higher in responders than in non-responders (P<0.001). There was no significant difference in the LAA% between the two groups (P=0.615). Responders had a higher inspiratory-expiratory density contrast and more pronounced ventilation asymmetry (both P<0.001). Responders had significantly lower levels of functional small airway disease than non-responders (P<0.001), and their ventilation-perfusion (V/Q) mismatch index was significantly lower (P<0.001). Furthermore, responders had larger local gas retention clusters, and a signifi-

Table 3. Comparison of heterogeneity in ventilation and air retention

Variable	Responder	Non-responder	t	P
Air-trapping heterogeneity index	18.55 ± 6.23	11.34 ± 7.26	6.546	<0.001
Expiratory LAA%	46.39 ± 11.02	47.30 ± 10.98	0.505	0.615
Inspiratory-expiratory contrast (HU)	121.20 ± 32.15	94.61 ± 39.13	4.569	<0.001
Ventilation asymmetry score	0.51 ± 0.16	0.32 ± 0.06	8.928	<0.001
Functional small-airway disease (%)	35.38 ± 8.75	44.66 ± 6.31	7.311	<0.001
Ventilation-perfusion (V/Q) mismatch index	0.47 ± 0.06	0.67 ± 0.08	18.072	<0.001
Regional gas trapping cluster size	72.50 ± 22.33	49.76 ± 26.41	5.715	<0.001
Expiratory flow-limiting voxel%	26.20 ± 5.85	40.18 ± 8.14	12.204	<0.001

LAA: low attenuation area.

Table 4. Comparison of fissure and collateral ventilation indicators

Variable	Responder	Non-responder	t	P
Fissure completeness (%)	94.03 ± 5.81	82.49 ± 6.15	11.781	<0.001
Collateral ventilation probability (CVP)	0.18 ± 0.02	0.39 ± 0.09	20.748	<0.001
Incomplete fissure length (mm)	8.65 ± 2.09	18.12 ± 2.75	23.937	<0.001
Fissure gap area (mm^2)	20.40 ± 6.19	31.03 ± 4.38	11.904	<0.001
Fissure roughness index	0.38 ± 0.11	0.57 ± 0.19	7.777	0.010
Lobar separation angle (°)	34.39 ± 8.78	31.02 ± 6.52	2.621	0.001
Functional fissure discontinuity (%)	6.08 ± 3.09	8.08 ± 4.17	3.372	<0.001

cantly lower proportion of expiratory flow-limiting voxels compared to non-responders (both P<0.001) (**Table 3**).

Comparison of fissure and collateral ventilation indicators between the two groups

Regarding lung fissure integrity, responders showed significantly higher lung fissure integrity, a greater proportion of lung fissures with integrity ≥90%, and a significantly lower probability of collateral ventilation (all P<0.001). Indicators of lung fissure defect severity, including incomplete lung fissure length, lung fissure interspace area, and lung fissure roughness, were all significantly lower in responders (all P<0.05). Responders had larger lobe separation angles (P=0.001) and reduced functional lung fissure discontinuity (P<0.001) (**Table 4**).

Comparison of visual CT phenotypic and pattern features

Compared to non-responders, responders had significantly thinner segmental airway wall thickness (P<0.01) and larger airway lumen diameter (P<0.001), indicating better preservation of airway geometry. Additionally, responders had significantly higher airway roundness indices (P<0.001), indicating better airway morphology. The Pi10 value, reflecting small airway size, was also significantly higher in responders (P<0.01). Responders had higher total airway count (TAC) (P<0.001) and higher terminal bronchiolar density (P<0.01), both indicating less airway impairment. In addition, responders had significantly lower airway resistance substitution index (P<0.001), indicating better overall airway function (**Figure 3**).

Comparison of visual CT phenotypic differences

The incidence of upper lobe dominance was higher in responders than in non-responders (65.9% vs. 45.6%, P=0.013). The incidence of heterogeneous visual patterns was also higher in responders (71.9% vs. 48.5%, P=0.003), while homogeneous patterns were more common in non-responders (28.0% vs. 51.5%, P=0.003). In contrast, there were no significant differences between the two groups in the presence of bullae >2 cm (18.3% vs. 26.5%, P=0.229) and paraseptal emphysema (35.4% vs. 44.1%, P=0.275). Notably, non-responders were more frequently found to have signs of airway obstruction (61.8% vs. 46.3%, P=0.001) and higher airway tortuosity scores (2.8 ± 1.0 vs. 2.4 ± 0.9, P=0.025), while there was no sig-

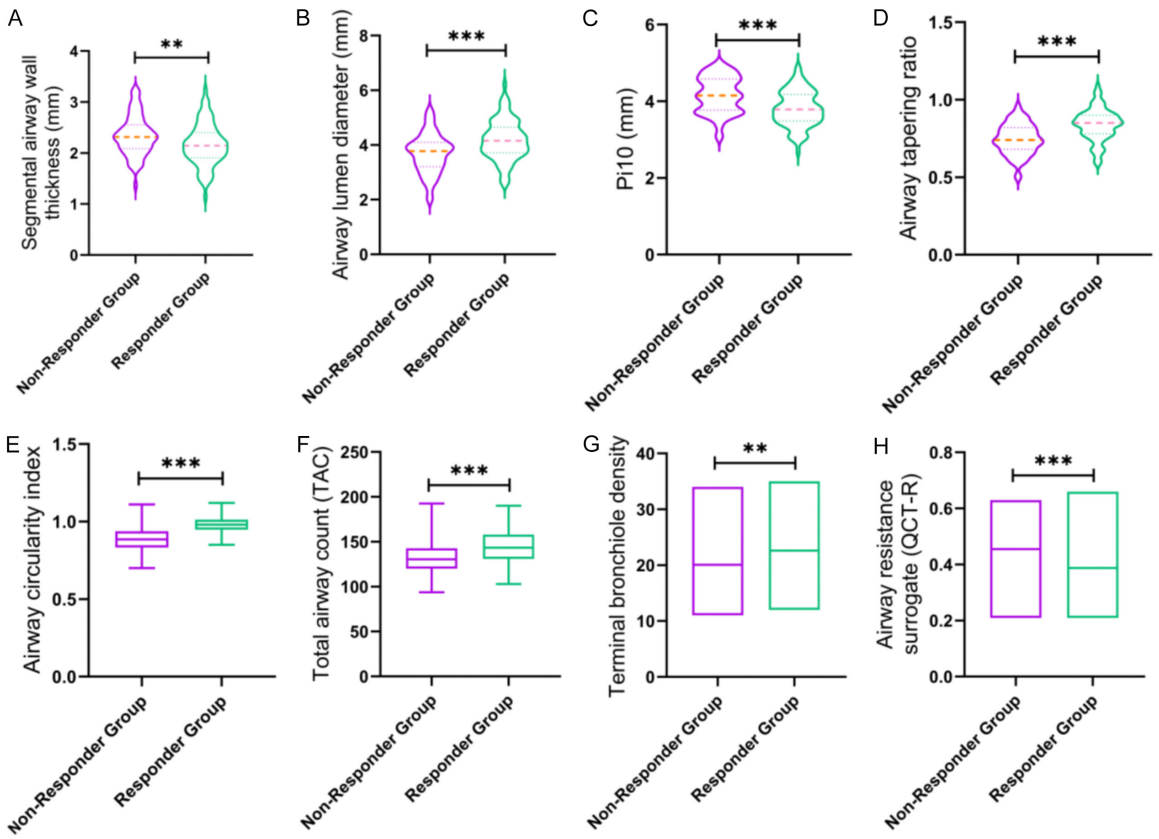

Figure 3. Comparison of visual CT phenotypic and pattern features. A. Segmental airway wall thickness. B. Airway lumen diameter. C. Pi10. D. Airway branching ratio. E. Airway circularity index. F. Total airway count (TAC). G. Terminal bronchiole density. H. Airway resistance surrogate (QCT). Compared to the non-responder group, **P<0.01, ***P<0.001.

nificant difference in subsegmental atelectasis before BLVR (25.0% vs. 14.6%, P=0.110) (**Table 5**).

Multivariate logistic regression analysis of BLVR response predictors

After identifying significant candidate predictors in the univariate analysis, we constructed a multivariate logistic regression model using a pre-specified, transparent model-building strategy. Specifically, variables with P<0.10 in the univariate logistic regression and/or variables with clear clinical relevance were considered eligible for inclusion. The number of covariates was limited due to the availability of responders to avoid overfitting. Because many quantitative CT-derived indices are often strongly correlated in quantifying overlapping emphysema burden/heterogeneity, we screened for collinearity using pairwise correlation assessments and variance inflation factors (VIFs); when significant collinearity was detected (e.g., VIF >5 or strong correlation), only the most clinically interpretable and statistically informative representative variables were retained. The final multivariate model was derived using a stepwise (likelihood ratio) selection procedure, and adjusted ORs and 95% CIs were reported. In the final model, a higher EHI remained an independent predictor of response (adjusted OR 0.114, 95% CI 0.059-0.223, P<0.001) ≥90% integrity of the lung fissure was also strongly associated with treatment response (adjusted OR 0.888, 95% CI 0.848-0.930, P<0.001), highlighting the importance of intact lung fissures for effective lobar collapse. Immediate postoperative TLVR ≥700 ml showed the strongest predictive value (adjusted OR 0.106, 95% CI 0.047-0.241, P<0.001) (**Table 6**).

Representative CT images before and after BLVR

Representative CT images illustrate the distinct morphologic changes in non-responders and

Table 5. Comparison of visual CT phenotypic differences

Variable	Responder (n=82)	Non-responder (n=68)	X^2	P
Upper-lobe predominance (%)	54 (65.9%)	31 (45.6%)	6.217	0.013
Heterogeneous visual pattern (%)	59 (71.9%)	33 (48.5%)	8.559	0.003
Homogeneous pattern (%)	23 (28.0%)	35 (51.5%)	8.559	0.003
Bullae >2 cm (%)	15 (18.3%)	18 (26.5%)	1.449	0.229
Paraseptal emphysema (%)	29 (35.4%)	30 (44.1%)	1.193	0.275
Evidence of airway plugging (%)	38 (46.3%)	42 (61.8%)	11.393	0.001
Subsegmental collapse pre-BLVR (%)	12 (14.6%)	17 (25.0%)	2.561	0.110

Note: BLVR: bronchoscopic lung volume reduction.

Table 6. Multivariate logistic regression analysis of BLVR response predictors

Independent Predictor	β	Adjusted OR	95% CI	*P* value
Emphysema heterogeneity index (EHI)	2.168	0.114	0.059-0.223	<0.001
Fissure completeness ≥90%	0.119	0.888	0.848-0.930	<0.001
Immediate TLVR ≥700 mL	2.244	0.106	0.047-0.241	<0.001

Note: TLVR: target-lobe volume reduction.

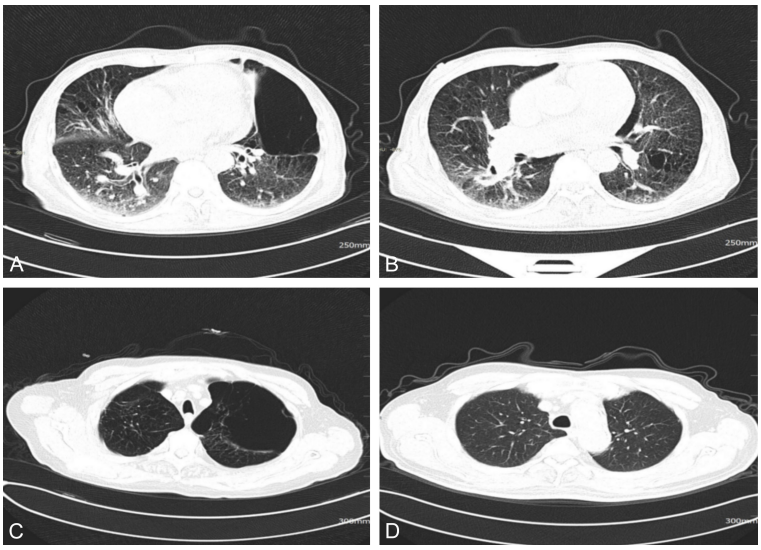

Figure 4. Representative CT images before and after BLVR in non-responder and responder patients. A. Pre-treatment CT image of a non-responder, showing heterogeneous emphysema with limited target-lobe hyperinflation. B. Post-treatment CT image of the same non-responder, demonstrating minimal lobar volume reduction and persistent hyperinflation. C. Pre-treatment CT image of a responder, showing marked target-lobe emphysematous destruction and hyperinflation. D. Post-treatment CT image of the responder, demonstrating substantial target-lobe volume reduction with compensatory expansion of adjacent lobes.

responders. after BLVR. In non-responders (**Figure 4A**, **4B**), pre-treatment CT showed heterogeneous emphysema in the target lobe with mild hyperinflation. However, post-treatment CT showed minimal lobe volume reduction and persistent hyperinflation, consistent with no clinical or functional improvement. In contrast, responders (**Figure 4C**, **4D**) showed significant emphysematous destruction and hyperinflation in the target lobe before treatment. Post-BLVR CT showed a significant reduction in target lobe volume with significant compensatory expansion of adjacent lobes, reflecting effective lobe collapse and successful bronchoscopic lung volume reduction.

Discussion

Our study demonstrated that quantitative CT-based measurements of emphysema heterogeneity, lung structural remodeling, and lung fissure integrity are complementary predictors of clinical response to BLVR. Responders exhibited significantly higher emphysema phenotype heterogeneity, more progressive but localized lung parenchymal injury, more pronounced air retention heterogeneity, more intact lung fissures, and lower collateral ventilation potential. These characteristics collectively constitute a comprehensive quantitative CT model with high-quality

discriminative power (AUC 0.94). In addition to confirming the central role of lung fissure integrity and immediate target lobe volume reduction (TLVR 700 mL), our findings complement the existing literature-we quantified EHI) as a unique predictor and integrated multiple structural, functional, and airway-based biomarkers from quantitative CT into a single response phenotype.

Existing evidence suggests that the heterogeneity of emphysema is an important predictor of the efficacy of BLVR, which reinforces the previous view that heterogeneous diseases with predominantly upper lobes are more likely to benefit from the positive effects of lung volume reduction. Previous surgical and bronchoscopic experiments have mostly been based on semi-quantitative or visually judged heterogeneity patterns and lobar ablation criteria, but a voxel-based or lobar-based heterogeneity measurement model has never been clearly established [15]. Our statistics show that for every unit increase in the EHI, the probability of response increases linearly by 12%, and when EHI = 17%, perfect discrimination can be achieved, that is, the relative difference between the target lobe and the adjacent lobe is more significant than simple lung tissue destruction. From a mechanical point of view, the more random the distribution of emphysema, the more selectively the most severely diseased lobe can be "ineffective", thereby optimizing the recovery of elastic recovery function and promoting the re-expansion of healthy lung parenchyma [16]. The clinical significance of these findings is that overall emphysema burden or visual impression should not be used as the sole indicator for screening candidate patients. Instead, it should be emphasized that heterogeneity must be systematically quantified when planning BLVR.

From a mechanistic perspective, the ability of emphysema heterogeneity to predict the efficacy of BLVR is closely related to the following three aspects: (I) target selection; (II) the "recoverable reserve" of relatively preserved lung tissue; and (III) the technically specific determinants of lobe collapse. First, a higher heterogeneous load provides an objective basis for the selection of target lobes: when lung tissue destruction and overinflation are significantly concentrated in a certain lobe, obstruction of that lobe is more likely to produce a significant decompression effect; while in diffuse/homogeneous lesions, regional mechanical differences are smaller, and therefore the potential benefit is also smaller [17]. Second, heterogeneous emphysema itself means that there is relatively intact lung parenchyma in the non-target area; after effective collapse of the target lobe (which can be reflected by the large reduction in the volume of the target lobe in the early stage), these relatively normal areas can expand and "compensate", improving diaphragmatic morphology, elastic recoil and V/Q redistribution - which is consistent with the compensatory expansion observed on follow-up CT in our cohort of responders [18]. Third, the role of heterogeneity is also affected by the BLVR technique. In valve-based BLVR (as in this study), heterogeneity has the greatest clinical value when combined with high fissure integrity and low collateral ventilation, as these conditions are necessary to achieve true lobar atelectasis and sustained volume reduction; this is consistent with the strong predictive value of fissure integrity and TLVR in our multivariate model [19]. In contrast, using techniques less dependent on fissure integrity (such as coil implantation or thermo/chemical methods), heterogeneity may influence outcomes primarily through regional compliance differences and mechanical re-stress rather than complete lobar collapse, potentially leading to different response patterns and endpoints. Overall, combining emphysematous heterogeneity with fissure integrity and functional asymmetry provides a biologically plausible framework for individualized target lobe planning and understanding why some patients benefit significantly from BLVR while others do not.

Structural and vascular quantitative CT measurements further identify responder phenotypes by reflecting the geometric significance of complex, localized, focal lesions [20]. The responders exhibited increased target lobe volume, higher lobe volume asymmetry index, increased target lobe destruction ratio, and decreased parenchymal vascular density, all of which suggest overexpansion, overinflation, and excessive vascular distribution in the lobe while other adjacent lobes were well preserved. These results are consistent with earlier studies on vascular trimming, lobe overinflation, and disease burden; however, here we show that this disproportionate alteration at the lobe level is directly associated with a successful

response to BLVR. This resulted in increased lobe sphericity index and mechanical strain in responders, indicating that the target lobes are not only enlarged but also mechanically overloaded to allow for further collapse and transfer of volume change effects to other areas [21]. This pattern of destruction may be one of the reasons for the significant TLVR in patients, although this also raises concerns that BLVR may offer little benefit or even greater surgical risks in patients with more symmetrical damage and smaller mechanical differences, without a significant chance of functional improvement.

Functional ventilation and air retention measurements indicate that their spatial distribution and aggregation behavior are not only due to the presence of air leakage, but more importantly, the spatial distribution of air affects the results of BLVR. Increased heterogeneity of air retention, a significantly larger difference between inspiratory and expiratory volumes, ventilation asymmetry, and an increased scale of localized gas retention aggregation all indicate significant and predominantly localized small airway dysfunction in the target lung lobe. Although preliminary imaging studies of COPD have associated gas retention with small airway disease-both are known to be functionally associated with airflow limitation and the risk of acute exacerbations [22, 23], previous studies have not systematically associated the variability of these two phenomena with the effectiveness of interventional treatment. In our cohort, the incidence of functional small airway disease was significantly higher in responders, but contrary to intuition, responders had a lower V/Q mismatch index and a lower proportion of expiratory flow-limiting voxels due to the presence of severely diseased lobes, while gas exchange and airflow dynamics were well regulated in the remaining lung tissues. This trend suggests that ideal BLVR patients may be those with localized lesions severe enough to warrant lung volume reduction, but with sufficient remaining functional lung tissue to compensate. This seems to suggest that BLVR carries a higher risk in patients with diffuse, homogeneous functional impairment, and is more likely to result in postoperative decompensation.

Our analysis validated and quantified the key impacts of fissure integrity and collateral ventilation on BLVR success and proposed new morphologic features of fissure defects. Consistent with previous studies using CT fissure analysis and Chartis assessment, fissure integrity of 90% or higher was a highly significant independent predictor of response (adjusted OR 5.06), and responders had a significantly lower probability of collateral ventilation. However, we found that, in addition to the binary integrity threshold, responders had significantly reduced incomplete fissure length, fissure gap area, fissure roughness and functional fissure discontinuity, and larger lobe separation angles were associated with successful lung volume reduction. These measurements may reflect less obvious anatomic signals and restraining structures through which collateral ventilation and lobar collapseability are regulated. Mechanistically, more intact fissures restrict interlobar gas redistribution, allowing the target lobe to collapse effectively after valve implantation [24, 25]. These results have clinical implications, suggesting that fissure analysis should not be limited to a single percentage of integrity, as even minor fissure defects can affect the effectiveness of fissure management; therefore, over-reliance on simplified fissure grading may lead to inappropriate patient selection.

Airway phenotypes and visual measurements of CT phenotypes add new dimensions to the characterization of responders and highlight the importance of maintaining airway structure during the mediation of BLVR benefits. Relevant indicators in responders included reduced airway wall thickness, enlarged airway lumen, increased roundness index, elevated Pi10, increased TAC, and increased terminal bronchiolar density, all indicating less airway remodeling and disruption compared to non-responders. Meanwhile, upper lobe-dominant emphysema and visually heterogeneous emphysema patterns were more common in responders, while airway obstruction and structural distortion were more common in non-responders. These results are consistent with previous studies that severe airway remodeling, mucus obstruction, and structural distortion are associated with poorer interventional therapy and bronchodilator response [26, 27]. Mechanistically, a more intact airway helps support uniform valve deployment, effective collapse of the target lobe, and redistribution of ventilation to healthier areas. Airway wall thickness alone had a moderate AUC (0.74), but the strong airway morphology in integrated quantitative CT mod-

els suggests that airway morphology cannot be used alone and must be interpreted in conjunction with lung parenchyma and fissure features [28]. Clinicians should be cautious about administering BLVR to patients with significant airway obstruction and distortion, as this is consistent with a less reversible, airway-dominant phenotype with minimal potential for volumetric-mechanical remodeling.

Despite these advantages, some limitations of this study warrant further investigation. First, this study was purely observational and was a single-center study, which could have introduced selection bias and limited the ability to generalize the findings to a broader COPD population, such as patients with other emphysema patterns or comorbidities. Second, even with a globally standardized quantitative CT protocol, differences may have existed between centers in the use of CT acquisition, reconstruction, and segmentation algorithms, affecting the reproducibility of the indicators. Therefore, standardized protocols and external validation are needed before replicating the study. Third, our research was limited to short- to medium-term responses to BLVR and did not comment on long-term outcomes such as the rate of acute exacerbations, survival, or valve-related complications that may be affected by other imaging predictors. Lastly, we found positive results in terms of correlation and predictive performance, but did not address causation, and unmeasured confounding factors (such as functional reserve, dynamic hyperinflation, or airway inflammation) may also affect treatment response.

In conclusion, this study demonstrates that quantitative emphysema heterogeneity derived by CT, combined with enhanced structural, functional, and fissure-based imaging findings, is a powerful predictor of BLVR outcomes, representing a significant improvement over the classic responder phenotype. Elevated EHI, near-closed lung fissures, and reduced immediate TLVR of 700 mL or more, combined with ventilation and air retention heterogeneity, vascular attenuation, and preserved airway geometry, can further stratify candidate patients. These results will justify the use of detailed quantitative CT analysis in routine preoperative BLVR assessment and are expected to improve patient selection, customized surgical planning, and assessment of the benefit-risk ratio in patients with severe emphysema.

Disclosure of conflict of interest

None.

Abbreviations

6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; AUC, area under the receiver operating characteristic curve; BLVR, bronchoscopic lung volume reduction; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CVP, collateral ventilation probability; DLCO, diffusing capacity of the lung for carbon monoxide; EHI, emphysema heterogeneity index; FEV1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRCT, high-resolution computed tomography; HU, Hounsfield unit; IHD, ischaemic heart disease; LAA, low-attenuation area; MCID, minimal clinically important difference; mMRC, modified Medical Research Council; OR, odds ratio; aOR, adjusted odds ratio; QCT, quantitative computed tomography; RV, residual volume; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; SPSS, Statistical Package for the Social Sciences; TAC, total airway count; TLVR, target-lobe volume reduction; VIF, variance inflation factor; V/Q, ventilation-perfusion ratio; Pi10, square root of the wall area of a theoretical airway with an internal perimeter of 10 mm.

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