Pulmonary Vascular Volume is Associated With DLCO and Fibrotic Score in Idiopathic Pulmonary Fibrosis: An Observational Study

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Abstract

Background: Idiopathic pulmonary fibrosis (IPF) is primarily a disease of old age. However, it is difficult to diagnose and has a complex disease course. High-resolution computed tomography (HRCT) and lung function test are crucial for its diagnosis and follow-up. However, the correlation of HRCT findings to lung function test results was not extensively investigated.

Methods: This study retrospectively analysed the medical records and images of patients with IPF. Patients with evident emphysema and lung cancer were excluded. All included cases would be investigated through a multidiscipline discussion to confirm the diagnosis. The correlation of CT findings including fibrotic score, CT lung volume, pulmonary artery trunk (PA) diameter and pulmonary vascular volume (PVV) to the lung function test such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) was analysed.

Results: A total of 32 patients were included. The fibrotic score and PVV were significantly correlated with DLCO ($r = 0.59$, $p = 0.01$; $r = -0.43$, $p = 0.03$, respectively) but not with FVC. The PVV was significantly correlated with fibrotic score ($r = 0.59$, $p<0.01$) and PA diameter ($r = 0.47$, $p = 0.006$).

Conclusion: Our study shows the structural and functional correlation of IPF. The extent of lung fibrosis (fibrotic score) and PVV were associated with DLCO but not with FVC, especially for patients with IPF without significant FVC deficiency. The PA diameter, which reflects the pulmonary artery pressure, was associated with PVV.

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrosing interstitial pneumonia of unknown cause primarily affecting elderly people with a very poor prognosis with a median survival of 3–5 years at post-diagnosis.[1] The diagnosis of IPF is difficult and usually needs multidisciplinary discussion (MDD) with a pulmonologist, radiologist and pathologist to make a more appropriate diagnosis.1 The disease course is also complex and difficult to predict.[2]

The lung function test is crucial to detect, diagnose and monitor IPF. The forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) are regarded as the most valuable measurements of lung function tests in IPF.[3] The rate of FVC decline has been used as a marker for disease progression because of its association with mortality.[4] DLCO also measures another physiological deficiency (gas diffusion) of lung fibrosis. DLCO was reportedly associated with pulmonary hypertension, important comorbidity of IPF. The GAP index combining age, gender, FVC and DLCO could predict mortality. However, the abnormality of lung function tests on IPF may be heterogeneous. Therefore, FVC and DLCO may not be affected equally. Lung function test may be normal in some patients with clinical or pathological IPF.[3]

The chest high-resolution computed tomography (HRCT) is another key examination for IPF. The fibrotic patterns on HRCT are important clues to classify and diagnose IPF.[1] Recently, tools were developed to quantify the chest HRCT of IPF, which may include the extent of pulmonary fibrosis and volume of the pulmonary vasculature. Despite the technological advances, the association of HRCT findings with lung function tests in IPF is still not extensively investigated. However, there is still no consensus about the relationship between CT pulmonary vasculature, the extent of fibrosis and lung function. A limited number of studies did not have unanimous results.[5–8] Therefore, this study aimed to demonstrate the relationship among the extent of fibrosis, pulmonary vasculature and lung function of patients with IPF.

Methods

Patient selection

This retrospective study on human subjects was approved by the local ethics committee (The Institutional Review Board of MacKay Memorial Hospital, Taipei Branch, Taipei, Taiwan). From December 2019 to April 2021, 106 cases discussed at the MDD meeting were enrolled for further investigation. Patients with confirmed IPF diagnosis were included, whereas those who were (1) diagnosed with the non-IPF disease (including connective tissue disease-related interstitial lung disease [CTD-ILD], lymphangioleiomyomatosis [LAM], lymphocytic interstitial pneumonia [LIP], chronic hypersensitivity pneumonitis [CHP], sarcoidosis, infection/airway disease, etc.), (2) diagnosed with indeterminate UIP pattern, (3) with concurrent pulmonary malignancy (primary or secondary), (4) without pulmonary function test results within 3 months of the CT scan, (5) cannot be diagnosed with IPF at MDD and (6) with acute exacerbation status (according to clinical conditions and CT images) were excluded from the study. This study complies with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at Mackay Memorial Hospital, Taipei, Taiwan (no. 21MMHIS180e). Data were analyzed anonymously.

CT scans revealing emphysema more than mild emphysema (Fleischner Society classification system)[9, 10] were also excluded because the pulmonary vasculature would be affected by the emphysema.[11]

Clinical information

Patient characteristics (including age and gender) and pulmonary function tests (FVC, FVC%, DLCO and DLCO%) were recorded.

CT imaging protocols

All CT studies were performed with a 128-slice (Somatom Definition AS, Siemens Healthcare, Forchheim, Germany) or a 256-slice (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) multidetector computed tomography (MDCT) scanner. CT images for all patients were identical with the same imaging parameters of the collimation of 128 × 0.6 or 256 × 0.6 mm, tube voltage of 120 kVp, tube current modulation, the gantry rotation speed of 0.5 s/r and reconstructed slice thickness of 1.5 mm in

one whole breath-hold. The scan coverage was from the lung apex to the lowest hemidiaphragm. All images were acquired in a supine position and at full inspiration status.

Image analysis and lung functional quantification

All CT images were reviewed by two radiologists (W.H. and C.Y.) with 8 and 18 years of experience in chest CT, respectively, and blinded to lung function information. The fibrotic score was made at six levels: 1) aortic arch, 2) 1 cm below the carina, 3) right pulmonary venous confluence, 4) halfway between the third and fifth section, 5) 1 cm above the right hemidiaphragm and 6) 2 cm below right hemidiaphragm (Figure 2).[12] The proportion of the content with at least one of the following characteristics was scored to the nearest 5%: honeycombing, traction bronchiectasis, subpleural reticulation and ground-glass opacity with traction bronchiectasis in each section, and the fibrotic score was the average of the percentage in these six sections.[13] The short-axis diameter of the pulmonary artery (PA) trunk on axial sections of the mediastinal window at the PA bifurcation level was measured.[14]

The principles of quantification for the lung, emphysema and vessel volumes

We adopted commercial software (QUIBIM Precision 2.8, QUIBIM SL, Valencia, Spain) for lung segmentation, vessel extraction and emphysema extraction based on several steps of image thresholding and classification. The first transformation in the raw data domain is a preliminary segmentation of lung parenchyma using −450 HU as the threshold value. The lung classification step involves the use of distance and the watershed transforms to localise the plane that passes between both lungs for an accurate lung separation.

The vessel volume extraction is performed using the Frangi filter, which is based on the eigenvalue decomposition of the local Hessian matrix of CT to derive geometrical tubular structures of the lung vessels (Figure 3). Since lung vessels have a different radius in the chest, it is significantly important to accurately extract vessel structures in a multi-scale framework using mature algorithms of the Hessian matrix and the vessel measurements introduced by Frangi.[15] The pulmonary vessel volume (PVV) score was calculated based on the ratio of the vessel and total lung volume.

The methodology for lung emphysema quantification was segmented and extracted using a fixed threshold of −950 HU. With this methodology, all pixel intensity values below the fixed threshold were considered emphysema, whereas pixel values above the threshold were considered lung parenchyma. Relative volumes in the percentage were computed as the ratio between the total absolute volume occupied by the structure divided by the total lung volume.

Statistics analysis

The correlation of lung function and CT parameters was examined using Spearman's correlation. The lung function parameters, DLCO and FVC, were expressed as percentiles from normal predicted values. The inter-rater reliability of the fibrotic score was assessed using the intraclass correlation coefficient

(ICC). All tests were two-sided, and p-values of <0.05 were considered statistically significant. The statistics were performed with R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 106 patients were included in the MDD from December 2019 to April 2021. Among them, 55 with an alternative diagnosis from IPF were excluded. Among the remaining 51 patients, 3 were excluded because of no lung function test within 3 months of chest HRCT, 11 due to moderate to severe emphysema, 5 due to subtle lung fibrosis and IPF diagnosis could not be made confidently. Finally, 32 patients diagnosed with IPF in MDD were arranged for investigation (Figure 1).

Basic characteristics

The basic characteristics of our population are shown in Table 1. Men accounts for 68.9% of the population, with the mean age of 74.7 (+/− 7.8) years, mean FVC (%) of 84.5% (+/− 22.5%) and mean DLCO of 63.0% (+/− 24.2%). CT parameters including CT lung volume, pulmonary vessel volume score, fibrotic score and PA trunk diameter are also showed in Table 1, which were 2959.3 (+/− 1047.1) cm3, 7.83 (+/− 3.01)%, 23.7 (+/− 10.9)% and 3.04 (+/− 0.46) cm, respectively.

Table 1
Background characteristics

	Patients (n = 32)
Age	74.7 (7.8)
Gender (M)	22 (68.9%)
FVC (%)	84.5 (22.5)
FEV1(%)	88.8 (23.6)
DLCO (%)	63 (24.2)
TLC (%)	74 (16.4)
FS (%)	23.7 (10.9)
PVV score	7.83 (3.01)
CT-LV	2959.3 (1047.1)
PA	3.04 (0.46)
FS: fibrotic score, PVV: pulmonary vessel volume, CT-LV: CT measured lung volume, PA: Pulmonary artery trunk diameter	

Inter-rater reliability of the fibrotic score

Fibrotic scores of chest CT were used to evaluate inter-rater reliability. A total of 32 chest CTs were evaluated by two radiologists. The intraclass correlation coefficient (ICC) was 0.91 ($p<0.001$).

Correlation

The correlation among lung function and CT parameters was demonstrated in the correlation matrix (Table 2). The fibrotic score was correlated with PVV ($r = 0.59$, $p<0.001$) and DLCO ($r = -0.59$, $p = 0.001$). No significant correlation was observed between the fibrotic score to the lung volume parameters, including FVC ($r = -0.20$, $p = 0.3$) and CT lung volume ($r = 0.09$, $p = 0.62$) and PA trunk diameter ($r = 0.19$, $p = 0.24$). Besides the fibrotic score, the DLCO was also significantly correlated with PVV ($r = -0.43$, $p = 0.03$). In addition, DLCO and FVC did not show significant parallel trend ($r = 0.36$, $p = 0.06$). FVC and CT lung volume were concordant ($r = 0.51$, $p = 0.005$). The PA trunk diameter was significantly positively correlated with PVV ($r = 0.47$, $p = 0.006$), but not with FVC ($r = -0.11$, $p = 0.58$) and DLCO ($r = 0.22$, $p = 0.28$).

Table 2
Correlation matrix

	FVC (%)	FEV1 (%)	DLCO (%)	CT-LV	FS	PVV score	PA
FVC (%)	1						
FEV1 (%)	0.88 (<0.001)	1					
DLCO (%)	0.36 (0.06)	0.22 (0.28)	1				
CT-LV	0.51 (0.005)	0.30 (0.12)	0.32 (0.10)	1			
FS	-0.20 (0.30)	-0.06 (0.76)	-0.59 (0.001)	-0.09 (0.62)	1		
PVV score	-0.30 (0.11)	-0.16 (0.40)	-0.43 (0.03)	-0.66 (<0.001)	0.59 (<0.001)	1	
PA	-0.11 (0.58)	0.002 (0.99)	-0.29 (0.14)	-0.25 (0.17)	0.19 (0.24)	0.47 (0.006)	1

Data were expressed as r (p-value).

FS: fibrotic score, PVV: pulmonary vessel volume, CT-LV: CT measured lung volume, PA: Pulmonary artery trunk diameter

Discussion

This study was conducted to evaluate the CT characteristics to measure the pulmonary vessel volume. Our current findings can be twofold. The fibrotic score of MDCT was significantly correlated with DLCO and PVV scores, but not with FVC. DLCO was significantly correlated with the PVV score but did not reveal the parallel trend with FVC.

In previous studies, the extent of fibrosis in MDCT was correlated with DLCO and FVC.[12, 16] This discrepancy with our results could be explained in two aspects. First, the study population of previous studies and that of our study did not greatly differ in FVC. It may lead to an insignificant association between FVC and the extent of lung fibrosis. On the contrary, the DLCO was remarkably reduced in our study. It has been observed that the lung volume and DLCO would not always change parallelly in IPF.[17, 18] A proportion of patients IPF had preserved FVC but remarkable DLCO deficiency. Meanwhile, DLCO

could decline earlier and more seriously than FVC in patients with IPF.[18] Traditionally, FVC decline was used as the primary end-point in previous clinical trials,[19–21] and recent studies showed that FVC alone cannot sufficiently define the severity of IPF and DLCO could provide another important aspect of physiology IPF deficiency, which could be associated with early diagnosis of fibrosis.[22] Second, the fibrotic score measures the extent of pulmonary fibrosis but does not distinguish different fibrotic patterns. In Fraser et al. and Wells et al.'s studies, the extent of fibrosis more significantly correlated with DLCO than FVC.[12, 23] These findings could reflect the fact that the influence of fibrosis on lung function is complex in IPF. The extent of fibrosis may have different impacts on FVC based on disease severity. However, it also affected the DLCO more profoundly.

Jacob et al. reported that PVV was significantly correlated with fibrotic score and DLCO using both CALIPER software and visual fibrotic score,[16] which is concordant with our results. However, in our study, patients with moderate and severe emphysema were excluded. Furthermore, the diagnosis of all patients included in this study was confirmed by MDD to further decrease the heterogeneity of our population.

The cause of the correlation between PVV and the fibrotic score remains unclear. Jacob et al. suggested that the high intrathoracic pressure generated by non-compliant fibrotic lung dilates the pulmonary vasculature, which would cause the high PVV in the fibrotic lung. Contrary to Jacob et al.'s studies, neither PVV nor fibrotic score was correlated to FVC in our study. FVC negatively reflects lung compliance in IPF.[24] Despite the irrelevance to FVC, the correlation of PVV to fibrotic score remains robust in our study. Another possible explanation may be the change of pulmonary vasculature concurrent with the extent of fibrosis.

The PA trunk diameter was believed to indirectly reflect the pulmonary arterial pressure (PAP).[25] In our study, we found that the PA trunk diameter was significantly correlated with PVV ($r = -0.47$, $p = 0.006$) but not with the fibrotic score ($r = 0.19$, $p = 0.24$). These findings were concordant to that of the previous studies. Jacob et al.'s study also showed the correlation of PVV with the right ventricular systolic pressure measured by echocardiography.[16] Fisher et al.'s study using the right heart catheter to measure PAP also showed that the extent of fibrosis was not associated with PAP in interstitial lung disease.[26] Although the pulmonary vasculature changes in IPF are still not fully illustrated, a recent study indicated that the pathogenetic process of pulmonary fibrosis may also be involved in vasculature changes.[27] Another study by Jacob et al. also reported that higher PVV was related to increased fibrosis and higher mortality.[8] The PVV may be an important radiological marker for interstitial pneumonitis and needs further studies to verify its significance on IPF.

In our study, FVC is significantly correlated to CT lung volume. Since the IPF is primarily the disease of elderly people. The lung function test may be too laborious to some elderly, especially for those with cognitive deficiciency.[28, 29] For patients with IPF who have difficulty performing lung function tests, the measurement of CT lung volume may be a possible surrogate to evaluate the lung mechanics. As the

FVC decline was used as the physiological marker for disease progression and prognosis prediction, reduced CT lung volume may serve as the quantitative image marker for the same purpose.

This study has some limitations. First, the population size is small. Most included patients did not have reduced FVC, although patients with evident emphysema and had MDD for every patient were excluded to enhance the diagnostic homogeneity. Considering the disease heterogeneity of IPF, our study may only represent a specific proportion of the IPF population (especially for those with preserved FVC), and the result may not be applied to all patients with IPF. Second, the fibrotic score measurement is a semi-quantitative method using the average percentage of fibrosis in six levels on chest CT to represent the whole lung fibrotic condition. Despite its high reproducibility among well-trained readers (both in our study and previous studies), there is a limitation in using a few CT slices to represent the whole lung fibrotic condition. Third, regarding the pulmonary vascular volume, there is still potential to capture the misclassified reticular pattern in the PVV in patients with extensive fibrosis. Fourth, this study did not obtain information on cardiac echography or right heart catheterisation. Therefore, an association of PA pressure, PA trunk diameter and pulmonary vascularity could not be further illustrated. Finally, because the lung function parameter is expressed by the percentile of expected value already considering the age, gender, body height and body weight, a multivariable analysis of the basic characteristics was not performed. Furthermore, CT parameters including fibrotic score, PVV, PA diameter and CT lung volume were correlated to each other. Considering the problems of collinearity, we could not perform the multivariable analysis of CT parameters.

Conclusion

Our study demonstrates the extent of fibrosis and the association of PVV with DLCO but not with FVC, especially for those IPF without significant FVC deficiency. The pulmonary trunk diameter reflects that the PAP was associated with PVV. This provides evidence of the structural (image findings of HRCT) and functional linkage (lung function test) in IPF.

Abbreviations

idiopathic pulmonary fibrosis (IPF); high-resolution computed tomography (HRCT); pulmonary artery trunk (PA); pulmonary vascular volume (PVV); forced vital capacity (FVC); diffusing capacity for carbon monoxide (DLCO); multidisciplinary discussion (MDD); connective tissue disease-related interstitial lung disease (CTD-ILD); lymphangioleiomyomatosis (LAM); lymphocytic interstitial pneumonia (LIP); chronic hypersensitivity pneumonitis (CHP); multidetector computed tomography (MDCT); intraclass correlation coefficient (ICC); pulmonary arterial pressure (PAP).

Declarations

Appendix

Acknowledgements

Not applicable.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study complies with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board at Mackay Memorial Hospital, Taipei, Taiwan (no. 21MMHIS180e). Data were analyzed anonymously.

Consent for publication

The images in this study were obtained from de-identified data and the informed consent was waived during institutional board review.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

WJW conceptualized this study, analyzed the data regarding the lung function and CT parameters and wrote the manuscript.

WMH analyzed the data regarding the CT parameters, obtained the fibrotic score and wrote the manuscript.

CHL provided the technique consultation of the quantification of CT

CHY validated the fibrotic score, revised the manuscript and supervised this study.

All authors read and approved the final manuscript.

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Figures

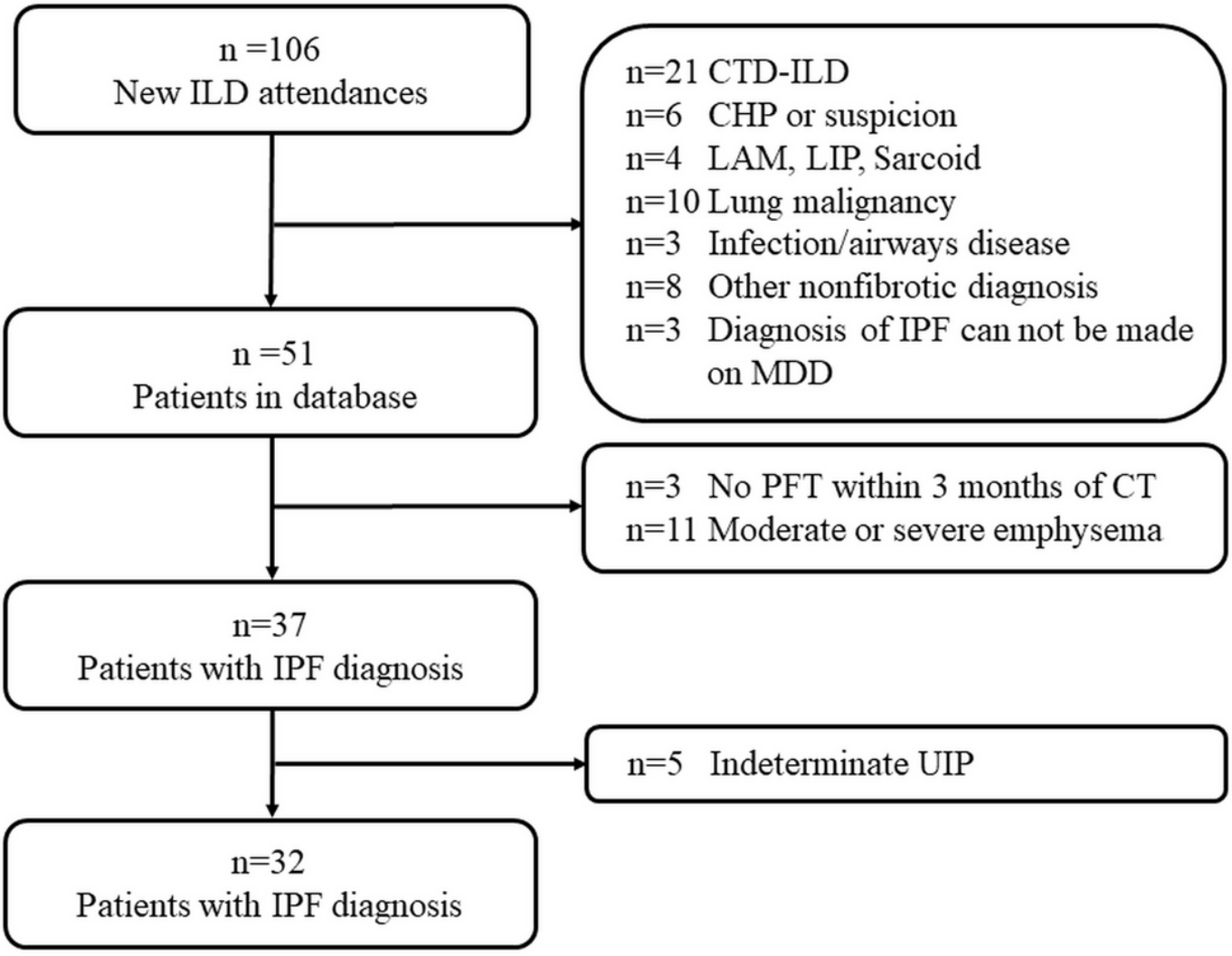

Figure 1

Flow of case selection of the retrospective study.

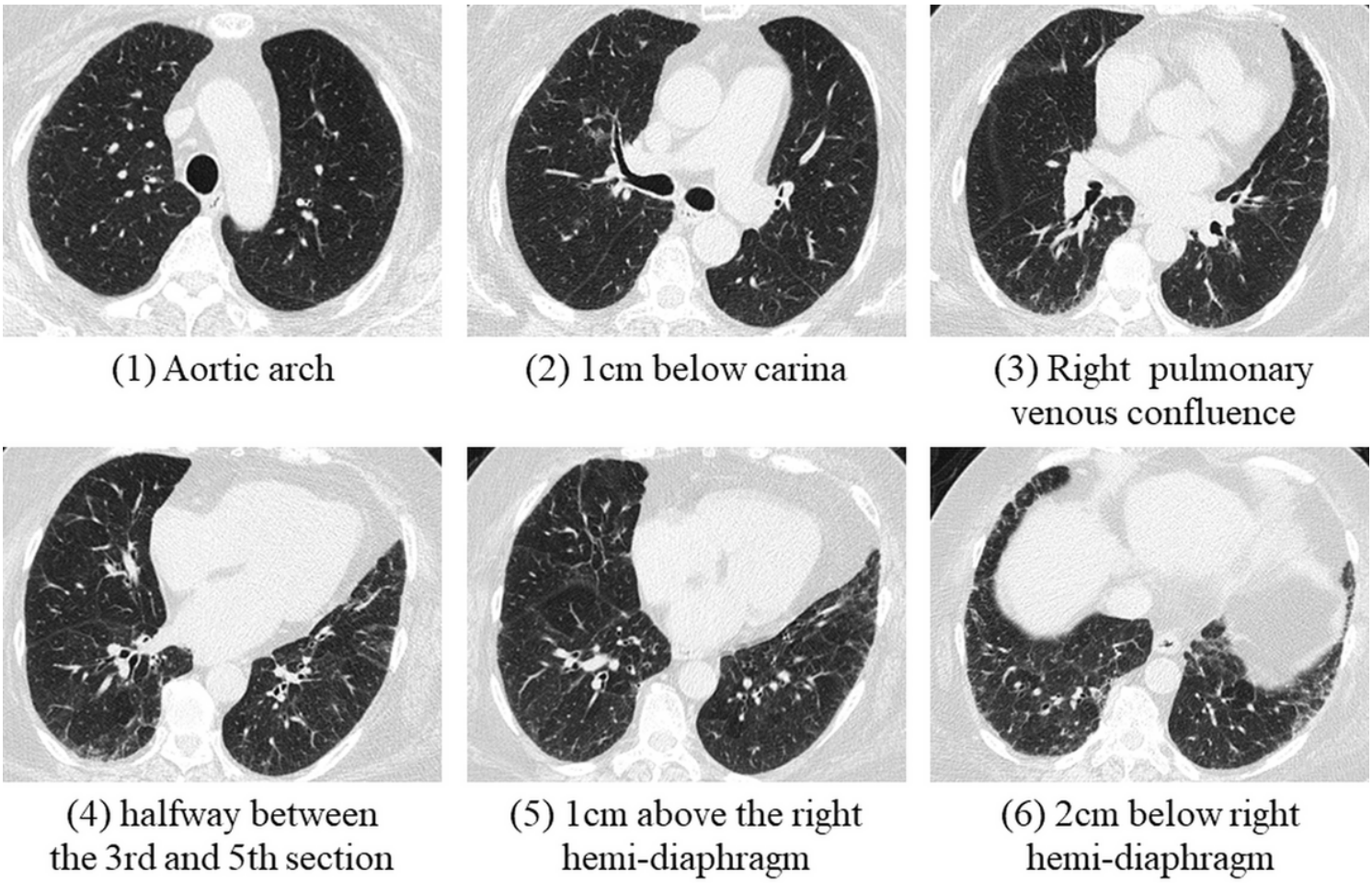

Figure 2

A 69-year-old woman was diagnosed with IPF with a probable UIP pattern by the MDD meeting. The percentage of fibrosis was calculated in these six levels, and the fibrotic score was the average percentage of these six sections.

Figure 3

The 3D reconstructed and quantitative assessment of the pulmonary vessels and lung volumes of a 59-year-old man diagnosed with IPF (pulmonary vessel volume, 203.21 ml; lung volume, 4834.92 ml; and PVV score, 0.04).