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ORIGINAL RESEARCH

Imaging Phenotypes Assessment by Using Quantitative Parameters for CT-Defined Subtypes of Chronic Obstructive Pulmonary Disease

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Purpose: To explore the quantitative imaging phenotype differences for CT-defined subtypes classified by the Fleischner Society in patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: A total of 228 COPD patients who underwent non-enhanced chest CT screening from 2018 to 2024 were included. All patients were divided into type-A (Absent emphysema that no or mild emphysema, Goddard score ≤8, regardless of bronchial wall thickening), type-E (Emphysema that significant emphysema, Goddard score >8, without bronchial wall thickening), and type-M (Mixed emphysema and bronchial wall thickening that both significant emphysema, Goddard score >8, and bronchial wall thickening ≥ grade 1 in ≥1 lung lobe). Imaging phenotype parameters included lung airspace analysis (LAA) and LAA size analysis (LAASA) in emphysema, airway wall, lung vessels and interstitial lung disease (ILD) extracted by a COPD-specific analysis software were analysis among three groups.

Results: Quantitative assessment of emphysema among three image phenotypes showed significant differences in full emphysema and full emphysema ratio based on LAA among three groups ($P < 0.05$). The areas of consolidation, ground-glass opacity, and reticular patterns were significantly larger in type-M than the other two types ($P < 0.05$). Quantitative assessment of small airways disease and small vessel parameters found smaller lumen-volume and larger wall-volume in whole lung level in the emphysema phenotype of type-M ($P < 0.05$) were found in the small vessel count in distance of 6 mm and 9mm from the pleura were significant differences among three groups ($P < 0.05$). The multivariate logistic regression analysis showed that the higher proportion of full emphysema ratio and wall-volume, a proportion of smaller lumen-volume, and a more noticeable interstitial lung alterations were associated with type-M.

Conclusion: A quantitative CT evaluation can further delineate the imaging phenotypes characteristics thereby in guiding to early diagnosis, severity assessment, and therapeutic recommendations in COPD patients.

Keywords: chronic obstructive pulmonary disease, computed tomography, image phenotypes, quantitative analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterised by persistent respiratory symptoms and progressive airflow obstruction. It is increasingly recognised as a complex, multifaceted disease that encompasses various clinical phenotypes and subtypes, each with distinct characteristics and treatment needs.

The clinical presentation of COPD can vary significantly among patients, leading to the identification of different phenotypes that may share certain clinical or biological traits but differ in prognosis and therapeutic requirements. For instance, some patients may exhibit severe airflow limitation and frequent exacerbations, while others may present with

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milder symptoms but have comorbid conditions such as obesity or cardiovascular disorders. This heterogeneity has prompted a shift towards a phenotypical approach in managing COPD, which aims to tailor treatment strategies based on individual patient profiles.[1,2]

Recent studies have focused on identifying clinically relevant subtypes of COPD, revealing that patients can be grouped based on their symptoms, lung function, and other clinical parameters.[3] The quantitative imaging methods technical development has led to their increased use in the diagnosis and management of patients with COPD. The Fleischner Society has outlined a classification system that utilizes both visual and quantitative CT imaging features to define phenotypic abnormalities in COPD. This approach aims to provide a structured method for assessing the extent of emphysematous lung destruction, airway wall changes, and expiratory air trapping, which are critical in understanding the heterogeneity of COPD and tailoring personalized treatment strategies.[4] Advances in imaging technologies have enabled clinicians to assess lung structure and function with greater precision. For instance, CT imaging provides in-vivo assessments that can inform patient stratification and prognostication. Moreover, the integration of quantitative computed tomography (QCT) imaging analysis is potentially valuable tool in objectively and non-invasively evaluate COPD phenotype and has enhanced the ability to detect subtle pathologic changes in the lungs.[5] As the field continues to evolve, the promise of these advanced imaging modalities in the clinical management of COPD remains substantial. Currently, there are limited studies investigating the differences in image phenotypes of COPD patients using CT classification, which is essential for clinical examination. The ability to phenotype patients through imaging can lead to more personalized approaches to treatment, potentially improving outcomes.

This study employs CT quantitative analysis methods to examine the differences in quantitative imaging phenotypes for CT-defined subtypes in COPD patients, aiming to identify biomarkers for disease evaluation. We seek to refine the accuracy of COPD diagnosis in clinical practice by examining the diversity among these phenotypes and use these results to create effective treatment options.

Materials and Methods

General Information

A retrospective analysis was conducted on the clinical and imaging data of patients who underwent non-enhanced chest CT screening for COPD at Wuhan Central Hospital from August 2018 to August 2024. Inclusion criteria: (1) Patients who met the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022; (2) CT scans with clear lung tissue display and no significant respiratory motion artifacts. Exclusion criteria: (1) History of lung lobectomy or segmentectomy; (2) lung cancer, severe pulmonary interstitial fibrosis, and extensive lung infections, significant pleural effusion; (3) Severe chest deformities leading to software analysis failure. The retrospective study was approved by the ethics committee of Wuhan central hospital, and the informed consent was waived due to non-invasively imaging analyzing assessment. This research was fully complied with the Declaration of Helsinki that we took all necessary preventive measures to respect the rights and confidentiality of patients.

Chest CT Scanning and Image Visual Evaluation

All patients underwent chest CT scans during an inspiratory breath-hold in the supine position. A multi-detector CT scanner (Somatom Definition flash, Siemens Medical Solutions or GE Discovery CT750 hD scanner, GE Healthcare, USA) was used to take the volumetric assessment at the end of maximum inspiration. The scanning range extended from the thoracic inlet to the level of the posterior costophrenic angle. Detailed methods for CT acquisition and analysis are available in Table S1.

A visual assessment of the CT scan for Imaging phenotype and subjective visual Goddard score was performed by two deputy chief radiologists with 8 and 10 years of experience, respectively in a blinded manner on lung window images. In case of disagreement, a consensus was reached after discussion. The Goddard scoring system was used to score the proportion of emphysema.[6] Bronchial wall thickening was evaluated using multiplanar reconstruction to observe subsegmental bronchi with diameters of 2–4 mm in each lung lobe, and graded as follows: grade 0 (bronchial wall diameter/adjacent pulmonary artery diameter < 30%), grade 1 (30% ≤ bronchial wall diameter/adjacent pulmonary artery diameter < 50%), and grade 2 (bronchial wall diameter/adjacent pulmonary artery diameter ≥ 50%).

Bronchial wall thickening was considered present when the grade was ≥1. Based on the degrees of emphysema and bronchial wall thickening, COPD patients were classified into three image phenotypes: type-A characterized by the absence or mild presence of emphysema, regardless of whether there is bronchial wall thickening (no or mild emphysema, Goddard score ≤8, regardless of bronchial wall thickening), type-E marked by the presence of significant emphysema without bronchial wall thickening (significant emphysema, Goddard score >8, without bronchial wall thickening), and type-M featuring both significant emphysema and bronchial wall thickening (both significant emphysema, Goddard score >8, and bronchial wall thickening ≥ grade 1 in ≥1 lung lobe).

Quantitative Image Analysis

The raw data from CT scans were imported into a COPD-specific analysis software (A-VIEW software, Suzhou Information Technology Co, Ltd) for image registration and quantitative measurements to obtain imaging phenotype parameters. The parameters included lung airspace analysis (LAA) and LAA size analysis (LAASA) in emphysema, airway wall, lung vessels and interstitial lung disease (ILD) analysis (shown in Figure 1). The emphysema was determined by evaluating the low attenuation area (values lower than −950 hU). Total lung capacity (TLCCT) was also calculated based on inspiratory CT images. Pulmonary small airways were defined as regions with lung density >-950 hU, representing gas trapping without emphysema. Pulmonary small vessel quantitative parameters included the number of vessels (N) and the number of vessels with cross-sectional areas <5 mm² (N-CSA < 5) at distances of 6, 9, 12, 15, 18, 21, and 25mm from the pleura throughout the lungs.

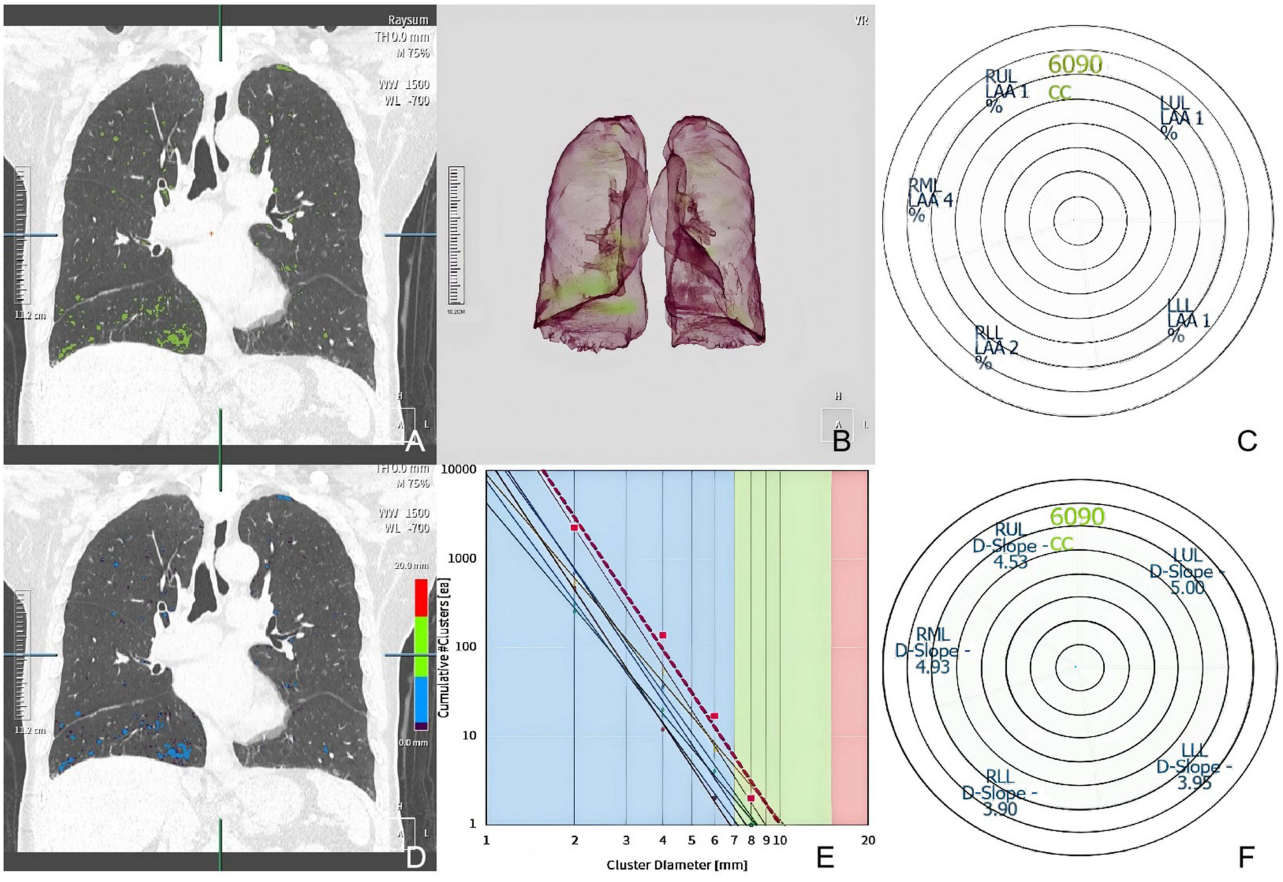

Figure 1 Inspiratory LAA and LAAsize Analysis for a 69-year-old man who belonged to type-A. (**A** and **D**) LAA&LAAsize coronal pseudo-color image, The default threshold is −950 hounsfield Units (HU); (**B**) LAA three-dimensional image; (**C** and **F**) LAA&LAAsize Chart to show the volume, LAA% and D-slope. (**E**) LAA Size Log-Log to show the cluster diameter.

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Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. The normality of measurement data was tested using the Kolmogorov–Smirnov method. Normally distributed data were expressed as mean ± standard deviation (EQN). Continuous variables were compared by Independent Samples *T*-test. Categorical variables were compared using χ^2-test. The one-way ANOVA and LSD tests were used to compare multiple groups comparison. ROC analysis was performed to evaluate the efficiency of Goddard score and quantitative assessment of emphysema. The DeLong's test was applied to test the statistical significance of AUC values. A univariate logistic regression analysis followed by multivariate analysis was used to identify determinants associated with imaging phenotype of COPD patients. $P < 0.05$ was considered significant in all statistical analyses.

Results

General Information

A total of 228 COPD patients were finally included, including 187 males and 41 females, with an age range of 40–74 years (mean age: 67 ± 5 years). Among the 228 patients, there were 14 cases of type-A, 126 cases of type-E, and 88 cases of type-M. Statistically significant differences were found in age among the three phenotypes ($P = 0.007$). However, there were no significant differences in gender among the three phenotypes ($P = 0.066$). The proportion of severe emphysema based on Goddard score was significantly higher in type-M than in type-A and type-E ($P < 0.001$).

Quantitative Assessment of Emphysema Among Three Image Phenotypes of COPD Patients

Significant differences were found in full emphysema and full emphysema ratio based on low attenuation areas (LAAs) among the three COPD image phenotypes ($P < 0.05$). Particularly observed in the volume of emphysema within the region larger than 15mm ($P = 0.013$), while, no significant differences were found in the volume of emphysema within the region of 7–15mm, 1–7mm and less than 1mm. For interstitial lung texture analysis, the areas of consolidation, ground-glass opacity, and reticular patterns were significantly larger in type-M than in type-A and type-E ($P < 0.05$). The details were provided in Table 1. Furthermore, we performed DeLong's test to analyze the efficiency between the AUC of Goddard score and LAA for type-M. The result showed that there was significant difference between two scores (0.616 vs 0.739, $P = 0.002$), which indicated that quantitative assessment of emphysema performed better than the Goddard score for type-M classification (seen in Figure 2).

Quantitative Assessment of Small Airways Disease and Small Vessel Parameters

In pulmonary small airways disease quantitative assessment, lumen-volume was significantly smaller; nevertheless, wall-volume in whole lung level were significantly larger in the emphysema phenotype of type-M than in type-A and type-E ($P < 0.05$). There were no significant differences in branch count and lumen-area among the three image phenotypes. Statistically significant differences were found in the small vessel count in distance of 6 mm and 9mm from the pleura among three image phenotypes ($P < 0.05$), while, no significant differences were found in distance of 12, 15, 18, 21, 24mm. The details are provided in Table 2.

Table 1 Quantitative Imaging Phenotypes Parameters in Different COPD subtypes

Variable	Overall, N = 228	Type-A= 14 (6.1%)	Type-E= 126 (55%)	Type-M = 88 (39%)	Statistics	p-value
LAA	1,623.67 [1,193.53, 2,167.44]	1,137.72 [904.04, 1,466.75]	1,456.84 [929.53, 1,907.70]	1,971.00 [1,570.39, 2,546.54]	39.08	<0.001
LAA%	32.79 [24.53, 39.83]1	23.89 [18.55, 27.83]	30.50 [19.16, 35.65]	38.30 [30.01, 45.19]	38.70	<0.001
$V^{emphysema>15mm}$	110.88 [30.34, 247.85]	24.05 [7.62, 172.69]	75.01 [26.58, 239.04]	148.61 [65.10, 270.13]	12.21	0.002
Consolidation	1.90 [0.71, 5.43]	1.43 [0.40, 1.76]	1.64 [0.61, 5.07]	3.23 [0.92, 6.40]	7.67	0.022
Ground-glass opacity	23.66 [7.11, 58.38]	7.71 [4.11, 18.78]	23.66 [8.43, 48.27]	33.08 [11.54, 91.82]	8.60	0.014
Reticular pattern	66.96 [26.34, 161.87]	37.64 [14.32, 63.06]	48.58 [23.29, 150.27]	118.01 [43.31, 222.08]	12.34	0.002
Honeycomb pattern	28.68 [2.75, 88.01]	4.86 [2.19, 29.13]	13.68 [1.79, 54.28]	78.51 [15.79, 184.39]	29.72	<0.001

Notes: Statistical quantifications were demonstrated with Median [IQR]; p-value: Kruskal–Wallis rank sum test.

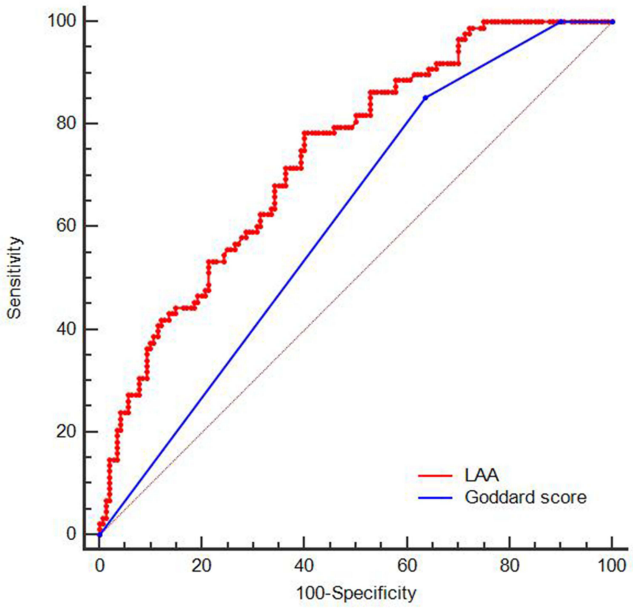

Figure 2 The predictive performance of LAA and Goddard score for type-M classification (0.616 vs 0.739, P=0.002).

The multivariate logistic regression analysis showed that the higher proportion of full emphysema ratio and wall-volume, a proportion of smaller lumen-volume, and a more noticeable interstitial lung alterations were associated with type-M (Figure 3).

Discussion

In this study, we analyzed the quantitative imaging phenotypes characteristics of COPD patients, who were categorized into three subtypes based on chest CT. The main image phenotypes is type-E (55.3%). Type-M was associated with more severe emphysema within the region larger than 15mm, larger areas of consolidation, ground-glass opacity, reticular patterns and smaller lumen-volume of small airways. Our quantitative CT evaluation shows great potential in evaluating and predicting different underlying pathobiological processes of emphysema, small airways disease, and small vessels

Table 2 Small Vessel Number in Different COPD subtypes

Variable	Overall, N = 228	Type-A=14 (6.1%)	Type-E=126 (55%)	Type-M= 88 (39%)	Statistics	p-value
6mm	1,078.00 [857.75, 1,434.25]	898.00 [762.25, 953.50]	955.50 [794.00, 1,246.75]	1,429.00 [1,119.50, 1,625.50]	57.01	<0.001
6mm$^{CSA<5mm2}$	940.76 (323.09)	699.57 (147.06)	870.08 (313.86)	1,080.33 (302.17)	31.05	<0.001
9mm	1,113.23 (317.32)	908.36 (87.34)	1,071.82 (305.28)	1,205.11 (331.52)	13.49	0.001
9mm$^{CSA<5mm2}$	817.00 [629.75, 953.25]	734.00 [623.25, 761.75]	815.00 [604.00, 939.50]	878.50 [664.00, 1,012.75]	10.89	0.004
12mm	909.00 [782.75, 986.25]	956.00 [901.50, 1,005.50]	893.50 [774.50, 976.75]	927.00 [782.50, 1,015.25]	3.59	0.17
12mm$^{CSA<5mm2}$	606.00 [491.75, 716.50]	628.50 [567.75, 676.75]	590.00 [452.75, 715.50]	630.50 [505.75, 733.50]	1.81	0.40
15mm	738.30 (144.87)	791.07 (82.16)	722.45 (122.27)	752.60 (176.78)	4.19	0.12
15mm$^{CSA<5mm2}$	440.00 [369.00, 549.25]	437.00 [410.25, 517.75]	436.50 [357.50, 533.00]	470.00 [372.25, 567.50]	1.48	0.48
18mm	587.00 [496.00, 657.25]	584.50 [562.75, 614.75]	587.00 [514.25, 650.50]	580.00 [477.75, 673.00]	0.26	0.88
18mm$^{CSA<5mm2}$	325.00 [243.25, 397.25]	300.50 [244.75, 360.25]	320.50 [238.00, 389.50]	351.00 [257.00, 417.25]	3.60	0.17
21mm	443.00 [359.75, 528.75]	432.50 [411.50, 507.25]	457.50 [367.25, 534.00]	426.00 [352.25, 522.75]	0.90	0.64
21mm$^{CSA<5mm2}$	237.50 [194.75, 270.25]	225.00 [196.00, 248.50]	240.50 [190.25, 271.75]	237.50 [202.50, 271.00]	1.05	0.59
24mm	197.00 [169.00, 237.25]	182.00 [154.75, 219.50]	189.00 [165.75, 222.75]	213.00 [175.75, 252.00]	4.86	0.088
24mm$^{CSA<5mm2}$	122.30 (35.23)	126.79 (43.67)	119.97 (33.44)	124.92 (36.46)	0.63	0.53

Abbreviations: Statistical quantifications were demonstrated with Median [IQR] or Mean (SD); p-value, Kruskal–Wallis rank sum test; One-way ANOVA; Variable was demonstrated the distance between the entire lung and the pleural membrane; CSA:cross-sectional area vessels.

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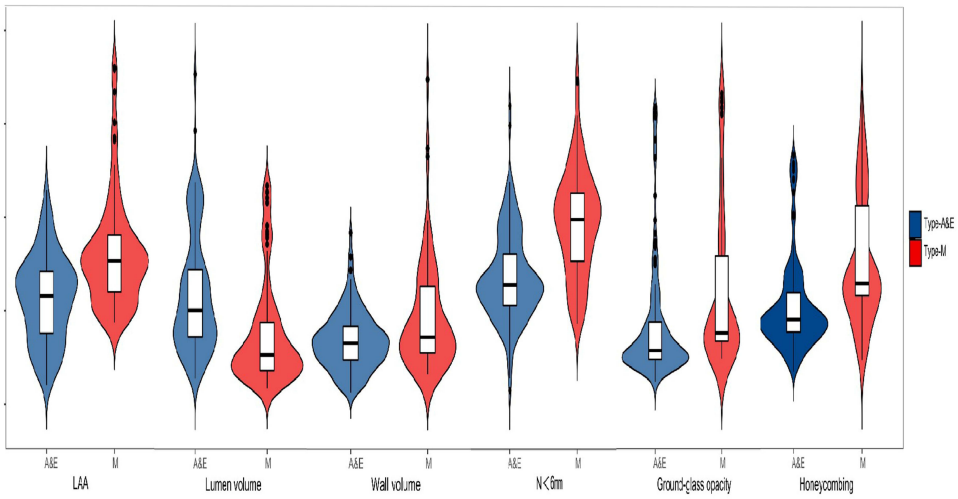

Figure 3 Multivariate logistic regression analysis of quantitative phenotypes parameters.
Abbreviations: LAA, low attenuation area; N < 6mm, the small vessel count in distance of 6 mm.

structural abnormality in COPD in a noninvasive perspective, which may hold significant clinical value in the severity assessment and lead to more personalized and effective treatment strategies.

COPD is a heterogeneous disease, manifesting substantial variations among patients in terms of etiology, pathological changes, symptoms, and CT findings. The effects of standardized treatment regimens vary significantly among different patients. Given the clear correlation between the imaging phenotypes of COPD and clinical staging, as well as therapeutic improvement, the imaging subtypes of COPD, as classified by the Fleischner Society, has been shown crucial role in understanding the disease's heterogeneity and underlying disease mechanisms, thereby providing insights into substantial differences in their rates of radiological, physiological, and symptom progression, as well as in mortality.[7] The result of this study showed significant higher score in full emphysema and full emphysema ratio based on low attenuation areas (LAAs) in the type-M, particularly observed in the LAAs within the region larger than 15mm, than in the other phenotypes, suggesting that earlier intensive therapeutic intervention for COPD, such as the addition of inhaled bronchodilators and pulmonary rehabilitation, should be applied to this phenotype than the other phenotypes. This observation aligns with findings from various studies that have utilized advanced imaging techniques to quantify emphysema in patients with COPD. For instance, one study demonstrated that artificial intelligence (AI)-based quantification of low attenuation volume percentage (LAV%) showed a significant correlation with visual emphysema grades, indicating that AI can enhance the assessment of emphysema severity in routine chest CT scans.[8] Moreover, Recent studies have highlighted the significance of accurately quantifying emphysematous changes in the lungs. A pilot study demonstrated the feasibility of computing lung volume and emphysema extent directly from 2-D scout images, which could revolutionize diagnostic approaches in COPD management.[9] The introduction of novel emphysema subtypes based on spatially informed lung texture learning has opened new avenues for understanding the disease's progression and its impact on lung function.[10] In addition, in the study of interstitial lung texture analysis, we found that the areas the mixed phenotype was associated with a higher proportion of consolidation, ground-glass opacity, and reticular patterns, which may contribute to acute exacerbations of COPD and co-existing respiratory infections not only impair patients' quality of life and increase mortality rates but also impose a significant economic burden on patients.

The earliest manifestation of COPD is often small airway disease dysfunction, which represents a significant lung abnormality characterized by airflow limitation without overt obstruction detectable by standard spirometry. Classical imaging classifications of COPD often indirectly reflect the severity of small airway disease in COPD by observing the thickening of proximal airways and the presence of emphysema. Research indicated that small airway dysfunction is prevalent even in mild forms of asthma, suggesting that it may serve as a precursor to more severe respiratory complications.[11] The identification of small airway disease can provide insights into the early stages of COPD, allowing

for timely intervention and management strategies.[12] In this study, we used airway inner luminal area as a parameter of bronchial wall thickness in the present study, which is relatively easy to apply in clinical practice. In the pulmonary small airway disease quantitative assessment, we found significantly smaller lumen volume and larger wall-volume in whole lung level in type-M, indicating a potential correlation between reduced lumen size and the severity of airway obstruction. This finding in associated with previous studies that have demonstrated the impact of emphysema and fSAD on intrapulmonary vascular volume (IPVV) in patients with COPD.[13] The relationship between airway dimensions and lung function parameters suggests that as the disease progresses, the structural changes in the airways may contribute to diminished pulmonary function.[13] Moreover, the assessment of lumen volume can provide valuable insights into the pathophysiology of COPD, particularly in understanding how emphysema and fSAD interact to affect overall lung health. Recent studies have highlighted the importance of small airways in the pathophysiology of COPD, indicating that changes in these regions can significantly contribute to the overall decline in lung function.[14,15]

Small vessel remodeling is also one of the major pathological manifestations of COPD. The mechanisms underlying small vessel remodeling in COPD are multifactorial, including chronic inflammation, oxidative stress, and the effects of cigarette smoke exposure. Research has shown that the remodeling of small vessels in the lungs contributes to the overall vascular changes observed in COPD, such as increased pulmonary vascular resistance and right ventricular hypertrophy.[16] Small airway narrowing is the primary cause of airflow limitation in COPD. However, due to their small size, most of these airways are not visible on conventional CT scans or are difficult to identify visually. In this quantitative study, we found the small vessel count of type-E significant decrease at distances of 6 mm and 9 mm from the pleura. This finding aligns with previous studies that have explored the morphological alterations in small pulmonary vessels in populations at high risk for COPD, indicating that the number of these vessels can vary significantly based on the severity of the disease.[17] In a study involving 1969 participants, it was demonstrated that individuals at high risk for COPD exhibited a lower count of small pulmonary vessels compared to those in the normal group, suggesting that vascular remodeling occurs as a consequence of the disease.[17] The assessment of small vessel characteristics could potentially serve as a biomarker for disease progression and help in tailoring therapeutic strategies for patients with COPD.[18]

Some limitations need to be considered in the interpretation of our study. First, this was a retrospective single-center study, and the sample size was small. Additional prospective studies should be performed with large study populations in order to confirm our results. Second, the relationship between imaging findings and definitions of COPD imaging phenotypes underscores the need for standardized imaging protocols to enhance the accuracy of phenotype identification and improve reproducibility. Third, the absence of clinical manifestations and treatment methods in this study leads to a disconnect between the research findings and their practical implications for patient care. To address this, relevant clinical data will be incorporated into future research, thereby enhancing the alignment of the findings with clinical practice.

In summary, a quantitative evaluation of CT imaging phenotypes is crucial for understanding the heterogeneity of COPD patients. Qualitative and quantitative assessment of lung density, airways, and small vessels using quantitative analysis technology are of great significance in guiding early diagnosis, severity assessment, and therapeutic evaluation of COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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