

Original paper

Threshold-based quantitative CT lung volumes and clinical outcomes in idiopathic pulmonary fibrosis

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Abstract

Purpose: The primary objective of our study was to evaluate the correlation between threshold-based quantitative lung volumetric measurements obtained from thoracic computed tomography (CT) scans and clinical data in patients with idiopathic pulmonary fibrosis (IPF), and to demonstrate their impact on prognosis and mortality.

Material and methods: Patients who underwent non-contrast thoracic CT at Ankara Bilkent City Hospital between January 2019 and December 2024 and exhibited a usual interstitial pneumonia pattern in the lung parenchyma were retrospectively screened. IPF patients meeting the inclusion criteria were enrolled, along with an equal number of age- and sex-matched control subjects without any chronic lung disease. Quantitative measurements of normally aerated lung volumes and fibrotic lung volumes were performed using the Thoracic VCAR (GE Healthcare) software, an artificial intelligence-based analysis package installed on a dedicated workstation. To ensure technical precision, all automated segmentations were manually reviewed by two experienced radiologists (intraclass correlation coefficient ≥ 0.90). All CT measurements were compared between the patient and control groups.

Results: Quantitative lung volume measurements of the patient group – including normally attenuated lung volume (NALV [l, %]), low-attenuation lung volume (LALV [%]), high-attenuation lung volume (HALV [l, %]), and total lung volume – were significantly lower than those of the control group ($p < 0.05$). The mean total lung volume in the gender-age-physiology (GAP) index, GAP stage 1 group was higher than that in the GAP stage 2 and 3 groups. Significant differences were observed in NALV (l, %), HALV (l, %), and total lung volume measurements between patients who desaturated and those who did not during the 6-minute walk test ($p < 0.05$). Significant positive correlations were found between total lung volume and forced vital capacity (l), forced expiratory volume in 1 second (l), vital capacity (l), and total lung capacity (l) ($p < 0.05$). Univariate Cox regression analysis revealed that NALV (%) was significantly associated with all-cause mortality, independent of other factors.

Conclusions: NALV (%) obtained through quantitative CT analysis may be a useful prognostic biomarker for predicting two-year mortality in IPF patients. This objective, effort-independent imaging biomarker may provide a valuable alternative for prognostic assessment, particularly in patients who exhibit limited ability to perform functional tests.

Key words: idiopathic pulmonary fibrosis, computed tomography, quantitative volume analysis, prognosis.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disease of unknown etiology and represents the most common form of idiopathic interstitial pneumonia [1]. Characterized by the progressive dyspnea and a steady decline in pulmonary function, IPF is

a disease with a poor prognosis; the average survival time for these patients is approximately 2.5 to 3.5 years [2]. In patients with IPF, pulmonary function tests (PFTs) typically reveal a restrictive pattern, with frequent reductions in lung volumes, forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and diffusing capacity of the lungs for carbon monoxide (DLCO) [3].

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While these functional tests are the clinical cornerstone, their effort-dependent nature can lead to inconsistent results, particularly in advanced cases. IPF is characterized both histologically and radiologically by the usual interstitial pneumonia (UIP) pattern [4]. This pattern is characterized by fibrosis demonstrating spatial and temporal heterogeneity, predominantly affecting the lower lobes and peripheral regions [4]. Thoracic computed tomography (CT) scans typically reveal irregular reticulation, traction bronchiectasis, volume loss, and honeycombing with a subpleural and lower lobe predominance [4].

The primary objective of this study is to evaluate the prognostic significance of quantitatively measured lung volumes on CT and their association with mortality in patients with IPF, by correlating these measurements with PFTs, DLCO, the 6-minute walk test (6MWT), and clinical classifications.

Material and methods

Study design and ethical approval

This study was conducted retrospectively and in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the local Clinical Research Ethics Committee of the tertiary care hospital (decision date: May 14, 2025; number: TABED 2-25-1170).

Patient selection and study population

Patients who underwent non-contrast thoracic CT and demonstrated a UIP pattern in the lung parenchyma were retrospectively screened. Among the 200 patients identified as having a UIP pattern, the following exclusion criteria were applied: known connective tissue disease ($n = 48$), history of occupational or environmental exposure ($n = 10$), known history of malignancy ($n = 13$), concomitant chronic obstructive pulmonary disease (COPD; $n = 11$), and CT images with significant artifacts ($n = 12$). These exclusions resulted in a final study population of 106 patients. The control group consisted of 106 age- and sex-matched subjects who had undergone non-contrast thoracic CT for other reasons, with no known history of chronic lung disease or malignancy.

Data collection

Clinical and demographic data were obtained from the institutional clinical portal system and the Pulmonology clinic of the tertiary referral hospital. Data regarding age, sex, height, weight, body mass index (BMI), PFTs, 6MWT results, GAP index scores and stages, follow-up duration (in months), and survival status were recorded for all participants.

CT acquisition protocol

All scans were performed in the supine position at full inspiration without intravenous contrast medium injection. Thoracic CT images were acquired using 128-slice multidetector scanners (Revolution EVO, General Electric Medical Systems, Milwaukee, Wisconsin, USA).

Quantitative CT analysis

Thoracic CT images were evaluated for quantitative analysis using the mediastinal window on an Advantage Workstation 4.7 (Revolution, General Electric Healthcare, USA) equipped with Thoracic VCAR software for lung volume measurement. The Thoracic VCAR (GE Healthcare) software, an artificial intelligence (AI)-based analysis package, performed automated segmentation of the lungs. It calculated lung volumes and their percentages relative to total lung volume for hyper-aerated, non-aerated, and poorly aerated parenchymal areas based on attenuation values.

The software included interstitial structures and segmental bronchi and vessels for both lungs while excluding the main pulmonary arteries and bronchi, mediastinal structures, and associated pleural effusions. To ensure maximum technical precision and reproducibility, all automated segmentations were manually reviewed by two experienced radiologists to exclude potential artifacts and major airway misclassifications (interobserver agreement, intraclass correlation coefficient [ICC] ≥ 0.90).

Threshold categorization

Consistent with established literature, lung volumes were categorized according to predefined Hounsfield unit (HU) thresholds:

- low-attenuation lung volume (LALV) (< -950 HU), representing emphysematous or hyperaerated lung regions;
- normally attenuated lung volume (NALV) (-950 to -705 HU), representing relatively normal lung parenchyma;
- high-attenuation lung volume (HALV) (> -705 HU), representing areas of ground-glass opacity, fibrosis, and consolidation [5].

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 26. The relationship between sarcopenia (determined based on the erector spinae and pectoral muscles) and survival status/two-year mortality was evaluated using the chi-square test. For significant χ^2 results, Bonferroni correction was applied for post hoc pairwise comparisons to identify the specific groups between which the differences originated.

Due to the small sample sizes in the three GAP stage categories, measurements were compared using the Kruskal-Wallis analysis method. For results that were statistically significant, pairwise comparisons were conducted using the Mann-Whitney *U* test. The relationship between continuous measurements in the patient group was assessed using Pearson's correlation coefficient.

Survival analyses were performed using the Kaplan-Meier method, and differences in survival between groups were assessed using the log-rank test. Univariate and multivariate analyses for two-year survival were conducted using the Cox regression model. A *p*-value of < 0.05 was considered statistically significant for all comparisons.

Results

Inter-observer reliability

To assess the reliability of the quantitative measurements, 25 patients were randomly selected from the IPF group, and their lung volumes were independently measured by two radiologists with five years of experience. The inter-observer ICC was ≥ 0.90 , indicating excellent inter-observer reliability.

Demographic and clinical characteristics

The demographic characteristics and CT measurements of the IPF patient group and the control group were compared using independent-samples *t*-tests (Table 1). While no significant differences were found between the groups regarding age and height ($p > 0.05$), the control group exhibited significantly higher mean weight and BMI values than the IPF group ($p < 0.05$).

Quantitative CT lung volume comparisons

CT measurements for both groups were compared using independent-samples *t*-tests (Table 2). Significant differences were observed across nearly all volumetric parameters. Patients in the IPF group demonstrated significantly lower NALV (l), NALV (%), and total lung volume than those in the control group ($p < 0.001$). Conversely, mean values for LALV (%), HALV (l), and HALV (%) were significantly higher in the IPF group compared to healthy controls (Figure 1 and 2).

Comparison of CT measurements by GAP stage

Due to the small sample sizes ($n < 20$) in advanced stages, non-parametric methods were utilized for subgroup analysis based on GAP staging. GAP stages 2 and 3 were combined for comparison against GAP stage 1 (Table 3). Mean total lung volume measurements in the

Table 1. Comparison of demographic characteristics between the idiopathic pulmonary fibrosis patient group and the control group

Variable	Patient group (<i>n</i> = 106)	Control group (<i>n</i> = 106)	<i>p</i> -value
Sex (<i>n</i> , %)			
Male	79 (74.5)	79 (74.5)	1*
Female	27 (25.5)	27 (25.5)	
Age (years)	58.9 $\pm$ 10.31	59.07 $\pm$ 6.29	0.885**
Height (cm)	167.39 $\pm$ 9.48	169.54 $\pm$ 8.14	0.078**
Weight (kg)	75.5 $\pm$ 14.33	80.37 $\pm$ 11.72	0.007**
BMI (kg/m ²)	26.87 $\pm$ 4.09	28.04 $\pm$ 4.3	0.044**

* χ^2 test. **Independent-samples *t*-test.

Data are presented as *n* (%) or mean $\pm$ SD, as appropriate.

BMI – body mass index

Table 2. Comparison of quantitative lung volume measurements between the idiopathic pulmonary fibrosis group and the control group

Variable	Patient group (<i>n</i> = 106)	Control group (<i>n</i> = 106)	<i>p</i> -value
NALV (l)	2.06 $\pm$ 1.32 (0.27-5.54)	3.99 $\pm$ 1.44 (1.33-7.74)	< 0.001
NALV (%)	56.93 $\pm$ 18.26 (17.52-87.2)	84.75 $\pm$ 8.11 (51.3-93.05)	< 0.001
LALV (l)	0.04 $\pm$ 0.07 (0-0.33)	0.03 $\pm$ 0.06 (0-0.47)	0.24
LALV (%)	1.14 $\pm$ 1.55 (0.01-6.51)	0.59 $\pm$ 0.94 (0-7.35)	0.002
HALV (l)	1.2 $\pm$ 0.34 (0.6-2.07)	0.6 $\pm$ 0.21 (0.35-1.3)	< 0.001
HALV (%)	41.9 $\pm$ 18.33 (12.69-82.05)	14.66 $\pm$ 8.32 (6.22-48.7)	< 0.001
Total lung volume (l)	3.3 $\pm$ 1.3 (1.09-7.7)	4.62 $\pm$ 1.4 (2.28-8.4)	< 0.001

Data are presented as mean $\pm$ standard deviation (minimum–maximum).

HALV – high-attenuation lung volume, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, *p* – independent-samples *t*-test significance value

GAP stage 1 group were significantly higher than in the combined GAP stage 2 and 3 group ($p < 0.001$). No significant difference in total lung volume was observed between patients in GAP stages 2 and 3.

6MWT correlations

Significant differences in NALV (l), NALV (%), HALV (l), HALV (%), and total lung volume measurements were observed between patients who desaturated and those who did not during the 6MWT ($p < 0.05$). Patients who did not experience desaturation had significantly higher mean NALV (l), NALV (%), and total lung volume than those who desaturated. In contrast, mean HALV (l) and

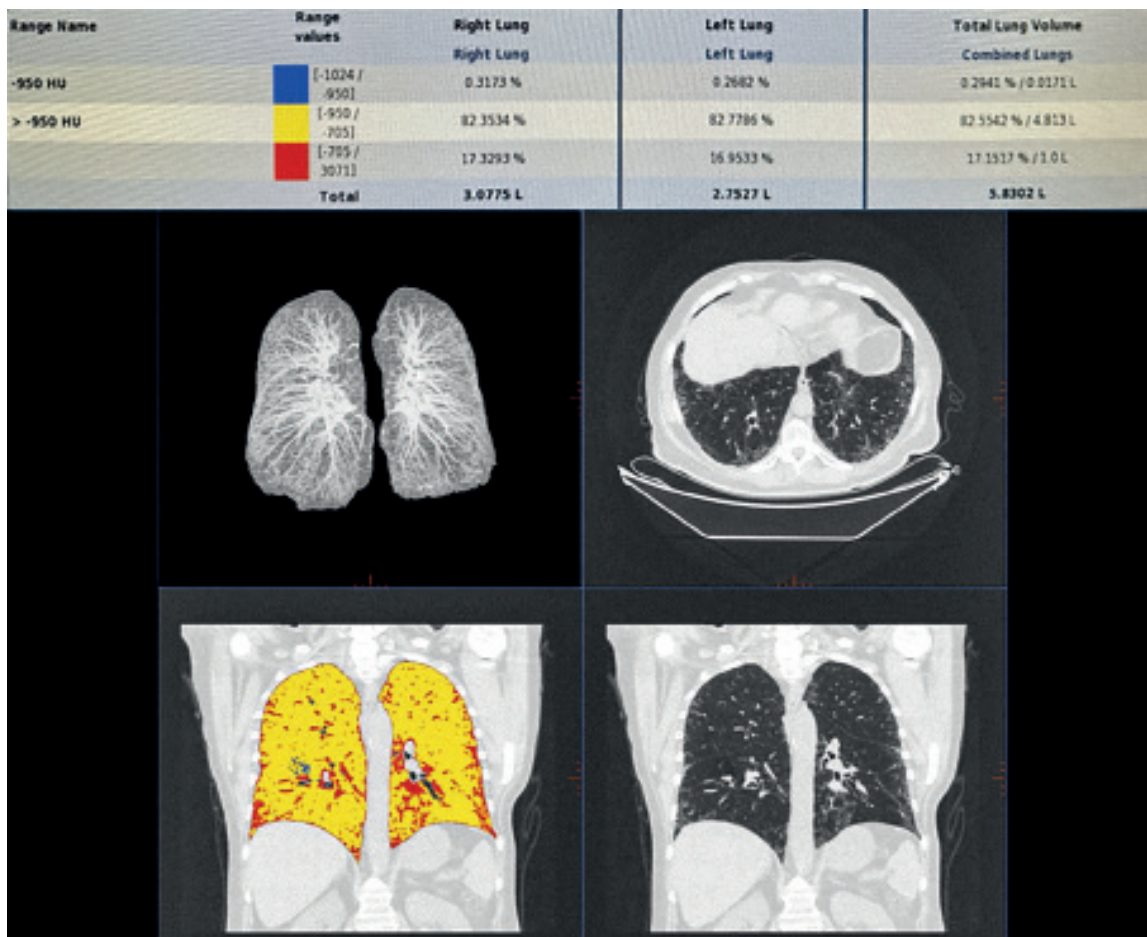


Figure 1. Automated lung segmentation and quantitative lung volume measurement performed using Thoracic VCAR (GE Healthcare) software

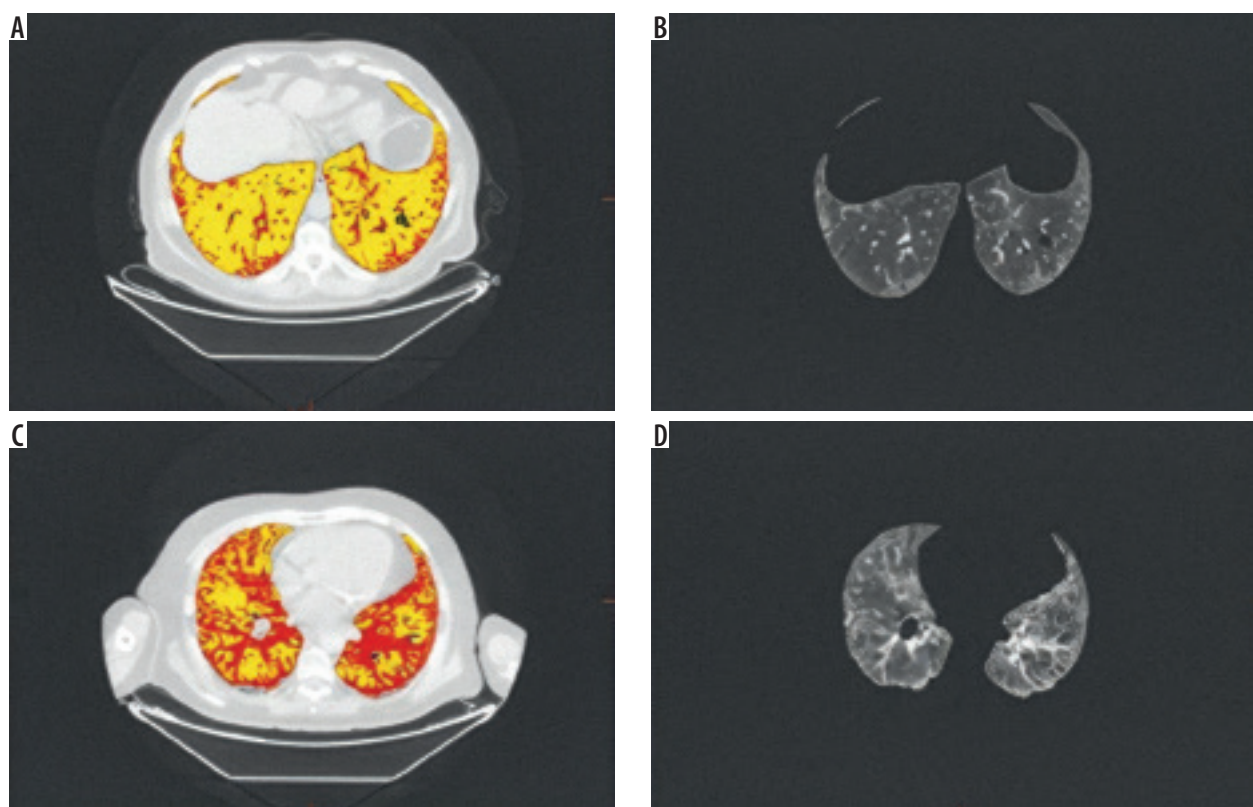


Figure 2. Quantitative lung volume analysis on the thoracic computed tomography (CT) scans of a 61-year-old male patient diagnosed with idiopathic pulmonary fibrosis. In the initial analysis, the normally attenuated lung volume (NALV) (highlighted in yellow) was measured as 4.813 liters (l, %) (left image). In the follow-up CT, the NALV (highlighted in yellow) was measured as 1.680 liters (l, %), demonstrating a significant longitudinal decline

Table 3. Comparison of computed tomography measurements according to the gender-age-physiology (GAP) staging

Variable	GAP stage 1 (n = 41)	GAP stage 2 (n = 38)	GAP stage 3 (n = 6)	p-value	Difference
NALV (l)	2.81 ± 1.47 (0.29-5.54)	1.52 ± 0.83 (0.27-4.05)	1.06 ± 0.78 (0.5-2.57)	< 0.001	1 > 2, 3
NALV (%)	65.9 ± 16.68 (20.84-87.2)	49.44 ± 16.13 (17.52-78.33)	40.24 ± 15.87 (21.17-65.06)	< 0.001	1 > 2 > 3
LALV (l)	0.06 ± 0.09 (0-0.33)	0.03 ± 0.04 (0-0.18)	0.04 ± 0.06 (0.01-0.17)	0.697	-
LALV (%)	1.21 ± 1.6 (0.01-5.78)	0.96 ± 1.23 (0.02-5.15)	1.47 ± 2.47 (0.35-6.51)	0.762	-
HALV (l)	1.14 ± 0.36 (0.62-2.07)	1.32 ± 0.29 (0.79-1.98)	1.35 ± 0.31 (1.04-1.9)	0.017	2, 3 > 1
HALV (%)	32.82 ± 16.79 (12.69-79.15)	49.6 ± 16.24 (20.3-82.05)	58.29 ± 15.84 (34.58-78.13)	< 0.001	3 > 2 > 1
Total lung volume (l)	4.01 ± 1.52 (1.38-7.7)	2.87 ± 0.84 (1.09-5.42)	2.45 ± 0.8 (1.71-3.94)	< 0.001	1 > 2, 3

Data are presented as mean ± standard deviation (minimum–maximum).

Difference – results of Mann-Whitney *U* pairwise comparison identifying the groups between which significant differences occurred.

HALV – high-attenuation lung volume, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, *p* – *p*-value from the Kruskal-Wallis test

Table 4. Comparison of quantitative computed tomography measurements based on desaturation status during the 6-minute walk test

Variable	Non-desaturating (n = 23)	Desaturating (n = 13)	p-value
NALV (l)	3.11 ± 1.43 (0.53-5.22)	1.87 ± 1.03 (0.29-4.34)	0.012
NALV (%)	72.17 ± 13.41 (35.4-87.2)	54.82 ± 16.69 (20.84-80.14)	0.003
LALV (l)	0.05 ± 0.08 (0-0.33)	0.04 ± 0.06 (0-0.19)	0.882
LALV (%)	0.87 ± 1.26 (0.01-5.17)	0.98 ± 1.27 (0.01-3.8)	0.705
HALV (l)	0.97 ± 0.28 (0.69-2.07)	1.27 ± 0.3 (0.89-1.97)	0.001
HALV (%)	26.96 ± 13.81 (12.69-64.59)	44.2 ± 17.06 (16.36-79.15)	0.004
Total lung volume (l)	4.13 ± 1.46 (1.48-6.69)	3.17 ± 0.99 (1.38-5.41)	0.040

Data are presented as mean ± standard deviation (minimum–maximum).

HALV – high-attenuation lung volume, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, *p* – *p*-value from the Mann-Whitney *U* test

HALV (%) measurements were significantly higher in the desaturating group (Table 4).

Furthermore, since the patient groups were asymmetric regarding walking distance, measurements were compared using the Mann-Whitney *U* test. Patients walking ≥ 250 meters had significantly higher mean NALV (l) and NALV (%) measurements than those walking < 250 meters. Conversely, patients with a walking distance < 250 meters exhibited higher HALV (l) and HALV (%) measurements than those walking ≥ 250 meters (*p* < 0.05). These findings are detailed in Table 5.

Correlation between quantitative CT lung volumes and PFTs

The relationship between quantitative CT (QCT) lung volume measurements and PFT results was evaluated in IPF patients. Strong, statistically significant positive correlations were found between total lung volume and FVC (l) (*r* = 0.878, *p* < 0.05), FEV₁ (l) (*r* = 0.849, *p* < 0.05), vital capacity (VC) (l) (*r* = 0.849, *p* < 0.05), and total lung capacity (TLC) (l) (*r* = 0.778, *p* < 0.05). In contrast, total lung volume was negatively correlated with the FEV₁/FVC ratio. Detailed correlation coefficients are presented in Table 6.

Table 5. Comparison of quantitative computed tomography measurements based on walking distance during the 6-minute walk test

Variable	Below 250 meters (n = 9)	250 meters and above (n = 27)	p-value
NALV (l)	1.76 ± 0.73	2.96 ± 1.47	0.021
NALV (%)	53.48 ± 15.14	70.03 ± 15.33	0.006
LALV (l)	0.03 ± 0.03	0.04 ± 0.08	0.295
LALV (%)	1.12 ± 1.13	0.84 ± 1.29	0.126
HALV (l)	1.40 ± 0.43	0.96 ± 0.16	0.006
HALV (%)	45.39 ± 15.21	29.12 ± 15.83	0.006
Total lung volume (l)	3.21 ± 0.61	3.97 ± 1.51	0.204

Data are presented as mean ± standard deviation.

HALV – high-attenuation lung volume, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, *p* – *p*-value from the Mann-Whitney *U* test

Predictors of two-year mortality

Univariate and multivariate Cox regression analyses were performed to identify clinical findings, PFT results, and QCT measurements associated with two-year mortality in IPF patients. In univariate analysis, lower BMI, higher GAP scores, lower NALV (l) and NALV (%), higher LALV (%),

Table 6. Correlation matrix between quantitative computed tomography lung volume measurements and pulmonary function test results in idiopathic pulmonary fibrosis patients

Measurements		NALV (l)	NALV (%)	LALV (l)	LALV (%)	HALV (l)	HALV (%)	Total lung volume
FVC (l)	<i>r</i>	0.852**	0.664**	0.519**	0.309**	-0.022	-0.683**	0.878**
FVC (%)	<i>r</i>	0.687**	0.663**	0.324**	0.125	-0.368**	-0.667**	0.614**
FEV ₁ (l)	<i>r</i>	0.816**	0.632**	0.493**	0.300**	0.005	-0.651**	0.849**
FEV ₁ (%)	<i>r</i>	0.664**	0.641**	0.320**	0.128	-0.358**	-0.646**	0.592**
FEV ₁ /FVC (%)	<i>r</i>	-0.383**	-0.371**	-0.17	-0.06	0.184	0.371**	-0.346**
FEF25-75 (l/s)	<i>r</i>	0.244*	0.161	0.272**	0.287**	0.139	-0.185	0.295**
DLCO (%)	<i>r</i>	0.567**	0.621**	0.048	-0.098	-0.466**	-0.611**	0.457**
TLC (l)	<i>r</i>	0.761**	0.610**	0.473**	0.317**	-0.048	-0.630**	0.778**
TLC (%)	<i>r</i>	0.665**	0.610**	0.348**	0.203	-0.252*	-0.622**	0.624**
VC (l)	<i>r</i>	0.827**	0.590**	0.562**	0.356**	0.03	-0.611**	0.849**
VC (%)	<i>r</i>	0.588**	0.544**	0.346*	0.17	-0.363**	-0.550**	0.498**

* $p < 0.05$, ** $p < 0.01$, r – Pearson correlation coefficient

DLCO – diffusing capacity for carbon monoxide, FEF25-75 – forced expiratory flow at 25-75% of FVC, FEV₁ – forced expiratory volume in 1 second, FVC – forced vital capacity, HALV – high-attenuation lung volume, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, TLC – total lung capacity, VC – vital capacity

Table 7. Univariate Cox regression analysis of factors associated with two-year mortality in idiopathic pulmonary fibrosis patients

Variables	HR	95% CI	<i>p</i> -value
Sex	0.587	0.227-1.517	0.272
Age	0.980	0.949-1.013	0.231
BMI	0.906	0.836-0.983	0.017
GAP score	2.148	1.554-2.971	< 0.001
NALV (l)	0.355	0.266-0.557	< 0.001
NALV (%)	0.948	0.930-0.967	< 0.001
LALV (l)	6.261	0.051-772.258	0.454
LALV (%)	1.226	1.020-1.474	0.026
HALV (l)	3.516	1.383-8.936	0.008
HALV (%)	1.052	1.031-1.072	< 0.001
Total lung volume (l)	0.437	0.296-0.645	< 0.001
FVC (l)	0.317	0.177-0.570	< 0.001
FVC (%)	0.952	0.932-0.971	< 0.001
FEV ₁ (l)	0.278	0.135-0.573	0.001
FEV ₁ (%)	0.957	0.939-0.976	< 0.001
FEV ₁ /FVC	1.036	0.980-1.094	0.212
TLC (l)	0.663	0.495-0.890	0.006
TLC (%)	0.969	0.952-0.986	< 0.001
VC (l)	0.288	0.099-0.839	0.022
VC (%)	0.946	0.916-0.976	0.001
DLCO (corrected)	0.869	0.799-0.946	0.001
DLCO (%)	0.960	0.940-0.981	< 0.001
6MWT walking distance	0.986	0.976-0.997	0.011

6MWT – 6-minute walk test, BMI – body mass index, CI – confidence interval, DLCO – diffusing capacity for carbon monoxide, FEV₁ – forced expiratory volume in 1 second, FVC – forced vital capacity, GAP – gender-age-physiology, HALV – high-attenuation lung volume, HR – hazard ratio, LALV – low-attenuation lung volume, NALV – normally attenuated lung volume, TLC – total lung capacity, VC – vital capacity

higher HALV (l) and HALV (%), lower total lung volume, lower FVC (l and %), lower FEV₁ (l and %), lower TLC (l and %), lower VC (l and %), lower DLCO (corrected and %), and shorter walking distance in the 6MWT were significantly associated with all-cause mortality in IPF patients. These results are summarized in Table 7.

Multivariate Cox regression models were developed to assess the independent associations of parameters that were significantly associated with two-year mortality in the univariate analysis. Due to the limited number of patients with available data, DLCO and 6MWT parameters were excluded from these multivariate models. Multivariate Cox regression Model 1 was developed to assess the association between NALV (%) and all-cause two-year mortality. Variables potentially affecting mortality, including sex, age, BMI, and FVC (%), were included in Model 1 along with NALV (%). After adjusting for age, sex, BMI, and FVC (%), NALV (%) remained significantly associated with all-cause mortality, independent of other factors (hazard ratio: 0.966; 95% confidence interval: 0.935-0.999; $p = 0.041$). The findings of the multivariate analysis are presented in Table 8.

Table 8. Multivariate Cox regression analysis for predicting two-year mortality (Model 1)

Variables	HR	95% CI	<i>p</i> -value
Sex	0.397	0.128-1.226	0.108
Age	0.996	0.949-1.046	0.886
BMI	0.968	0.857-1.095	0.609
NALV (%)	0.966	0.935-0.999	0.041
FVC (%)	0.970	0.937-1.004	0.084

Model 1 was adjusted for age, sex, BMI, and FVC (%).

BMI – body mass index, CI – confidence interval, FVC – forced vital capacity, HR – hazard ratio, NALV – normally attenuated lung volume

Discussion

The role of quantitative thoracic CT analysis in the clinical evaluation and management of diffuse lung diseases is expanding rapidly. In these conditions, lung parenchymal characteristics can be classified using threshold-based, histogram-based, morphological, and texture analysis methods. QCT has been successfully applied across a spectrum of obstructive, infiltrative, and restrictive lung diseases, including emphysema, cystic fibrosis, asthma, IPF, hypersensitivity pneumonitis, and connective tissue disease-associated interstitial lung disease [6]. In our study, we utilized an AI-based software analysis package (Thoracic VCAR, GE Healthcare) to evaluate IPF patients via threshold-based volumetric measurements. While this method is well established for estimating the extent and severity of diseases characterized by decreased lung density, such as emphysema, its application in IPF remains less established but promising [7].

To date, various computer-aided CT analysis methods have been reported for the quantitative assessment of disease extent and progression in IPF [8]. Threshold-based techniques that distinguish fibrotic tissue from relatively normal lung parenchyma have shown significant correlations with PFTs in patients with diffuse interstitial lung disease. In these studies, a threshold value of -700 HU has been used to differentiate relatively normal or aerated lung parenchyma from interstitial abnormalities [9].

In our study, 85 patients with accessible clinical data were staged according to the GAP (Gender, Age, Physiology) staging system as GAP stage 1, stage 2, and stage 3. Comparison across these groups revealed that patients in GAP stage 1, which is associated with a lower risk of mortality, had significantly higher mean values for NALV (l), NALV (%), and total lung volume than those in GAP stages 2 and 3. Conversely, patients in GAP stage 3, which is associated with higher mortality, had significantly higher mean values for HALV (l) and HALV (%) than those in the other stages. These findings suggest an association between more advanced clinical stage and less favorable lung volumetric parameters.

Correlation analyses between QCT-derived lung volumes and PFT results revealed statistically significant relationships across multiple parameters. NALV (l) showed strong positive correlations with FVC (l), FEV₁ (l), VC (l), and TLC (l), while showing moderate positive correlations with FVC (%), FEV₁ (%), DLCO (ml/min/mmHg), DLCO (%), TLC (%), and VC (%). Similarly, total lung volume measurements demonstrated strong positive correlations with FVC (l), FEV₁ (l), VC (l), and TLC (l). NALV (%) also showed significant moderate positive correlations with FVC (l, %), FEV₁ (l, %), TLC (l, %), VC (l, %), and DLCO (total and %). These findings support an association between QCT-derived lung volumes and pulmonary function and suggest that CT-based volumetric analysis may provide complementary information to conventional physiological assessment in IPF.

Regarding the 6MWT, an important functional and prognostic measure in IPF, our comparison based on walking distance and desaturation status revealed significant findings. Patients with a walking distance of less than 250 meters and those who experienced desaturation during the test exhibited statistically lower mean values for NALV (l) and NALV (%) compared to non-desaturating patients who walked 250 meters or more. Similarly, total lung volume was significantly lower in patients who experienced desaturation than in those who did not. Furthermore, patients with a walking distance below 250 meters and those who desaturated had significantly higher mean HALV (l) and HALV (%) values compared to other patients. These findings, which have not been extensively investigated in previous studies, suggest that poorer 6MWT performance is associated with less favorable quantitative lung volume parameters. While our relatively small sample size remains a limitation, larger studies are warranted to confirm these associations and determine their prognostic significance.

To identify clinical findings, PFT parameters, and QCT measurements associated with two-year mortality in IPF patients, we performed univariate Cox regression analyses. These analyses demonstrated that lower BMI, higher GAP scores, lower NALV (l) and NALV (%), higher LALV (%), higher HALV (l) and HALV (%), lower total lung volume, and lower pulmonary function parameters (FVC [l, %], FEV₁ [l, %], TLC [l, %], VC [l, %], corrected DLCO, and DLCO [%]), as well as shorter 6MWT walking distance, were significantly associated with all-cause mortality. To compare the relative contributions of these parameters to two-year mortality, multivariate Cox regression models were developed. The results showed that NALV (%) remained significantly associated with mortality after adjustment for other clinical and physiological factors.

Our results are consistent with the study by Ohkubo *et al.* [10] on 27 IPF patients, where they utilized threshold-based volumetric CT analysis (using a normal lung attenuation range of -950 HU and -701 HU) to evaluate the relationship between normal lung volume (NL), whole lung volume (WL), and the NL/WL ratio (NL%) and pulmonary physiology parameters. Their correlation analyses identified strong associations between WL and TLC, and between NL and FVC. Additionally, NL% showed a moderate positive correlation with DLCO measurements. Similarly, our study found strong positive correlations between NALV (l, %) and FVC/FEV₁ results, as well as between total lung volume and TLC (l). We also identified moderate positive correlations between NALV (l, %) measurements and DLCO results. These findings suggest that quantitative NALV measurements may provide complementary information on pulmonary function and could potentially be useful when pulmonary function testing is not feasible. Furthermore, Ohkubo *et al.* [10] found that NL% was associated with differentiation between GAP stages 1 and 2-3. In our study, we categorized 85 IPF

patients by GAP stage and compared their quantitative lung volumes. NALV (%) was significantly higher in GAP stage 1 than in stages 2 and 3, and was significantly higher in stage 2 than in stage 3. Based on these results, quantitative threshold-based lung volume measurements may provide complementary prognostic information to the GAP index in patients with IPF.

In another study involving 175 patients, Ohkubo *et al.* [5] investigated the prognostic value of threshold-based NL (%) for mortality in IPF patients. In their study, patients were categorized into three stages based on NL% measurements: stage I (> 71%), stage II (63-71%), and stage III (< 63%). Survival analysis revealed mean survival times of 58.2 months for stage I, 41.9 months for stage II, and 29.9 months for stage III. The findings showed patients with lower NL% had shorter survival times and higher mortality. Furthermore, their univariate analyses established FVC (%), DLCO (%), GAP score and stage, and NL% as significant prognostic factors. Multivariate Cox regression models further confirmed that NL% was independently associated with mortality after adjustment for other variables. In line with these findings, our univariate analyses of factors associated with two-year survival in IPF patients demonstrated that lower NALV (l) and NALV (%), higher LALV (%), higher HALV (l) and HALV (%), and lower total lung volume were significantly associated with all-cause mortality.

In a study published in 2024, Zhang *et al.* [11] examined the relationship between pulmonary function tests and quantitative thoracic CT measurements in 52 IPF patients. They reported that the percentage of normal lung areas was significantly lower in the IPF group compared to healthy controls, while the percentages of ground-glass opacity, fibrotic areas, and abnormal lesion areas were significantly higher in IPF patients. Our study yielded similar results when comparing the IPF and control groups. Zhang *et al.* [11] also investigated the correlations between QCT indices and pulmonary function parameters, finding the highest correlation coefficients between the percentage of fibrosis and TLC%, FEV₁%, and FVC% ($r = -0.571, -0.520, -0.521$, respectively; $p < 0.001$). Similarly, we performed correlation analyses between volumetric CT measurements and PFT results in our IPF cohort, identifying significant negative correlations between HALV (%) and FVC (%), FEV₁ (%), and TLC (%) ($r = -0.667, -0.646, -0.622$, respectively; $p < 0.05$).

Distinct from previous threshold-based volumetric studies in IPF patients, we compared the lung volume measurements of 35 patients who underwent the 6MWT, an important functional and prognostic assessment in IPF. Our comparison between patients who desaturated and those who did not revealed that desaturating patients had significantly lower mean NALV (l), NALV (%), and total lung volume. Furthermore, we found that patients with a walking distance below 250 meters had significantly lower mean NALV (l) and NALV (%) values than those

walking 250 meters or more. These findings suggest that quantitative NALV measurements (l and %) obtained by thoracic CT are associated with functional impairment during the 6MWT and may provide useful prognostic information in patients with IPF.

Kitaguchi *et al.* [12] utilized a density-mask technique via a QCT analysis software to measure LALV (%) and HALV (%) in 40 IPF and 40 COPD patients. They compared these results with visual scores obtained by radiologists and pulmonary function tests. The sum of HALV (%) and LALV (%) was defined as the diseased lung volume percentage (DLV %). In IPF patients, HALV (%) showed a strong negative correlation with FVC (%), while DLV (%) correlated negatively with DLCO (%); these results are consistent with our findings. Their findings suggested that increasing DLV% values were associated with greater disease severity and poorer prognosis in both COPD and IPF. In our study, we identified strong correlations between quantitative lung volume measurements (NALV [%], HALV [%], and total lung volume) obtained using AI-based software and functional tests such as PFT and the 6MWT. These findings further support the potential value of QCT analysis for assessing disease severity and providing prognostic information in patients with IPF.

It is important to note that PFT and DLCO tests require a high degree of patient cooperation and effort. In contrast, thoracic CT scans require relatively little patient cooperation. Therefore, QCT analysis may be significantly more beneficial when a patient is in poor physical condition or has difficulty cooperating during respiratory maneuvers. Our findings demonstrate that QCT analysis not only allows for the precise quantification of specific lesion percentages in the lungs but also effectively evaluates functional lung impairment. Given that the most widely used prognostic parameters in IPF – FVC (%) and DLCO (%) – show strong correlations with our quantitatively measured lung volumes, we believe that CT quantification may provide useful complementary information for prognostic assessment in IPF.

Limitations

This study has certain limitations. First, it was conducted as a single-center, retrospective study. Second, pulmonary function data were available for only 95 of the 106 included IPF patients, while 6MWT results were available for only 36 patients, limiting the sample size for analyses involving these functional measures. Therefore, future studies involving larger patient cohorts with serial CT scans and longitudinal functional tests are warranted. Despite these limitations, the high reproducibility of the quantitative thoracic CT measurements and the relatively limited number of studies investigating the prognostic and survival implications of threshold-based quantitative lung volumes in IPF represent important strengths of our study.

Conclusions

Our study demonstrates that quantitative NALV (%) and HALV (%), obtained using AI-based threshold analysis on routine thoracic CT scans, are significantly associated with clinical and prognostic parameters in IPF patients. Most notably, NALV (%) remained significantly associated with all-cause two-year mortality after adjustment for other clinical and physiological factors. Furthermore, quantitative lung volume measurements showed significant correlations with established functional and prognostic parameters in IPF, including PFTs, DLCO, 6MWT performance, and the GAP index and staging system.

While PFT and DLCO tests require substantial patient cooperation, NALV (%) obtained through QCT analysis may provide useful objective and complementary information for prognostic assessment, particu-

larly in patients who exhibit difficulty performing functional tests. Larger prospective studies are warranted to validate the prognostic value of QCT lung volumes and to determine their potential role alongside established functional and clinical assessments in IPF.

Disclosures

1. Institutional review board statement: This study was conducted retrospectively and in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the local Clinical Research Ethics Committee of the respective tertiary care hospital (decision date: May 14, 2025; number: TABED 2-25-1170).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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