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Computed tomography findings as determinants of pulmonary function tests in fibrotic interstitial lung diseases—Network-analyses and multivariate models

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Abstract

The aim was to evaluate the impact of multiple high-resolution computed tomography (HRCT) features on pulmonary function test (PFT) biomarkers in fibrotic interstitial lung disease (FILD) patients. HRCT of subsequently ILD-board-discussed FILD patients were semi-quantitatively evaluated in a standardized approach: 18 distinct lung regions were scored for noduli, reticulation, honeycombing, consolidations, ground glass opacities (GGO), traction bronchiectasis (BRK) and emphysema. Total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC, diffusion capacity for carbon monoxide (DLCO) and transfer coefficient (KCO) were assessed. Interactions between each PFT biomarker and all HRCT scores were visualized by network analyses, modeled according to the Schwarz Bayesian Information Criterion and incorporated in uni- and multivariate stepwise regression analyses. Among 108 FILD patients (mean age 67 years, 77% male), BRK extent was a major significant uni- or multivariate determinant of all PFT analyzed. Besides that, diffusion-based variables DLCO and KCO showed a larger dependency on reticulation, emphysema and GGO, while forced expiratory volume-based measures FEV1, FVC and FEV1/FVC were more closely associated with consolidations. For TLC, the only significant multivariate determinant was reticulation. In conclusion, PFT biomarkers derived from spirometry, body plethysmography and diffusion capacity in FILD patients are differentially influenced by semi-quantified HRCT findings.

Keywords

Traction bronchiectasis, emphysema, forced vital capacity, total lung capacity, diffusion capacity, transfer coefficient

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Introduction

High-resolution computed tomography (HRCT) imaging plays a pivotal role in diagnosis and management of interstitial lung diseases (ILD).[1–4] Characteristic HRCT patterns like usual interstitial pneumonia (UIP) or non-specific interstitial pneumonia (NSIP) are being widely recognized and multidisciplinary ILD boards providing a high degree of diagnostic accuracy have become standard of care.[1,5–7] A radiologically assessed definite or probable UIP pattern together with coherent results of a standardized diagnostic work-up and ILD-board discussion is regarded sufficient for the diagnosis of idiopathic pulmonary fibrosis (IPF) and initiation of antifibrotic treatment.[5,6] Similarly, in other frequent ILD like chronic hypersensitivity pneumonitis (CHP) or ILD associated with autoimmune disorders, typical imaging together with a sufficiently clear clinical background and a multidisciplinary diagnostic work-up can frequently render histological evaluation unnecessary.[3,8,9]

Contrary to diagnosis, for follow-up of ILD patients there is only little consensus on the value of HRCT.[3] For IPF, yearly CT scans have been suggested due to the increased risk of lung cancer.[2,10] Serial HRCT imaging in ILD may also be warranted in order to increase the diagnostic yield in unclear cases and some publications suggest, that longitudinal HRCT changes may also have prognostic implications.[2,3,11] Given the uncertainty on the role of HRCT in follow-up, patients are usually monitored using pulmonary function tests (PFT) biomarkers derived from spirometry like forced vital capacity (FVC), measurement of diffusion capacity for carbon monoxide (DLCO) and exercise testing.[12]

Associations of qualitative or quantitative HRCT findings with single PFT variables are well established.[2,3] However, typical ILD-associated HRCT imaging features like honeycombing or traction bronchiectasis (BRK) usually do not occur alone but rather coincide and their complex interaction finally defines functional impairment. Thus, one may doubt that only one PFT variable like FVC or DLCO can be an equally valuable biomarker in every ILD, given their complex pathogenesis and variable presentation in HRCT scans.

In this exploratory analysis, we thus aimed to assess, how individual routine PFT variables are determined by distinct HRCT findings using a semi-quantitative scoring system, network analyses and multivariate models.

Methods

We retrieved patient data relevant to this analysis from the ILD registry of Kepler University Hospital Linz. The registry as well as the present evaluation have been conducted in concordance with the World Medical Association Declaration of Helsinki and were approved and re-assessed on a yearly basis by the ethics committee of the federal state of Upper Austria (study number I-26-17).

Patients included in that registry provided written informed consent and have been subsequently discussed by the monthly local ILD board. By that time, all patients had undergone a standardized ILD evaluation program including standardized assessment of patient history, physical examination, HRCT imaging, laboratory analyses, PFT including spirometry, body plethysmography and measurement of diffusion capacity (JAEGER MasterScreen PFT/Body/Diffusion, CareFusion, San Diego, United States of America). Most evaluations were accomplished within 2 or 3 days in an inpatient setting. In the other case, the maximum accepted time between HRCT and the other examinations was 3 weeks, but only in patients with no current ILD-specific medication.

For this analysis, the following PFT parameters were evaluated: total lung capacity (TLC, % predicted), forced vital capacity (FVC, % predicted), forced expiratory volume in 1 second (FEV1, % predicted), FEV1/FVC ratio, DLCO (single breath method, % predicted) and transfer coefficient (KCO, % predicted). Normal values for spirometry were based on the GLI-2012 equations,[13] those for body plethysmography and diffusion capacity on the 1993 ERS/ECCS regressions.[14] HRCT images were acquired according to protocols suggested by the relevant guidelines.[3,4,6,12] If clinically feasible, prone imaging was preferred in order to differ opacities in dependent lung areas from true interstitial lung abnormalities.

Prior to this study, we had devised a semi-quantitative scoring system for ILD HRCT scans based on four elementary lesion types: nodular pattern (noduli (NDL)), reticular abnormalities (interlobular septal and intralobular interstitial thickening (reticulation (RET)) and honeycombing (HON)), increased (consolidations (CON), ground glass opacities (GGO)) and reduced lung attenuation (emphysema (EMP)) findings.[3,4,15–17] Additionally, we screened for the presence of a pulmonary artery (PA): aorta (A) diameter ≥ 1 (PAD), measured at the largest

diameter of the PA bifurcation level, of mosaic attenuation (MOS), visual signs of volume reduction (VOL) and the extent of traction bronchi(-ol)ectasis (BRK).[5,18] HRCT findings were visually quantified by a specialist ILD radiologist during the respective ILD board session: both lungs were separated in an upper-, middle- and lower lung area defined by thirds of the largest cranio-caudal diameter in the sagittal reconstructions, further divided into a subpleural region (directly involving the pleura and the adjacent 2 millimeters toward the hilum),[19] a peripheral and a central region (divided by half distance between hilum and the subpleural region), delineating a total of 18 distinct portions. For each quantifiable HRCT finding (BRK, RET, HON, EMP, GGO, NDL, CON) the individual extent was defined as the sum of all involved defined lung areas, leading to scores ranging from 0 to 18. Variables PAD, MOS and VOL were graded as present or absent. For the reported analysis, only patients with fibrotic ILD defined as a RET and/or HON score of $\geq$1 were included. In a preliminary attempt to evaluate the validity of the described scoring system, all HRCT imaging studies were retrospectively re-assessed in a blinded-fashion with the same scoring approach by two individual radiologists (SW and BH), both with more than 5 years of professional experience. Concordance between them and with the results assessed in the ILD board were calculated using coincidence rates of present/absent HRCT patterns and weighted Cohen's kappa for the ordinal HRCT finding scores.

The association of the selected PFT variables with the multiple evaluated HRCT scores was evaluated applying statistical analyses in three steps:

First, all scored HRCT finding variables were assessed for coincidence in a binary (present or absent) way as well as by using their ordinal scaling to calculate Spearman correlation coefficients. Also, network analyses (using R Version 3.6.0. and the qgraph package) were performed for each PFT variable with all quantifiable HRCT finding scores.

As second step, optimized models for each HRCT variable score and each PFT were determined by visual analysis of bubble-plot diagrams and consecutive determination of cut-off values using regression. The respective model with the lowest Schwarz Bayesian Information Criterion (SBC) value was chosen. A visualized example of such a model, depicting the relationship of the extent of BRK with DLCO is shown in the Supplementary Figure 1. Significance of the binary variables PAD, MOS and VOL concerning each functional parameter was assessed by unpaired-samples t-tests.

As third step, using the SBC optimized HRCT variable cut-off values, uni- and multivariate analyses for each PFT variable were calculated with stepwise selection based on the SBC.

For all analyses, a p-value <0.05 was regarded statistically significant.

Results

We evaluated n = 108 fibrotic ILD patients consecutively discussed by the multidisciplinary ILD board of Kepler University Hospital Linz, Austria between February 2017 and September 2018. Clinical, PFT and radiological patient characteristics are shown in Tables 1 and 2 and in Supplementary Table 1.

To evaluate the direct interaction and possible multicollinearity between the HRCT findings, coincidence rates of presence/absence as well as Spearman correlation coefficients between the respective scores were evaluated (Table 3). Major coincidences were seen for reticulation and traction bronchiectasis (85%) and for emphysema and honeycombing (74%). However, when analyzing the interaction between the ordinal HRCT scores, no strong correlation (defined as a Spearman correlation coefficient $\geq$0.5) could be found. Multicollinearity related to linear combinations was also excluded using regression models.

Results for interobserver variability in presence/absence of the reported HRCT findings as well as for the HRCT finding scores are displayed in Supplementary Table 2.

Network analyses for each PFT and all quantifiable HRCT scores together with SBC-optimized models, uni- and multivariate analyses are shown in Figures 1 to 3.

For the TLC, network analysis showed major correlations with BRK (Spearman correlation coefficient -0.36) and RET (-0.19). Significant cut-off models and univariate results could be shown for BRK, GGO and visual signs of volume reduction, however multivariate testing resulted in RET as the only significant finding.

FVC was similarly associated with BRK (-0.38) and additionally with CON (-0.21) in the network analyses and a comparable situation was shown for FEV1 with BRK and CON (both -0.28, respectively). Concordantly, FVC and FEV1 were mainly determined

Table 1. Patient characteristics at the time of ILD evaluation before ILD board discussion.[a]

Patient Characteristics (n = 108)			
Mean age (years, SD)	67 (14)	Clinical examination findings (%)	
Age range (years)	18–92	None	31 (29)
Male Sex (%)	77 (71)	Basal crackles	65 (60)
Previously diagnosed ILD (%)	57 (53%)	Obstruction	10 (9)
Family history of ILD (%)	7 (6%)	Congestive heart failure	17 (16)
Mean latency since reported symptom onset (years, SD)	4.5 (5.9)	Comorbidities (%)	
		Cardiovascular	57 (53)
ILD board diagnosis (%)		Pulmonary	43 (40)
IPAF	22 (20)	Autoimmune	20 (19)
IPFTables and	23 (21)	Malignancy	11 (10)
CHP	16 (15)	GERD	30 (28)
iNSIP	16 (15)	Diabetes	16 (15)
aILD	10 (9)	Exposure history (%)	
Unclassified ILD	10 (9)	None	37 (34)
Other ILD	11 (10)	Smoke (active or passive)	68 (63)
Symptoms (%)		Anorganic dust	29 (27)
None	8 (7)	Organic dust	28 (26)
Exertional dyspnea	89 (82)	Chemical fumes	12 (11)
Cough	60 (56)	Pneumotoxic medication	13 (12)
Chest pain	8 (7)	Smoking history (%)	
Muscle weakness	15 (14)	Mean pack years (SD)	21 (26)
Fever/night sweats	11 (10)	Never smoker	38 (35)
Joint pain	5 (5)	Former smoker	48 (44)
Weight loss	6 (6)	Current smoker	14 (13)
Skin rash	5 (5)	Solely passive smoker	6 (6)
Relevant ILD-specific medication (%)		Inhaled long-term medication (%)	
Oral steroid monotherapy	5 (5)	LAMA	1 (1)
Azathioprin[b]	4 (4)	LAMA/LABA[c]	6 (6)
Methotrexate[b]	3 (3)	LABA/ICS[c]	11 (10)
Golimumab + methotrexate	1 (1)	LAMA/LABA/ICS[c]	4 (4)
Mycofenolate mofetil + tacrolimus + oral steroid	1 (1)		
Nintedanib	2 (2)		

SD: standard deviation; ILD: interstitial lung disease; IPAF: interstitial pneumonia with autoimmune features; IPF: idiopathic pulmonary fibrosis; CHP: chronic hypersensitivity pneumonitis; iNSIP: idiopathic non-specific interstitial pneumonia; aILD: autoimmune-associated ILD; GERD: gastroesophageal reflux disease; LAMA: long-acting muscarinic antagonist; LABA: long-acting beta-adrenoceptor agonist; ICS: inhaled corticosteroid.

[a] Values are given as n (%) unless otherwise specified.

[b] With or without oral steroid.

[c] One device or in combination.

by the BRK and CON scores in the SBC-based models, whereupon FEV1 showed an additional significant finding for honeycombing extent in uni- and multivariate analyses. The ratio of FEV1/FVC was most markedly correlated with reticulation (0.4), emphysema (−0.34) and BRK (0.29), which corresponded to the FEV1/FVC

Table 2. PFT and HRCT characteristics.

PFT and HRCT findings (n = 108)			
Pulmonary function tests	n (%)	Mean (SD)	Median (IQR)
TLC (% pred.)	104 (96)	85.1 (19.7)	83.6 (30)
FVC (% pred.)	105 (97)	79.2 (20.6)	80 (30)
FEV1 (% pred.)	105 (97)	78.9 (20.4)	78 (24)
FEV1/FVC	103 (95)	0.8 (0.09)	0.8 (0)
DLCO (% pred.)	99 (92)	56.1 (15.9)	59.7 (17)
KCO (% pred.)	99 (92)	70 (20.2)	70.7 (29)
HRCT findings	n (%)	Mean (SD)	Median (IQR)
Noduli	30 (28)	2.2 (4.8)	0 (2)
Reticulation	108 (100)	7.6 (4.8)	6 (8)
Honeycombing	22 (20)	1 (2.6)	0 (0)
Ground glass opacities	45 (42)	4.7 (6.9)	0 (6)
Consolidations	36 (33)	1.2 (2.4)	0 (1)
Emphysema	20 (19)	1.4 (3.7)	0 (0)
Traction bronchiectasis	92 (85)	6.7 (5.2)	6 (10)
Mosaic attenuation	29 (27)		
PA: A $\geq$ I	16 (15)		
Volume reduction	50 (46)		

PFT: pulmonary function tests; HRCT: high-resolution computed tomography; PA: A: pulmonary artery: aortic diameter; SD: standard deviation; TLC: total lung capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV1/FVC: fraction of FEV1 and FVC; DLCO: diffusion capacity for carbon monoxide; KCO: carbon monoxide transfer coefficient.

score model where BRK, RET, EMP and CON prove significant (Figures 1 and 2).

Concerning diffusion-based variables, DLCO had major correlations with BRK (−0.4), GGO (−0.28), EMP (−0.24) and RET (−0.22) in the network analyses, while KCO was mainly related to emphysema extent (−0.38). In the corresponding SBC-based score models, major determinants of DLCO were BRK, RET, EMP and GGO, while EMP did not prove significant in multivariate testing. Concerning KCO, the major association with EMP could also be shown in the uni- and multivariate model, with another significant finding for RET (Figure 3).

Discussion

This study aimed to evaluate, how findings typically detectable in HRCT influence different PFT usually measured to assess the degree of physical limitation in fibrotic ILD patients.

Reviewing the network analyses and the PFT-HRCT models including the uni- and multivariate analyses together, one major determinant of PFT impairment became apparent: Traction bronchiectasis, which was proven significant in all univariate and most multivariate models except for TLC and KCO. Of interest, in those two, reticulation prove significant, which may be explained by the close relationship between the BRK and RET scores as shown in Table 3 and as visible the network analyses. Traction bronchiectasis is a hallmark finding of fibrotic ILD, partly constitutes the typical UIP pattern, and—given the proper clinical background—is highly indicative of its presence even when honeycombing is absent.[4–6,20] The extent of BRK has been shown to have major prognostic implications in IPF as well as in other ILD.[21,22] Its association with lower lung volumes is unsurprising and was also documented in studies using automated computer-based evaluation.[23]

Reticulation was present in all 108 patients and showed significant implications for TLC, FEV1/FVC, DLCO and KCO, but interestingly not for FVC and FEV1. These two and their ratio FEV1/FVC were however significantly related to consolidations. It seems obvious that the explanation for these differences is of biomechanical nature, reflecting the difference between measurement of forced expiratory volumes versus total lung capacity by body plethysmography. As we could find a significant interaction

Table 3. Binary coincidence rates of presence/absence of HRCT finding categories in percent (a) and Spearman correlation coefficients for all quantifiable HRCT finding scores (b).

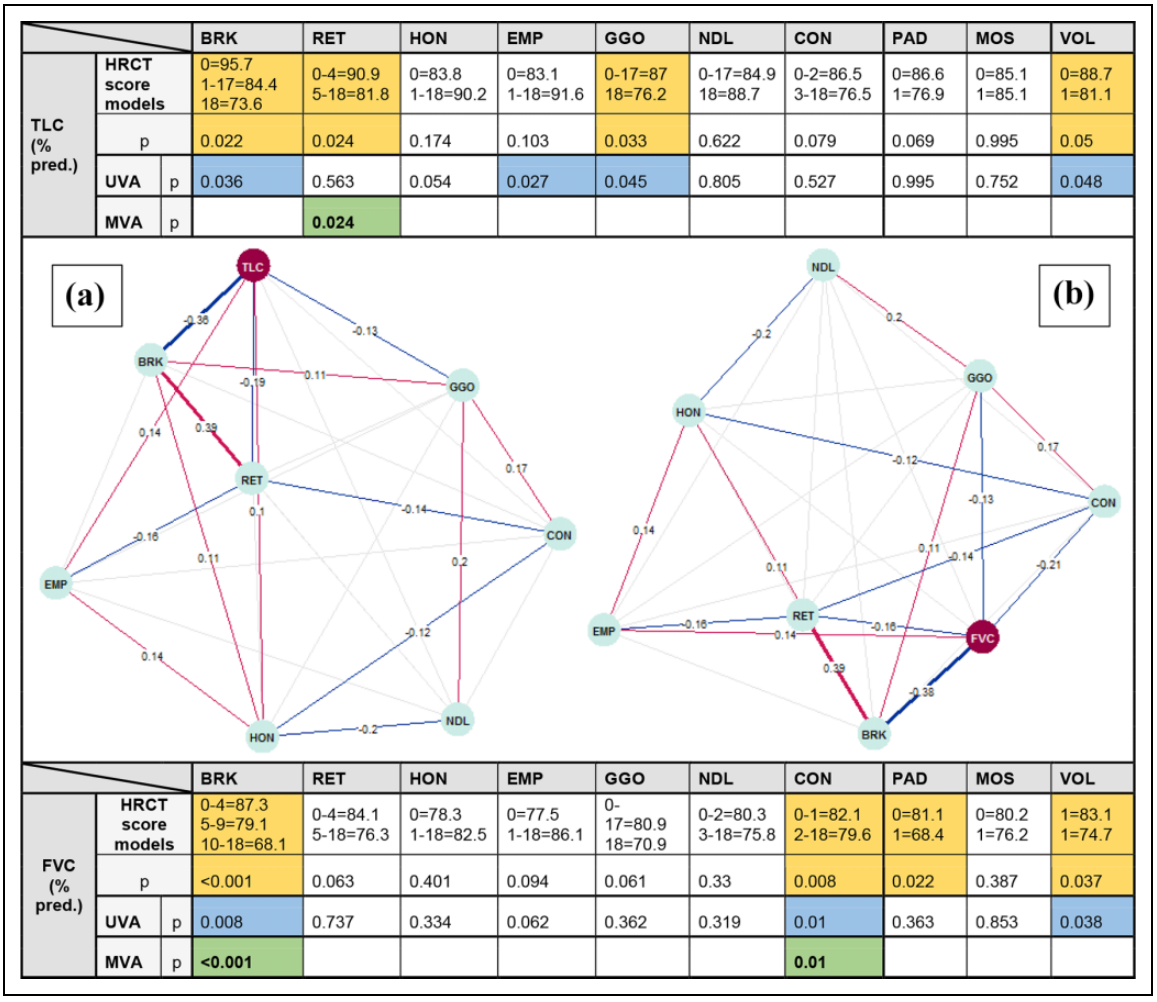
(a)	BRK	RET	HON	EMP	GGO	NDL	CON
BRK		85	30	30	47	33	33
RET	85		20	19	42	28	33
HON	30	20		74	51	56	56
EMP	30	19	74		56	65	59
GGO	47	42	51	56		62	60
NDL	33	28	56	65	62		56
CON	33	33	56	59	60	56	
(b)	BRK	RET	HON	EMP	GGO	NDL	CON
BRK		0.39	0.11	0.09	0.11	0.01	−0.07
RET	0.39		−0.07	−0.16	0.10	0.10	−0.14
HON	0.11	−0.07		0.14	−0.06	−0.20	−0.12
EMP	0.09	−0.16	0.14		0.08	0.00	−0.02
GGO	0.11	0.10	−0.06	0.08		0.20	0.17
NDL	0.01	0.10	−0.20	0.00	0.20		−0.07
CON	−0.07	−0.14	−0.12	−0.02	0.17	−0.07	

BRK: traction bronchiectasis; RET: reticulation; HON: honeycombing; EMP: emphysema; GGO: ground glass opacities; NDL: noduli; CON: consolidations; PAD: pulmonary artery: aortic diameter; MOS: mosaic attenuation; VOL: volume reduction.
[a]Coincidence rates ≥70% in (a) are highlighted in color.

between a higher extent of consolidations and lower FEV1 and FEV1/FVC in uni- and multivariate analyses, concomitant bronchial obstruction may play a role. Contrary, reticulation is traditionally associated with restriction and increased lung stiffness, both of which could be shown for TLC and FEV1/FVC. A hypothetical reason for the discrepancies seen for TLC and forced expiratory volume parameters (FEV1 and FVC) concerning reticulation and consolidations may be, that unlike reticular abnormalities usually representing irreversible scarring of lung tissue, consolidations may rather be areas of recent inflammation, were volume reduction by fibrosis has not yet occurred. An interaction of both reticulation and consolidations having caused the observed findings seems unlikely, as they had low rates of coincidence and correlation coefficients as shown in Table 3 and in the network analyses.

Of interest, we could also find marked differences between measures of lung volumes (TLC, FVC, FEV1, FEV1/FVC) and those primarily reflecting gas transfer (DLCO, KCO) especially concerning GGO and emphysema. Ground glass opacities had only significant multivariate implications on DLCO but not on measures of lung volumes. An explanation for this finding could be, that oxygen transfer may already be influenced by more subtle changes to the alveolo-capillary level like fine reticulation or GGO before lung volumes even deteriorate due to fibrosis. This consideration can also be supported by literature: In IPF, the prototypic progressive fibrotic ILD, data on functional impairment and prognosis are mainly based on FVC.[5,24] Contrary, in diseases considered more inflammatory like systemic sclerosis-associated ILD, DLCO has repeatedly been reported be a better predictor of prognosis as compared to FVC.[25,26]

Emphysema on the other hand univariately had significant impact on TLC, FEV1/FVC, DLCO and KCO, whereas in multivariate models only FEV1/FVC and KCO showed an interaction. The especially close association of emphysema extent with FEV1/FVC and KCO is unsurprising, as both PFT are corrected for lung volume which highlights the presence of emphysematous lung abnormalities. Emphysema usually leads to an increase in residual volume and may be associated with obstructive ventilation



			BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
TLC (% pred.)	HRCT score models		0=95.7 1-17=84.4 18=73.6	0-4=90.9 5-18=81.8	0=83.8 1-18=90.2	0=83.1 1-18=91.6	0-17=87 18=76.2	0-17=84.9 18=88.7	0-2=86.5 3-18=76.5	0=86.6 1=76.9	0=85.1 1=85.1	0=88.7 1=81.1
	p		0.022	0.024	0.174	0.103	0.033	0.622	0.079	0.069	0.995	0.05
	UVA	p	0.036	0.563	0.054	0.027	0.045	0.805	0.527	0.995	0.752	0.048
	MVA	p		**0.024**								

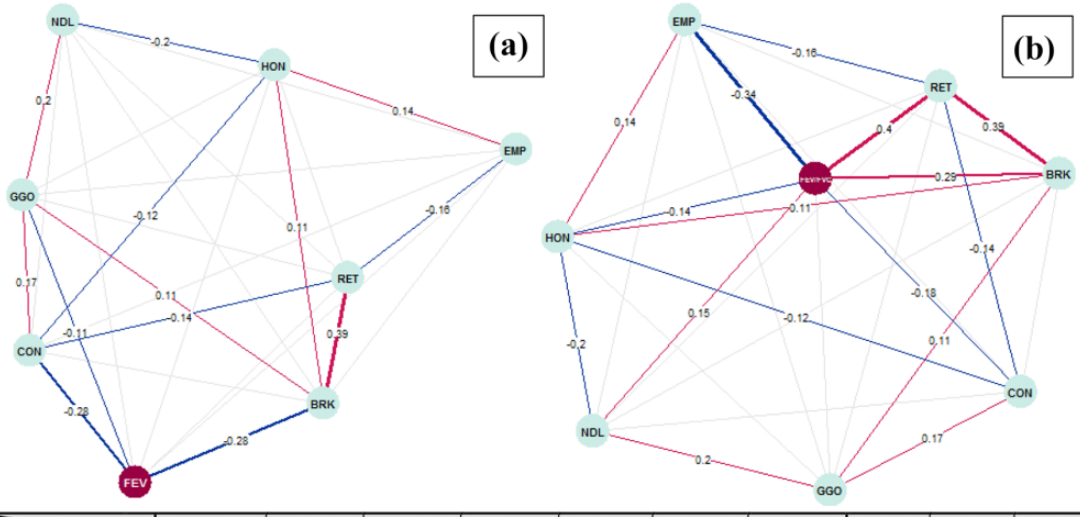
			BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
FVC (% pred.)	HRCT score models		0-4=87.3 5-9=79.1 10-18=68.1	0-4=84.1 5-18=76.3	0=78.3 1-18=82.5	0=77.5 1-18=86.1	0- 17=80.9 18=70.9	0-2=80.3 3-18=75.8	0-1=82.1 2-18=79.6	0=81.1 1=68.4	0=80.2 1=76.2	1=83.1 1=74.7
	p		<0.001	0.063	0.401	0.094	0.061	0.33	0.008	0.022	0.387	0.037
	UVA	p	0.008	0.737	0.334	0.062	0.362	0.319	0.01	0.363	0.853	0.038
	MVA	p	**<0.001**						**0.01**			

Figure 1. HRCT score models and network analyses for TLC (a) and FVC (b). Top lines show SBC-defined HRCT score groups with predicted PFT values; PAD, MOS and VOL are given as present (1) or absent (0), p values are for differences between the respective HRCT score groups. Network analyses depict figures for Spearman correlation coefficients, with red lines for positive, blue lines for negative correlations. Correlation coefficients $\leq \pm 0.1$ are represented as thin gray lines without figures. TLC: total lung capacity; FVC: forced vital capacity; HRCT: high-resolution computed tomography; UVA: univariate analysis; MVA: multivariate analysis; BRK: traction bronchiectasis; RET: reticulation; HON: honeycombing; EMP: emphysema; GGO: ground glass opacities; NDL: noduli; CON: consolidations; PAD: pulmonary artery: aortic diameter </≥1; MOS: mosaic attenuation; VOL: volume reduction; SBC: Schwarz Bayesian Information Criterion; PFT: pulmonary function test.

impairment affecting expiratory volume measurements. The absence on an interaction of emphysema with FVC and FEV1 in our analysis is explainable: In patients with both fibrotic ILD and emphysema, volume reduction by fibrosis can counterbalance the augmented volume of emphysema, thus leading to falsely normal lung volumes.[24,27] In patients without ILD, emphysema extent was reported to be negatively correlated to FVC, but positively to TLC.[28]

Due to its retrospective, single-center, registry-based approach this study has several inherent shortcomings that need to be addressed. Its limited number of patients resulting in small sample sizes also in various subgroups limits the validity of multivariate analysis findings. Thus, all reported findings require validation in larger-scale and prospective study settings. The reported collective represents a heterogenous group of several different fibrotic ILD entities unlike most other studies on ILD imaging and PFT that were focused on distinct diagnoses like IPF. Moreover, our study collective was derived from patients subsequently discussed by the local ILD board which could have led to the situation, that rather more complex ILD may have been included, while

			BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
FEV1 (% pred.)	HRCT score models		0-6=83.6 7-18=71.4	0-2=75.4 3-18=79.5	0-17=79.3 18=30	0=79.2 1-18=77.5	0-17=80.3 18=71.7	0-17=78.8 18=79.6	0-3=81.1 4-18=61.1	0=80.8 1=68.2	0=79.3 1=77.7	0=82.1 1=75.1
	p		0.003	0.445	0.015	0.744	0.104	0.924	0.001	0.023	0.728	0.079
	UVA	p	0.016	0.2	0.017	0.905	0.423	0.661	0.006	0.393	0.977	0.565
	MVA	p	0.008		0.016				0.001			



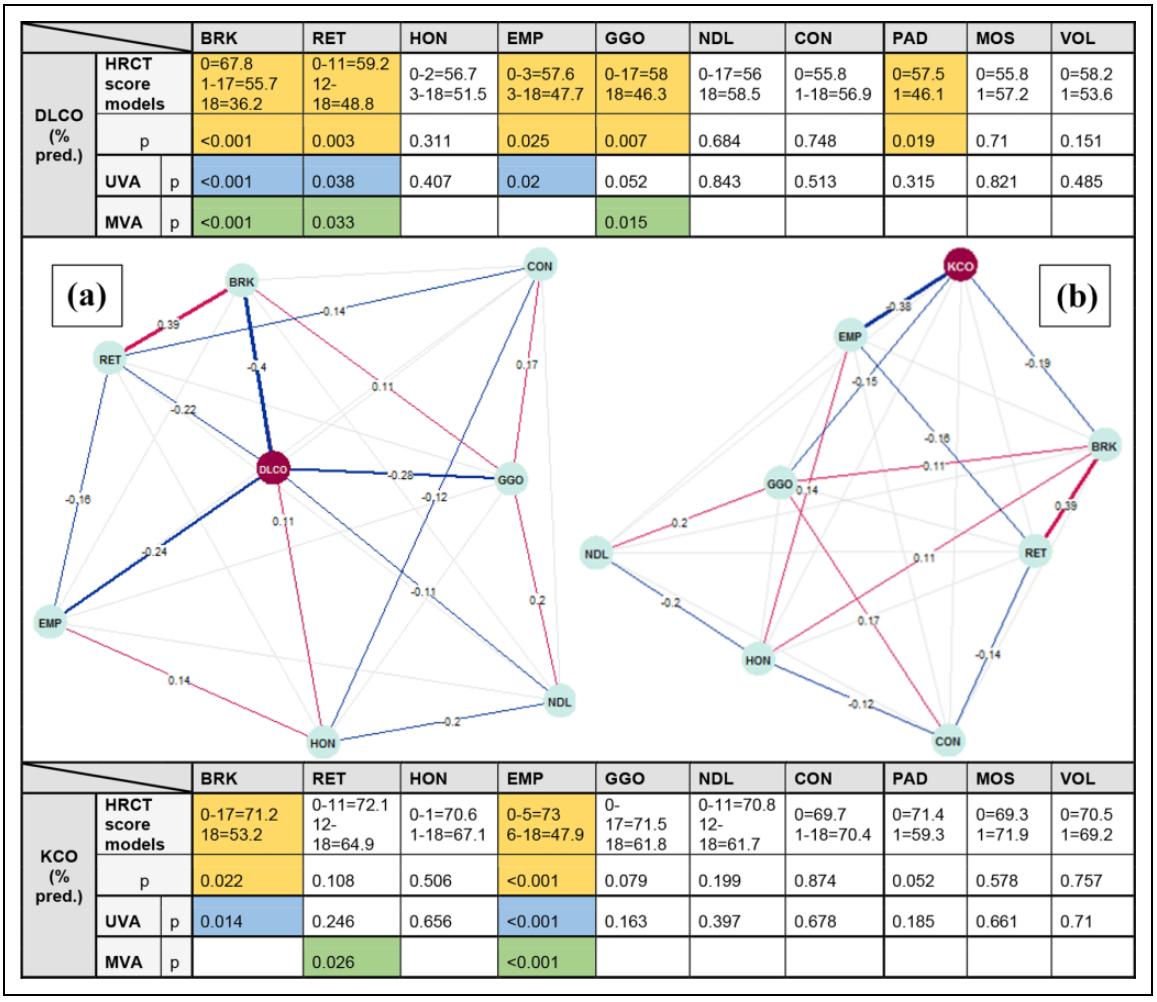
			BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
FEV1/ FVC	HRCT score models		0-1=0.76 2-18=0.81	0-4=0.75 5-18=0.82	0=0.81 1-18=0.77	0=0.82 1-18=0.73	0-17=0.8 18=0.8	0=0.79 1-18=0.81	0=0.81 1-18=0.77	0=0.8 1=0.8	0=0.79 1=0.82	0=0.79 1=0.81
	p		0.014	<0.001	0.109	<0.001	0.992	0.327	0.019	0.597	0.27	0.196
	UVA	p	0.032	0.017	0.283	<0.001	0.782	0.212	0.029	0.946	0.611	0.199
	MVA	p	0.026	0.005		<0.001			0.028			

Figure 2. HRCT score models and network analyses for FEV1 (a) and FEV1/FVC (b). Top lines show SBC-defined HRCT score groups with predicted PFT values; PAD, MOS and VOL are given as present (1) or absent (0), p values are for differences between the respective HRCT score groups. Network analyses depict figures for Spearman correlation coefficients, with red lines for positive, blue lines for negative correlations. Correlation coefficients $\leq \pm 0.1$ are represented as thin gray lines without figures. FEV1: forced expiratory volume in 1 second; FEV1/FVC: FEV1/forced vital capacity; HRCT: high-resolution computed tomography; UVA: univariate analysis; MVA: multivariate analysis; BRK: traction bronchiectasis; RET: reticulation; HON: honeycombing; EMP: emphysema; GGO: ground glass opacities; NDL: noduli; CON: consolidations; PAD: pulmonary artery: aortic diameter </≥1; MOS: mosaic attenuation; VOL: volume reduction; SBC: Schwarz Bayesian Information Criterion; PFT: pulmonary function test.

other more typical ILD may be underrepresented. Due to those points, the comparability of our results is limited. However, with regard to that issue, our analysis did explicitly not focus on diagnostic entities, but on functional alterations and imaging findings in a mixed collective of FILD patients.

Radiological assessment was conducted in a simple, semi-quantitative approach that can be accomplished in a very short time and does not require costly additional tools like special software. Our approach has not been validated in a larger patient cohort, however, using the described statistical modeling approach we have sought to overcome those limitations still allowing for the evaluation of not only the presence, but also the extent of various radiological findings and their influence on PFT variables. Preliminary data on interobserver variability analyses for the reported patient cohort are presented in the Supplementary Appendix.

In conclusion, our findings suggest that the performance of PFT biomarkers to assess physical limitation in fibrotic ILD may substantially differ according to the prevalent radiological findings. These observations could have immediate practical implications: In an FILD patient with concomitant emphysema for example, KCO should rather not be used as a



		BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
DLCO (% pred.)	HRCT score models	0=67.8 1-17=55.7 18=36.2	0-11=59.2 12-18=48.8	0-2=56.7 3-18=51.5	0-3=57.6 3-18=47.7	0-17=58 18=46.3	0-17=56 18=58.5	0=55.8 1-18=56.9	0=57.5 1=46.1	0=55.8 1=57.2	0=58.2 1=53.6
	p	<0.001	0.003	0.311	0.025	0.007	0.684	0.748	0.019	0.71	0.151
	UVA p	<0.001	0.038	0.407	0.02	0.052	0.843	0.513	0.315	0.821	0.485
	MVA p	<0.001	0.033			0.015					

		BRK	RET	HON	EMP	GGO	NDL	CON	PAD	MOS	VOL
KCO (% pred.)	HRCT score models	0-17=71.2 18=53.2	0-11=72.1 12-18=64.9	0-1=70.6 1-18=67.1	0-5=73 6-18=47.9	0-17=71.5 18=61.8	0-11=70.8 12-18=61.7	0=69.7 1-18=70.4	0=71.4 1=59.3	0=69.3 1=71.9	0=70.5 1=69.2
	p	0.022	0.108	0.506	<0.001	0.079	0.199	0.874	0.052	0.578	0.757
	UVA p	0.014	0.246	0.656	<0.001	0.163	0.397	0.678	0.185	0.661	0.71
	MVA p		0.026		<0.001						

Figure 3. HRCT score models and network analyses for DLCO (a) and KCO (b). Top lines show SBC-defined HRCT score groups with predicted PFT values; PAD, MOS and VOL are given as present (1) or absent (0), p values are for differences between the respective HRCT score groups. Network analyses depict figures for Spearman correlation coefficients, with red lines for positive, blue lines for negative correlations. Correlation coefficients $\leq \pm 0.1$ are represented as thin gray lines without figures. DLCO: diffusion capacity for carbon monoxide; KCO: carbon monoxide transfer coefficient; HRCT: high-resolution computed tomography; UVA: univariate analysis; MVA: multivariate analysis; BRK: traction bronchiectasis; RET: reticulation; HON: honeycombing; EMP: emphysema; GGO: ground glass opacities; NDL: noduli; CON: consolidations; PAD: pulmonary artery: aortic diameter </>1; MOS: mosaic attenuation; VOL: volume reduction; SBC: Schwarz Bayesian Information Criterion; PFT: pulmonary function test.

biomarker to monitor increasing fibrosis, as KCO may also largely be affected by emphysema. On the other hand, DLCO may be a good biomarker for follow-up in patients with ground glass opacities, while ILD presenting with consolidations may be depicted well by FVC or FEV1. Our findings require further validation in larger and prospective study settings, and it is likely that in the future, composite biomarkers rather than single PFT variables will be used in trials and in clinical practice. However, in consideration of the essential quest for a more individualized ILD patient care, our current results may represent a first step toward functional assessment individually adjusted to the ILD patient's HRCT appearance.

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Authorship statement

All authors have approved the paper, are able to verify the validity of the results reported and meet the criteria for

authorship as established by the International Committee of Medical Journal Editors.

Data availability statement

As mandated by the ethics committee of Upper Austria, publication or dissemination of any possibly identifiable patient data from the Kepler University Hospital ILD registry is strictly prohibited. The dataset used for the present analyses contains very detailed and thus possibly identifiable patient data, so that a publication of the database is not possible. However, upon reasonable request to the Authors and if permitted by the Ethics Committee of Upper Austria in an amendment to the study protocol, anonymized data may under certain circumstances be shared.

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Supplemental material

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