European Review for Medical and Pharmacological Sciences 2021; 25: 3254-3263

Quantitative and visual analysis of idiopathic pulmonary fibrosis with different methods: the relationship between clinical correlation and mortality risk model

F. KAYA[1], E. ÖZGÜL[1], A. BALCI[2]

[1]Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Radiology, Afyonkarahisar, Turkey
[2]Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Chest Diseases, Afyonkarahisar, Turkey

Abstract. – OBJECTIVE: To test the correlation between the visual semi-quantitative score (VSQS) and different quantitative computed tomography (QCT) analyses and pulmonary physiology variables, and to determine the performance of these types of analyses on the Gender, Age, and Physiology (GAP) model for the prediction of mortality risk of idiopathic pulmonary fibrosis (IPF).

PATIENTS AND METHODS: High-resolution computed tomography (HRCT) images of IPF patients were reviewed and the VSQS was calculated. Evaluations were made of the QCT score of interstitial lung disease (ILD) using four different previously defined methods. Respiratory function tests (RFT) and the 6-minute walk test (6MWT) were applied to all the patients. The GAP model was used to evaluate the mortality risk. The performance of the VSQS score and QCT methods on the GAP model to predict the mortality risk of the disease was calculated with ROC analysis.

RESULTS: The study included 40 patients who met the criteria. A statistically significant correlation was determined between all the quantitative and semi-quantitative measurement results ($p<0.001$). A significant correlation was determined between the VSQS and QCT parameters and the RFT and 6MWT. In the ROC analysis, method 4 of the QCT parameters (a value of the voxels between -700 and -950 HU) and the VSQS showed the best performance in the differentiation of stage I, stage II, and stage III, according to the GAP model.

CONCLUSIONS: The selection of a quantitative method was useful in the evaluation of spread in patients with IPF. According to the GAP model, VSQS performed best in predicting mortality risk. Furthermore, method 4 of the QCT parameters, which shows well-aerated lungs, were deemed to have good potential for the estimation of mortality risk.

Key Words:
High resolution computed tomography, Idiopathic pulmonary fibrosis, Prognosis and mortality, Quantitative evaluation.

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most commonly seen chronic idiopathic interstitial lung disease in adults. The typical radiological finding of IPF is known as the usual interstitial pneumonia (UIP) pattern and is characterized by a honeycomb lung appearance[1,2]. Several visual scoring systems and computer-supported computed tomography (CT) analysis have been reported for IPF for the evaluation of both the spread and the progression of the disease. Skewness, kurtosis, and average lung weakening calculated from fine-slice CT histograms have been reported to be related to the parenchymal pathological changes of the disease[3]. Previous studies[4,5] have shown the clinical benefits of quantitative analysis in the diagnosis and monitoring of the progression of IPF. In addition, methods differentiating fibrotic lungs from normal lungs, based on CT density value thresholds, have a reported association with pulmonary function tests in diffuse interstitial lung disease[6]. Clinical factors, respiratory function tests (RFT), high-resolution CT (HRCT) findings or scores, and molecular biomarkers have been used as variables in IPF mortality estimation models in previous studies[7-11]. In addition, age, gender, and pulmonary function test results have been used in the Gender, Age, and Physiology (GAP) model (index and stage) described by Ley et al[12].

Corresponding Author: Furkan Kaya, MD; e-mail: furkaya157@hotmail.com

The aim of the present study was to test the correlations between pulmonary physiology variables and the VSQS and different quantitative computed tomography (QCT) analyses in patients diagnosed with IPF and to determine the efficacy of these types of analyses in estimating the mortality risk of the disease with the GAP model.

Patients and Methods

Patient Selection

The study included patients in our hospital who underwent HRCT examination and were diagnosed with IPF according to the 2018 IPF/ATS/ERS/JRS/ALAT guidelines between January 2017 and October 2020[13]. A retrospective scan identified 71 patients diagnosed with IPF in the specified period. A total of 31 patients were excluded. Thus, the study included 40 patients who met the criteria (Figure 1).

Computed Tomography Imaging

The HRCT examinations were performed with the patient positioned supine, with maximum inspiration and no administration of intravenous contrast material. The scans were obtained with a multi-detector (160 Slice) CT system (Aquilion Prime, Toshiba Medical Systems, Nasu, Japan) from the apex to the base of the lung in full inspiration with the following scanning parameters: 120 kV, 300 mAs, slice thickness 1 mm, 0.5 s rotation time.

Respiratory Function test, 6-Minute Walk Test, and GAP Model

Measurements included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC), and single breath diffusion capacity (DLCO). RFTs were obtained using widely accepted techniques, and the results were expressed as percentage of estimated performance[14]. The 6-minute walk test (6MWT) values were also recorded[15].

GAP index scores were determined according to the system described by Ley et al[12] (Table I). The GAP index was determined as 0-8 points. The GAP stage was determined based on the total GAP index score: stage I (0-3 points), stage II (4-5 points), and stage III (6–8 points). The patients were evaluated in two groups according to the GAP model as low mortality risk (GAP stage I) and high mortality risk (GAP stage II and III).

Visual Semi-Quantitative CT Analysis

All the HRCT images were obtained in the lung window settings of window center between -500 and -600 Hounsfield units (HU) and window width of 1600 HU and were evaluated in consensus by two observers blinded to the clinical findings and RFT results. The HRCT examination was made separately by two radiologists (Observer 1, Observer 2) using the semi-quantitative visual scoring method described by Warrick et al[16]. Each abnormality was scored as follows: frosted glass appearance=1, irregular pleural borders=2, septal/subpleural lines=3, honeycomb appearance=4, and subpleural cysts=5. A total score was obtained by counting and summing the number of bronchopulmonary segments containing each abnormality: involvement (1-3 segments + 1 point, 4-9 segments +2 points, >9 segments +3 points) to give a total score ranging from

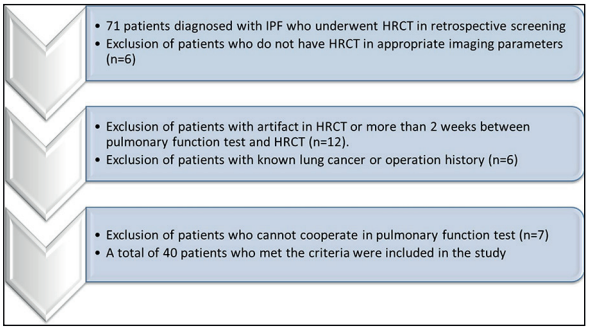

Figure 1. Flow diagram of the patient selection protocol.

Table I. GAP (gender, age, and physiology) index.

	Predictor	Points
Gender	Female	0
	Male	1
Age years	< 61	0
	61-65	1
	> 65	2
Physiology		
FVC % predicted	> 75	0
	50-75	1
	< 50	2
DLCO % predicted	> 55	0
	36-55	1
	≤ 35	2
	Cannot perform	3

FVC, forced vital capacity; DLco, diffusing capacity of the lung for carbon monoxide.

0-30. In cases where the observers could not reach agreement, the case was re-evaluated, discussed in a second session, and a consensual decision was made.

Quantitative CT Analysis

The HRCT images were evaluated by a single trained radiologist. The HRCT images were viewed with OsiriX software (Pixmeo, Switzerland, https://www.osirix-viewer.com), which is an open access DICOM viewer, and threshold values of -200 HU to -1024 HU were used to calculate total lung volume (TLV) with the threshold of -950 HU to exclude areas of emphysema[6]. The observer made small corrections if incorrect segmentation areas, such as lobular or segmental bronchi, were evident. Four different methods were used for QCT analysis.

Method-1: İnterstitial lung disease (ILD) volume was calculated in the voxel range of -200 to -700 HU using OsiriX software[17,18]. The ILD volume was calculated as the percentage of TLV (Figure 2).

Method-2: The ILD volume was calculated in the voxel range of -260 to -600 HU using OsiriX software[19]. The ILD volume was calculated as the percentage of TLV.

Method-3: To isolate the lungs, all voxels between -200 and -1024 HU were selected. The mean lung density of the lung parenchyma was calculated (MLA-3). Skewness (SKEW-3) and kurtosis (KURT-3) values were also calculated[20].

Method-4: The well-aerated lung (WAL) volume was calculated in the voxel range of -700 to -950 HU using OsiriX software. The WAL volume was calculated as a percentage of TLV[21,22].

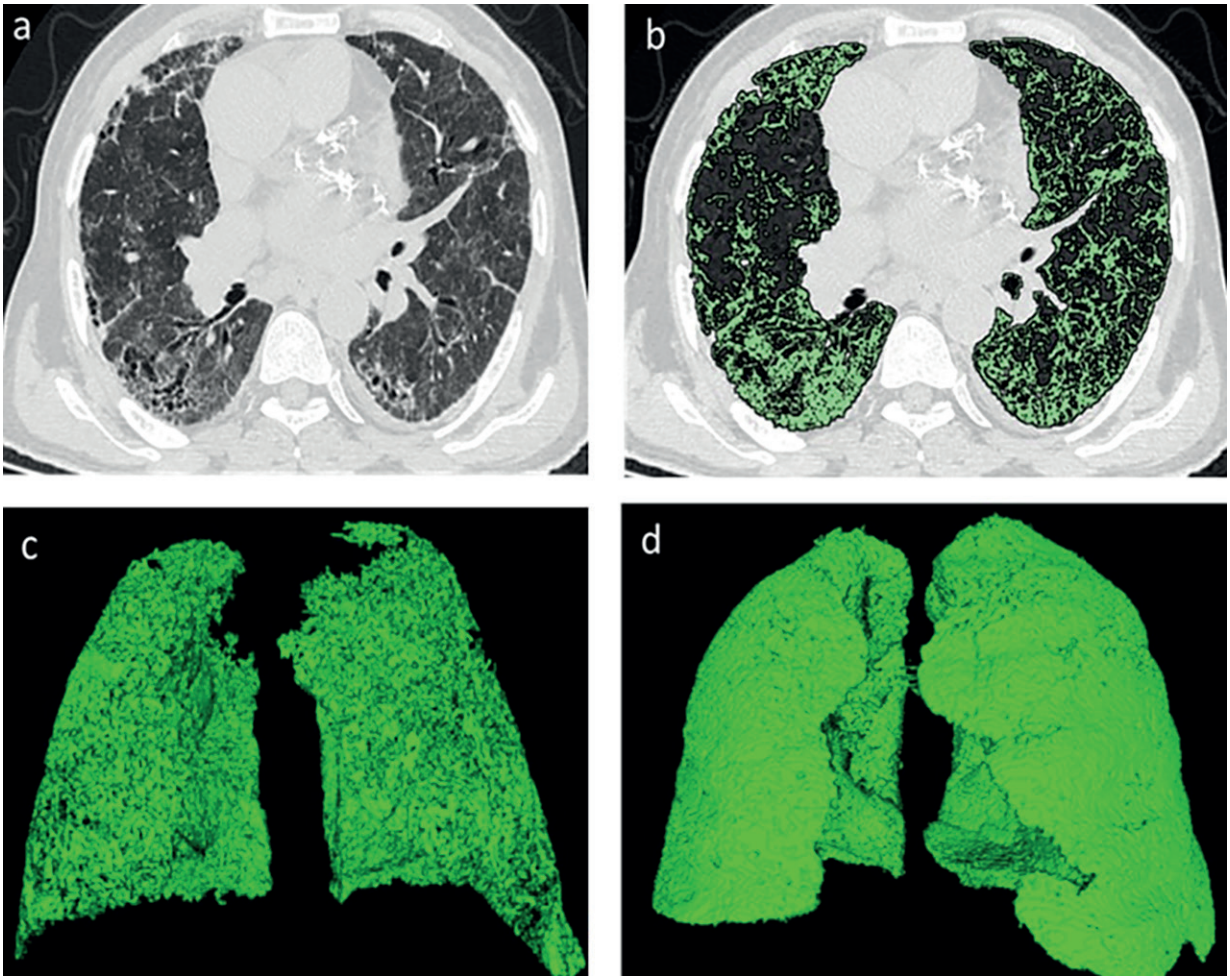

Figure 2. A, A 65-year-old male patient diagnosed with IPF; bilateral interstitial thickening, subpleural honeycomb, traction bronchiectasis, and ground glass areas are observed. **B,** Quantitative lung assessment images taken from the same HRCT section using Method-1. **C,** All voxels between −200 and 700 HU show the volume of ILD and were 2072 cm^3. **D,** All voxels between −200 and −1024 HU show total lung volume and were 3480 cm^3.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±Standard Deviation (SD) values and categorical variables as number (n) and percentage (%). The independent samples Student's *t*-test was applied in the analysis of differences between paired independent groups of continuous variables, and the Chi-square test was used for categorical variables. Differences between the VSQ and QCT scores and the laboratory test results were analyzed with the Pearson Correlation test. A Spearman r value was considered to indicate fair (0-0.30), moderate (0.31-0.50), good (0.51-0.70), and excellent (0.71-1.00) correlation. The Kruskal-Wallis test was applied for evaluation of the differences in the VSQS and QCT values between the GAP stage groups. The mortality risk in the GAP model was evaluated according to the different performances of the VSQS and QCT points by applying Receiver Operating Characteristic (ROC) curve analysis. A value of $p<0.05$ was accepted as statistically significant.

Results

Evaluation was made of 40 patients, comprising 33 males and 7 females. Males were significantly taller than females ($p=0.001$). No statistically significant difference was determined between the genders in terms of weight, BMI, FVC%, FEV1, DLCO, and 6MWT. The mean GAP index was 3.85±1.42 points (range, 1-6). In total, 15 (37.5%) patients were at GAP stage I, 19 (47.5%) at GAP stage II, and 6 (15%) at GAP stage III. A statistically significant difference was determined between the GAP stage groups with respect to the VSQS and QCT parameters ($p<0.05$). The patient characteristics and RFT results are shown in Table II.

Correlations Between VSQS, RFT, and 6MWT Results

The mean VSQS of the whole study group was 18.08±3.81 (range, 9-25). The VSQS, evaluated separately by two observers, was moderately negatively correlated with the FVC% (r= -0.455, $p=0.003$) and FEV 1% (r= -0.396, $p=0.011$). The VSQS also showed a strong negative correlation with TLC (r= -0.643, $p<0.001$), DLCO% (r=-0.667, $p<0.001$), and the 6MWT (r= -0.641, $p<0.001$) (Table III).

Correlations Between the QCT Results and RFT and 6MWT Values

A significant correlation was observed between all the QCT methods ($p<0.001$) (Table IV). The mean disease extent values in the quantitative methods are shown in Table V. The QCT methods showing the best correlations were between FVC% and SKEW-3 (r= -0.495, $p=0.001$), between DLCO% and Method-4 (r= 0.750, $p<0.001$), between TLC and SKEW-3 (r= 0.795, $p<0.001$), and between 6MWT and Method-4 (r= 0.744, $p<0.001$) (Table III).

Table II. Baseline characteristics of the patients with İPF.

	Total population mean ± SD (range) (N = 40)	Female mean ± SD (N = 7)	Male mean ± SD (N = 33)	*p*-value
Age (years)	65 ± 14 (25-90)	65.43 ± 14.55	66.47 ± 12.52	0.848
Height (cm)	167 ± 11 (145-190)	153.86 ± 7.49	169.88 ± 9.07	0.001
Weight (kilograms)	76 ± 14 (50-120)	78 ± 23.28	76.06 ± 11.77	0.747
Body mass index (kg/m^2)	27.64 ± 6.08 (16.62-46.88)	32.77 ± 8.43	26.61 ± 5.03	0.014
FVC (% of predicted)	59 ± 14(29-88)	52.57 ± 12.72	60.44 ± 14.08	0.183
FEV1 (% of predicted)	68 ± 19(27-95)	62.57 ± 20.99	69.25 ± 19.31	0.419
DLCO (% of predicted)	58 ± 23(12-88)	54.71 ± 23.65	57.91 ± 23.18	0.744
Total lung capacity (L)	3.87 ± 1.24(1.75-6.02)	3.68 ± 1.13	3.90 ± 1.26	0.674
6MWT (meters)	429 ± 127(100-615)	392.86 ± 85.04	432.19 ± 133.07	0.461
GAP İndex	3.85 ± 1.42(1-6)	3.71 ± 0.75	3.88 ± 1.53	0.785
GAP Stage I/II/III	15/19/6			

FVC forced vital capacity, FEV1 forced expiratory volume in 1 s, DLCO single breath diffusing capacity, 6MWT: 6 minute walking test, GAP: Gender, Age, and Physiology.

Table III. Semi-quantitative visual score, correlation of quantitative methods with PFT and 6MWT.

		Method-1	Method-2	MLA-3	Method-4	SKEW-3	KURT -3	VSQS
VSQS	r value	0.673	0.629	0.654	-0.743	-0.774	-0.703	–
	p value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	–
FVC%	r value	-0.445	-0.431	-0.453	0.412	0.495	0.480	-0.455
	p value	0.004	0.006	0.003	.0.008	.0.001	.0.002	.0.003
FEV1%	r value	-0.360	-0.336	-0.359	0.359	0.427	0.407	-0.396
	p value	.0.023	0.034	0.023	0.023	0.006	0.009	0.011
DLCO%	r value	-0.692	-0.701	-0.658	0.750	0.687	0.527	-0.667
	p value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
TLC	r value	-0.781	-0.742	-0.766	0.784	0.795	0.683	-0.643
	p value	< 0.001	<0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
6MWT	r value	-0.692	-0.671	-0.664	0.744	0.691	0.587	-0.641
	p value	< 0.0001	< 0.001	< 0.0001	< 0.001	< 0.001	< 0.001	< 0.001

VSQS: Visual semiquantitative score, FVC forced vital capacity, FEV1 forced expiratory volume in 1 s, DLCO single-breath diffusing capacity, TLC: Total lung capacity, MLA-3 mean lung attenuation value of Method-3, SKEW-3: Skewness value of Method-3, KURT-3: Kurtosis value of Method-3.

Correlations Between QCT and VSQ Score Results

Good-excellent correlation was observed between the VSQS results and QCT methods ($p <$ 0.001). The highest correlation was seen between SKEW-3 (skewness value of Method-3) and the VSQS (r= -0.774, p<0.001), and the lowest correlation was between the VSQS and Method-2 (value of the voxels between -260 and -600 HU) (r= -0.629, p<0.001) (Table III).

The Relationship Between VSQS and QCT Methods in the GAP Model of Mortality Estimation

An excellent correlation was determined between VSQS and the GAP index (r=0.912, p<0.001). From the QCT parameters, Method-2 and MLA-3 showed a moderate correlation with the GAP index (r=0.465, p=0.003, and r=0.485, p=0.002, respectively). Method-1 and Method-4 showed a good correlation with the GAP index (r=0.506, p=0.001, and r= -0.600, p<0.001, respectively).

A good correlation was seen between the SKEW-3 and KURT-3 values and the GAP index (r= -0.630, p<0.001, and r=-0.554, p<0.001, respectively). The parameter showing the best performance in the differentiation of low (GAP stage I) and high (GAP stage II and III) mortality risk was the VSQS at a cut-off value of ≥17.5, with 96% sensitivity and 100% specificity, and an area under the curve (AUC) of 0.997 (95% CI, 0.98.9-1) (Figure 3). The QCT parameter showing the best performance in the prediction of low mortality risk was Method-4 at a cut-off value of ≥63.65, with 73% sensitivity and 80% specificity and an AUC of 0.80 (95% CI, 0.654–0.946) (Table VI).

Table IV. Correlation of quantitative methods.

		Method-1	Method-2	MLA-3	Method-4	SKEW-3	KURT -3
Method-1	r value	1	0.980	0.991	-0.919	-0.930	-0.815
	p value		0.001	0.001	0.001	0.001	0.001
Method-2	r value	0.980	1	0.965	-0.897	-0.875	-0.745
	p value	0.001		0.001	0.001	0.001	0.001
MLA-3	r value	0.991	0.965	1	-0.877	-0.932	-0.836
	p value	0.001	0.001		0.001	0.001	0.001
Method-4	r value	-0.919	-0.897	-0.877	1	0.879	0.723
	p value	0.001	0.001	0.001		0.001	0.001
SKEW-3	r value	-0.930	-0.875	-0.932	0.879	1	0.948
	p value	0.001	0.001	0.001	0.001		0.001
KURT -3	r value	-0.815	-0.745	-0.836	0.723	0.948	1
	p value	0.001	0.001	0.001	0.001	0.001	

MLA-3 mean lung attenuation value of Method-3, SKEW-3: Skewness value of Method-3, KURT-3: Kurtosis value of Method-3.

Table V. Results of quantitative methods.

QCT Methods	Mean	SD	Minimum	Maximum
Method-1	31.26	16.13	3.27	67.61
Method -2	14.08	9.80	0.22	37.31
MLA-3	-735.39	69.1740	-871	-597.18
Method-4	57.20	13.04	25.48	81.50
SKEW-3	1.18	0.53	0.28	2.51
KURT-3	1.00	1.85	-0.68	7.30

QCT: Quantitative computed tomography, MLA-3 mean lung attenuation value of Method-3, SKEW-3. Skewness value of Method-3, KURT-3 Kurtosis value of Method-3.

Discussion

In this study, previously defined QCT methods were investigated in patients with IPF, and the results showed a significant correlation between all QCT methods (p<0.001). Furthermore, a significant correlation was seen between all QCT method semiquantitative evaluations and RFT (FVC, FEV 1), TLC, DLCO, and 6MWT. Of the QCT methods and VSQS, the most successful method in the differentiation of low-risk and high-risk mortality according to the GAP model was the VSQS. Of the QCT methods, Method-4 showing the WAL value (value of the voxels between -700 and -950 HU) showed the best performance in the prediction of low-risk mortality according to the GAP model.

Ufuk et al[18] reported a correlation at an excellent level (r=0.933, p<0.001) between VSQS and Method-1 (value of the voxels between -200 and -700 HU) in interstitial lung disease related to Sjögren syndrome. Matsuoka et al[23] also found an excellent correlation between VSQS and high-density volume percentage (value of the voxels between 0 and -700 HU) in patients with pulmonary fibrosis (r=0.911, p<0.001). In the current study, a correlation at a good level was observed between Method-1 and the VSQS (r=0.673, p<0.001). Ninaber et al[19] found a moderate-good correlation between Method-2 (value of the voxels between -260 and -600 HU) and the RFT results. However, as that study did not use a semi-quantitative (visual) ILD evaluation, the relationship between quantitative (Method-2) and semi-quantitative evaluation was not known[19]. A study of interstitial lung disease related to scleroderma by Ufuk et al[24] determined a good correlation between a similar quantitative method (Method-2) and the visual score (r=0.619, p<0.001). In the current study, a good correlation was also observed between Method-2 and the VSQS (r=0.629, p<0.001). The study of 25 patients with ILD by Koyama et al[20], who investigat-

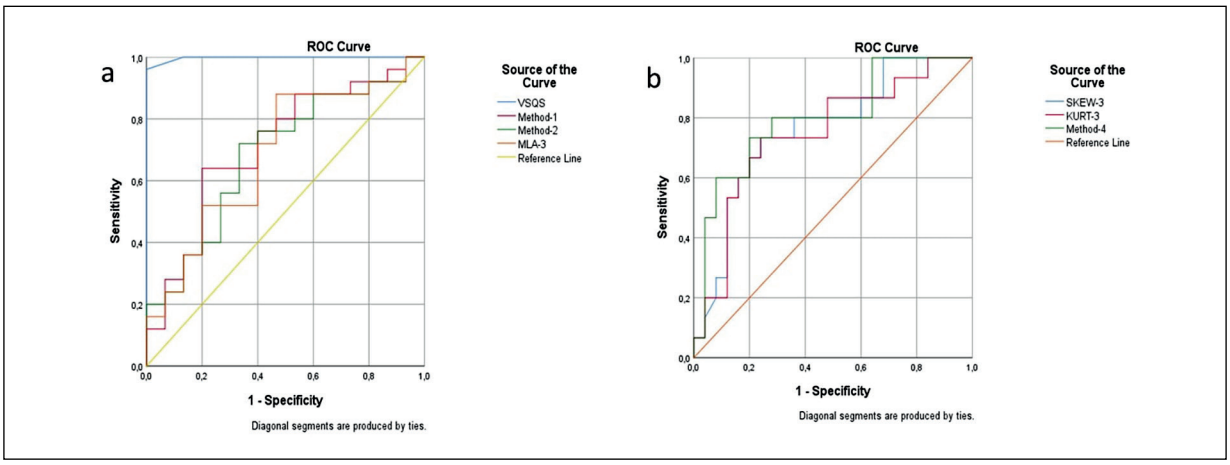

Figure 3. The ability to distinguish between low mortality risk (GAP stage I) and high risk of mortality (GAP stage II and III) was tested in HRCT with a ROC curve. **A,** VSQ score, Method-1, Method-2, MLA-3 analysis. **B,** SKEW-2, KURT-3 *vs.* Method-4 analysis. ROC analysis showed that the best parameter was the VSQ score and the area under the curve (AUC) was 0.997 (95% CI, 0.98.9-1) and the best QCT parameter was Method-4 (AUC 0.80, [95% CI] 0.654-0.946).

Table VI. Diagnostic performances of VSQ score and QCT parameters according to ROC analysis for clinical prediction of low and high-risk mortality compared to the GAP model.

	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cut-Off
VSQS	99.7 (98.9-100)	96	100	≥ 17.5
Method-1	71.2 (54.4-88)	64	80	≥ 31.83%
Method-2	68.5 (51.4-85.6)	72	68	≥ 11.74
MLA-3	68.5 (51.2-85.8)	72	60	≥ -750
SKEW-3	76 (60.7-91.5)	73	76	≤ 1.118
KURT-3	75 (58.5-90.8)	73	76	≤ 0.62
Method-4	80 (65.4-94.6)	73	80	≥ 63.65%

VSQS: Visual semi-quantitative score, method-1: value of the voxels between – 200 and – 700 HU, method-2: value of the voxels between − 260 and – 600 HU, MLA-3: mean lung attenuation value of Method-3 (value of the voxels between − 200 and – 1024 HU), method-4: value of the voxels between − 700 and – 950 HU, SKEW-3: Skewness value of Method-3, KURT-3: Kurtosis value of Method-3, AUC: area under the curve.

ed quantitative ILD evaluations using the MLA, skewness, and kurtosis values (Method-3) in CT histogram analyses, reported a moderate-to-good correlation between the quantitative values and the FVC, DLCO, and TLC results. Similarly, in the current study, a moderate-to-good correlation was determined between Method-3 and the FVC, DLCO, and TLC values. Koyama et al[20] did not use ILD evaluation with a visual score so quantitative (Method-3) and visual score evaluations were not examined. Ufuk et al[24] observed a good-to-excellent correlation between the visual score and Method-3 values in scleroderma-related interstitial lung disease. In the current study, an excellent correlation was determined between the quantitative Method-3 and the VSQS (p<0.001). Okhubo et al[25] showed a good correlation between normal aerated lung percentage (value of the voxels between -701 and -950 HU) and RFT. However, as the study did not use semi-quantitative ILD evaluation, the relationship between the quantitative (Method-4) and semi-quantitative evaluation could not be determined. In the current study, an excellent negative correlation was determined between Method-4 (value of the voxels between -700 and -950 HU) and the VSQS (r=-0.743, p<0.001). The small differences observed between the current study and previous studies that have evaluated the correlation between quantitative methods and the VSQS in interstitial lung disease can be attributed to the use of different visual score methods and different ILD groups.

RFTs are used in the routine follow-up of ILD patients and are important in the evaluation of treatment[16]. The DLCO and FVC are the parameters reported to be most related to quantitative and semi-quantitative evaluations[26]. The DLCO is thought to be most related to the ILD severity in HRCT, but the specificity of DLCO is low. The FVC values in ILD patients could be affected by muscle weakness; therefore, the FVC values sometimes cannot be associated with the severity of ILD in IPF patients[26,27]. The QCT method results were significantly correlated with the RFT results in the current study. Therefore, when determining the disease progression and evaluating the prognosis of patients undergoing HRCT, QCT methods may reduce the need for RFT.

The 6MWT is a simple test and is widely used to evaluate the functional exercise capacity in patients with IPF[28]. The 6MWT results are also affected by various factors, such as age, body dimensions, comorbidities, and the use of additional oxygen during the test, and these must be kept in mind when interpreting the results of individual and serial tests[29]. Sanchez et al[30] observed a significant correlation between the visual score and the 6MWT (r=-0.45, p<0.01). In the current study, a correlation at a good level was determined between the VSQS and the 6MWT (r=-0.641, p<0.001). Moreover, a significant correlation was observed between different QCT parameters and the 6MWT, with Method-4 (value of the voxels between -700 and -950 HU) having the best correlation (r= 0.744, p<0.001).

The GAP model related to clinical and physiological parameters can be used in the determination of mortality associated with IPF. The GAP model is a clinical estimation tool that estimates prognosis in IPF patients[12]. Ley et al[31], in their study on patients with IPF, stated that the extension of fibrosis is associated with the mortality risk and it can be added to the GAP model of quantitative CT scoring. Nakagawa et al[32] reported that the FVC% of the honeycomb pattern area (HA)

in the HRCT test was significantly related to the GAP model. In the same study, the authors stated that the HA derived from quantitative CT could be an independent significant predictor of mortality in patients with IPF with a definite UIP pattern. Torrisi et al[33] evaluated survival with HRCT parameters in patients with IPF and concluded that the high-density area percentage was statistically significant in the prediction of mortality. Ohkubo et al[25] reported that the measurement of normal aerated lung (NL) percentage (value of the voxels between -701 and -950 HU) with threshold-based CT analysis could be useful in evaluating IPF grading. In the same study, a NL% cut-off value of 66.0% was evaluated with 87% sensitivity and 75% specificity in the differentiation of GAP stage II and III. Similarly, in the current study, the cut-off value of Method-4 (value of the voxels between -700 and -950 HU) of ≥63.65% in the prediction of low-risk mortality (GAP stage I) had 73% sensitivity, 80% specificity, and AUC of 0.80 (95% CI, 0.654-0.946). The accuracy of the parameters derived from CT histograms and different QCT methods can be considered not to have been sufficiently tested in the evaluation of the survival of patients with IPF. Unlike previous studies, different VSQS[16] and different QCT methods were used in the current study. In the differentiation of low-risk and high-risk mortality in this study, VSQS showed the best performance, with a cut-off value of ≥17.5 at 96% sensitivity, 100% specificity and AUC of 0.997 (95% CI, 0.98-1).

This study had some limitations. Primarily, it was retrospective, and the study population was relatively small. Nevertheless, to the best of our knowledge, this is the first study to have evaluated the relationship between different QCT methods and the GAP model in patients with IPF. Another limitation was that the mortality rate of patients during follow-up was not known. However, the effect of quantitative and semi-quantitative evaluation results has been clearly shown in previous studies, and the disease extent is a strong determinant of prognosis[25,33,34]. Therefore, the effect of quantitative and semi-quantitative evaluations on prognosis and mortality was examined on the GAP model in the current study.

Conclusions

QCT methods can be used in the evaluation of the extent of disease in patients with IPF. The results of this study can be considered useful in the selection of the quantitative method in these patients. VSQS performed best in predicting mortality risk. Furthermore, method -4 of the QCT parameters, which shows well-aerated lungs, were deemed to have good potential for the estimation of mortality risk.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics

This study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/536).

Authors' Contribution

Kaya F designed this study. Kaya F and Balcı A searched for articles. Özgül E performed statistical analyses. Özgül E and Balcı A performed data extraction. Kaya F wrote this article. Özgül E and Kaya F made academic language and grammer editing.

Orcid ID

0000-0001-8619-7593.

References

1) Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D; ATS/ERS Committee on Idiopathic Interstital Pneumonias. An official AmericanThoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188: 733-748.

2) Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty K, Lasky J, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Kohdoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss

BS, Protzko SL, Shunemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.

3) Best AC, Meng J, Lynch AM, Bozic CM, Miller D, Grunwald GK, Lynch DA. Idiopathic pulmonary fibrosis:physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology 2008; 246:935-940.

4) Iwasawa T, Ogura T, Sakai F, Kanauchi T, Komagata T, Baba T, Gotoh T, Morita S, Yazawa T, Inoue T. CT analysis of the effect of pirfenidonein patients with idiopathic pulmonary fibrosis. Eur J Radiol 2014; 83: 32-38.

5) Park SO, Seo JB, Kim N, Lee YK, Lee JL, Kim DS. Comparison of usual interstitial pneumonia and nonspecific interstitial pneumonia: quantification of disease severity and discrimination between two diseaseson HRCT using a texture-based automated system. Korean J Radiol 2011; 12: 297-307.

6) Shin KE, Chung MJ, Jung MP, Choe BK, Lee KS. Quantitative computed tomographic indexes in diffuse interstitial lung disease: correlation with physiologic tests and computed tomography visual scores. J Comput Assist Tomogr 2011; 35: 266-271.

7) King, TE, Tooze, JA, Schwarz, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: Scoring system and survival model. Am J Resp Crit Care 2001; 164: 1171-1181.

8) Du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, Lancaster L, Noble PW, Raghu G, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, King TE. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011; 184: 459-466.

9) Richards TJ, Kaminski N, Baribaud F, Flavin S, Brodmerkel C, Horowitz D, Li K, Choi J, Vuga LJ, Lindell KO, Klesen M, Zhange Y, Gibson KF. Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012; 185: 67-76.

10) Lee SH, Shim HS, Cho SH, Kim SY. Prognostic factors for idiopathic pulmonary fibrosis: clinical, physiologic, pathologic, and molecular aspects. Sarcoidosis Vasc Diffuse Lung Dis. 2011; 28: 102-112.

11) Mura M, Porretta MA, Bargagli E, Sergiacomi G Zompatori M, Sverzellati N, Taglieri A, Mezzasalma F, Rottoli P, Saltini C, Rogliani P. Predicting survival in newly diagnosed idiopathic pulmonary fibrosis: a 3-year prospective study. Eur Respir J 2012; 40: 101-109.

12) Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD, King TE, Collard HR. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Annals Intern Med 2012; 156: 684-691.

13) Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr H, Cottin V, Danoff SK, Morell F, Flaherty KR, Wells A, Martinez FJ, Azuma A, Bice TJ, Bouros D, Brown KK, Collard HR, Duggal A, Galvin L, Inoue Y, Jenkins RG, Johkoh T, Kazerooni EA, Kitaichi M, Knight SL, Mansour G, Nicholson AG, Pipavath SNJ, Buendia-Roldan I, Selman M, Travis WD, Walsh S, Wilson KC, American Thoracic Society, European Respiratory Society, Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 2018; 198: e44-68.

14) Miller MR. ATS/ERS task force: standardisation of spirometry. Eur Respir J 2005; 26: 319-338.

15) ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.

16) Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991; 18: 1520-1528.

17) Salaffi F, Carotti M, Bosello S, Ciapetti A, Gutierrez M, Bichisecchi E, Giuseppetti G, Ferraccioli G. Computer-aided quantification of interstitial lung disease from high resolution computed tomography images in systemic sclerosis: correlation with visual reader-based score and physiologic tests. Biomed Res Int 2015; 2015: 834262.

18) Ufuk F, Demirci M, Altinisik G, Karasu U. Quantitative analysis of Sjogren's syndrome related interstitial lung disease with different methods. Eur J Radiol 2020; 128:109030

19) Ninaber MK, Stolk J, Smit J, Le Roy EJ, Kroft LJ, Bakker ME, de Vries Bouwstra JK, Schouffoer AA, Staring M, Stoel BC. Lung structure and function relation in systemic sclerosis: application of lung densitometry. Eur J Radiol 2015; 84: 975-979.

20) Koyama H, Ohno Y, Yamazaki Y, Nogami M, Kusaka A, Murase K, Sugimura K. Quantitatively assessed CT imaging measures of pulmonary interstitial pneumonia: effects of reconstruction algorithms on histogram parameters. Eur J Radiol 2010; 74: 142-146.

21) Colombi D, Bodini FC, Petrini M, Maffi G, Morelli N, Milanese G, Silva M, Sverzellati N, Michieletti E. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology 2020; 296: E86-E96.

22) Chen A, Karwoski RA, Gierada DS, Bartholmai BJ, Koo CW. Quantitative CT analysis of diffuse lung disease. Radiographics 2020; 40: 28-43.

23) Matsuoka S, Yamashiro T, Matsushita S, Fujikawa A, Yagihashi K, Nakajima Y. Objective quantitative CT evaluation using different attenuation ranges in patients with pulmonary fibrosis: correlations with visual scores. Int J Respir Pulm Med 2016; 3: 3-7.

24) Ufuk F, Demirci M, Altinisik G. Quantitative computed tomography assessment for systemic sclerosis–related interstitial lung disease: comparison of different methods. Eur Radiol 2020; 30: 4369-4380.

25) Ohkubo H, Kanemitsu Y, Uemura T, Takakuwa O, Takemura M, Maeno K, Ito Y, Oguri T, Kazawa N, Mikami R, Niimi A. Normal lung quantification in usual interstitial pneumonia pattern: the impact of threshold-based volumetric CT analysis for the staging of idiopathic pulmonary fibrosis. PLoS One 2016 ;11: e0152505.

26) Tashkin DP, Volkmann ER, Tseng CH, Kim HJ, Goldin J, Clements P, Furst D, Khanna D, Kleerup E, Roth MD, Elashoff R. Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. Ann Rheum Dis 2016; 75: 374-381.

27) Salaffi F, Carotti M, Di Donato E, Di Carlo M, Ceccarelli L, Giuseppetti G. Computer-aided tomographic analysis of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Correlation with pulmonary physiologic tests and patient-centred measures of perceived dyspnea and functional disability. PLoS One 2016; 11: e0149240.

28) Swigris JJ, Wamboldt FS, Behr J, du Bois RM, King TE, Raghu G, Brown KK. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax 2010; 65: 173-177.

29) Lancaster LH. Utility of the six-minute walk test in patients with idiopathic pulmonary fibrosis. Multidiscip Respir Med 2018; 13: 45.

30) Sánchez EF, Samper GJ, Domingo ML, Montañana MLD, Vilar LN. Visual HRCT score to determine severity and prognosis of idiopathic pulmonary fibrosis. Int J Respir Pulm Med 2018; 5: 084.

31) Ley B, Elicker BM, Hartman TE, Ryerson CJ, Vittinghoff E, Ryu JH, Lee JS, Jones KD, Richeldi L, King TE Jr, Collard HR. Idiopathic pulmonary fibrosis: CT and risk of death. Radiology 2014; 273: 570-579.

32) Nakagawa H, Ogawa E, Fukunaga K, Kinose D, Yamaguchi M, Nagao T, Tanaka-Mizuno S, Nakano Y. Quantitative CT analysis of honeycombing area predicts mortality in idiopathic pulmonary fibrosis with definite usual interstitial pneumonia pattern: A retrospective cohort study. PloS One 2019;14: e0214278.

33) Torrisi SE, Palmucci S, Stefano A, Russo G, Torcitto AG, Falsaperla D, Gioè M, Pavone M, Vancheri A, Sambataro G, Sambataro D, Mauro LA, Grassedonio E, Basile A, Vancheri C. Assessment of survival in patients with idiopathic pulmonary fibrosis using quantitative HRCT indexes. Multidiscip Respir Med; 13: 43.

34) Brun AL, Egashira R, Karwoski R, Kokosi M, Wells AU, Hansell DM.Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study. BMC medicine 2016; 14: 1-3.