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Functional and prognostic effects when emphysema complicates idiopathic pulmonary fibrosis

Joseph Jacob[1], Brian J. Bartholmai[2], Srinivasan Rajagopalan[3], Maria Kokosi[4], Toby M. Maher[4], Arjun Nair[1], Ronald Karwoski[3], Elisabetta Renzoni[4], Simon L.F. Walsh[1], David M. Hansell[1], Athol U. Wells[4].

[1]Department of Radiology, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, London, UK.

[2]Division of Radiology, Mayo Clinic Rochester, Rochester, Minnesota, USA.

[3]Department of Physiology and Biomedical Engineering, Mayo Clinic Rochester, Rochester, Minnesota, USA.

[4]Interstitial Lung Disease Unit, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, London, UK.

Corresponding author: Joseph Jacob, 10 Wolsey road, Northwood, Middlesex, UK HA6 2HW.

Tel: 0044 7511033666

Email: joseph.jacob@nhs.net

Authors contributions

JJ, MK, TM, AN, ER, SLFW, AUW, DMH were involved in either the acquisition, or analysis or interpretation of data for the study.

JJ, AUW and DMH were also involved in the conception and design of the study.

BJB, RK and SR invented and developed CALIPER. They were involved in processing the raw CT scans and in generation of figures but were not involved with the analysis or interpretation of the data in the study.

Ethics committee approval

Approval for this study of clinically indicated CT and pulmonary function data was obtained from the Institutional Ethics Committee of the Royal Brompton Hospital and Mayo Clinic and informed patient consent was not required.

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Take home message

Emphysema in IPF patients has no effect on outcome beyond that explained by combined fibrosis and emphysema extents.

Abstract

To investigate whether the combination of fibrosis and emphysema has an effect greater than the sum of its parts on functional indices and outcome in IPF using visual and computer-based (CALIPER) CT analysis.

Consecutive patients (n=272) with a multi-disciplinary IPF diagnosis had CT extents of interstitial lung disease (ILD) scored visually and by CALIPER. Visually-scored emphysema was subcategorized as isolated or mixed with fibrotic lung. CT scores were evaluated against functional indices (FVC, DLco, Kco and CPI) and mortality.

The presence and extent of emphysema had no impact on survival. Results were maintained following correction for age, gender, smoking status and baseline severity using DLco, and combined visual emphysema and ILD extent. Visual emphysema quantitation indicated that relative preservation of lung volumes (FVC) resulted from tractionally-dilated airways within fibrotic lung ventilating areas of admixed emphysema ($p<0.0001$), with no independent effect on FVC from isolated emphysema. Conversely, only isolated emphysema ($p<0.0001$) reduced gas transfer (DLco).

There is no prognostic impact of emphysema in IPF, beyond that explained by the additive extents of both fibrosis and emphysema. Emphysema distribution with respect to the location of pulmonary fibrosis determines the functional effects of emphysema.

KEY WORDS: idiopathic pulmonary fibrosis, quantitative CT of ILD, emphysema

INTRODUCTION

Patients with co-existing emphysema form a sizeable proportion of idiopathic pulmonary fibrosis (IPF) cohorts, [1-4] a possible consequence of an association with smoking pertinent to both diseases.[5, 6] A unique phenotype ascribed to patients with combined fibrosis and emphysema (CPFE) rested with the identification of a worsened survival in patients with CPFE over those with isolated fibrosis. [7-10] The basis for a poor outcome has been suggested to be partly related to an increased predisposition to developing pulmonary hypertension (PHT). [7, 10, 11] However subsequent analyses of CPFE cohorts have provided conflicting data on the survival implications of emphysema coexisting with fibrosis [4, 12-15] and the question of whether the co-existence of pulmonary fibrosis and emphysema constitutes a discreet clinical syndrome remains unresolved. [16, 17] Conflicting CPFE data has also led to a belief that CPFE should be viewed as a different disorder from IPF in terms of progression to death and this in turn has caused some clinicians to have doubts about using anti-fibrotic therapy in CPFE.

A common constraint in the study of CPFE cohorts has been the limited quantification of CT emphysema extent, be that by visual or automated means. Simply ascertaining the presence or absence of emphysema restricts the precision with which a dose-effect of emphysema may be shown to influence survival. Similarly, the delineation and quantitation of emphysematous areas admixed within fibrotic lung as opposed to emphysematous foci isolated from areas of fibrosis has not been definitively examined to date. Yet quantifying emphysematous destruction

within areas of fibrosis may inform and improve our understanding of the complex physiological effects that result from CPFE.[4, 10, 13, 16, 18]

In the current study, we therefore quantified the cumulative (morphological or functional) extents of emphysema and interstitial lung disease (ILD) in patients with IPF, utilizing visual and computer-based CT analysis. Our primary aim was to identify whether a unique synergistic effect exists in IPF patients with emphysema, which results in a worsened outcome to a degree greater than that expected from the cumulative extents of ILD and emphysema. Secondarily we wanted to investigate the functional impact of emphysema when it occurs both separate to and within fibrotic regions of lung in IPF.

METHODS

Clinical data

A retrospective analysis of an ILD database identified all consecutive, newly attending patients, who on re-analysis received a multidisciplinary team (MDT) diagnosis of IPF according to published guidelines, [19] over a four and a half year period (January 2007 to July 2011)[n=283][20]. Following publication of the INPULSIS study[21], all patients with a possible UIP CT pattern were re-examined. 4 patients were found to have a possible UIP pattern without traction bronchiectasis, whilst 7 patients had CT findings inconsistent with a UIP diagnosis and no surgical lung biopsy. Accordingly, following exclusion of these 11 patients, the final study population was 272 IPF patients. All patients had a departmental, non-contrast, supine, volumetric CT.

CT, pulmonary function test protocols and CALIPER data processing steps are included in the supplementary appendix. The study population has been previously described in two studies [20, 22]. Approval for this retrospective study of clinically indicated CT and pulmonary function data was obtained from the institutional ethics committee and informed patient consent was not required.

CT evaluation

CALIPER evaluation was performed as previously described and scores of ILD and emphysema extent and pulmonary vessel volume (PVV) were considered in the analyses.[22] CTs were visually scored on a lobar basis with extents of ILD, emphysema and honeycombing estimated to the nearest 5%. Traction bronchiectasis [23] was

assigned on a lobar basis with a categorical “severity” score as previously described.[22] Calculation of admixed and isolated emphysema extents are explained in the supplementary appendix.

Development of the modeling strategy

In all analyses, adjustment was made for patient age, gender and smoking status. When analyses were re-examined unadjusted, cardinal results did not change. Visual emphysema scores were found to be clearly superior to CALIPER emphysema scores as described in the Supplemenatry Appendix. Therefore in all subsequent analyses, visual emphysema scores were taken as the primary measure of emphysema. When the ILD score that best complimented visual emphysema was examined against our co-primary end points (mortality and relationships to baseline DLco), CALIPER ILD extent was only marginally stronger than visual ILD scores at mortality prediction (Table 6 and Supplementary Table 3). Both ILD measures were therefore used in all subsequent analyses to ensure than conclusions reached when using CALIPER in the model were robust when visual ILD was substituted.

Three separate indices were used to adjust for baseline disease severity in all mortality analyses. The first index was functional, namely DLco. The other two indices were morphological. To enable the evaluation of an extra-effect of CPFE on disease progression in excess of that expected from a combination of fibrosis and emphysema, the combined severity of emphysema and ILD was captured by summing visual emphysema extent scores with ILD extent scores to create two indices of parenchymal damage: CILDemph=CALIPER ILD extent + Visual emphysema

extent; VILDemph=Visual ILD extent + Visual emphysema extent. On linear regession analyses, there was a complete absence of colinearity between visual emphysema presence and CILDemph or VILDemph.

Statistical analysis

Data are given as medians or means with standard deviations depending on distributions, or numbers of patients with percentages where appropriate. Differences between groups were evaluated using a Chi-squared test for categorical variables or a two-sample T test for parametric continuous variables. Statistical significance was evaluated at a value of $p<0.05$. Linear regression analyses were used to identify relationships between CT and functional indices, and PVV and emphysema. Univariate and multivariate Cox regression analyses were used to investigate variables predictive of mortality. Survival estimation was performed via the Kaplan Meier method. Two-sample survival comparisons were performed using the Log rank test. Assumptions of linearity and proportional hazards were tested by visual inspection of Martingale residuals and scaled Schoenfeld residuals and were satisfied. Statistical analyses were performed with STATA (version 12, StatCorp, College Station, TX, USA).

RESULTS

Demographic data

272 patients diagnosed with IPF (Supplementary Figure 1) had vital status completed on 268/272 (99%) cases with 4 patients lost to follow up. 55/272 (20%) cases had biopsy confirmation of the diagnosis. No difference in patient age or gender was identified between patients with and without emphysema. Patients with emphysema were significantly more likely to develop lung cancer however. Demographic details for patients with and without visually scored emphysema are shown in Table 1. The single determination standard deviation for the visual emphysema scores was 4.80 (Supplementary Table 2).[24] The kappa value for interobserver variation scoring of the presence of emphysema was 0.59.

Characterization of the CPFE pulmonary function phenotype

The presence of emphysema was associated with a relative preservation of lung volumes (FVC) whilst disproportionately reducing gas transfer (DLco) and the gas transfer coefficient (Kco). The results were maintained when emphysema was analysed as a continuous extent score (Table 2) and when analysed at thresholds of >0%, >5% and >10% of visual emphysema (Table 3). Linkages between ILD and emphysema extents and DLco are shown in Supplementary Table 3. The increase in FVC with emphysema in multivariate models reflects a relatively diminished FVC reduction for a given extent of fibrosis, and does not imply that emphysema causes an intrinsic rise in FVC.

No relationship was identified between total visual emphysema extent (or its isolated and admixed subcategories) with ILD extent scored either visually or by CALIPER. The extents of both isolated and admixed emphysema were associated with obstructive functional indices as determined by correlations of isolated (R^2=0.32, p<0.0001) and admixed emphysema (R^2=0.14, p<0.0001) with FEV1/FVC ratios.

Characterization of functional effects of emphysema location

Examination of the functional effects of isolated and admixed emphysema demonstrated that isolated emphysema was independently associated with lower DLco and Kco but had no impact on FVC or VA (Table 4). Admixed emphysema was associated with preserved FVC and VA with no independent effect on DLco, and opposing effects on VA and Kco (Table 4).

Effects of supervening emphysema on CT markers of fibrosis

Evaluation of CT determinants of traction bronchiectasis demonstrated that emphysema had a negative correlation with traction bronchiectasis whilst ILD extent and honeycombing demonstrated positive correlations (Table 5). When isolated and admixed emphysema were substituted for total emphysema extent in the same model, only admixed emphysema demonstrated a strong negative linkage with traction bronchiectasis (Table 5).

The pulmonary vessel volume has been previously shown to strongly predict outcome in patients with IPF[20], and consequently links between PVV and

emphysema were explored. After adjusting for the extent of ILD scored by CALIPER (Beta Coefficient=0.08, CI 0.08 to 0.09, p<0.0001), the presence of emphysema (Beta Coefficient=-0.31, CI -0.52 to -0.10, p=0.005) was independently associated with a minor (6.0%) reduction in PVV (mean PVV=5.13%) with a model R^2=0.75.

Impact of emphysema on survival in IPF

On univariate analysis, when emphysema was evaluated as a continuous variable, a binary absence-presence score or as a four-point categorical variable (0=no emphysema, 1=0-5% emphysema, 2=5-15% emphysema, >15% emphysema),visually scored emphysema did not significantly predict mortality (Table 6). The presence of emphysema did not alter outcome on Kaplan-Meier analyses (Figure 2a) with results maintained in patients with severe disease (DLco<35% predicted)[Figure 2b].

Emphysema is, on average, much less extensive than pulmonary fibrosis. For this reason, there is much less variation in the extent of emphysema than in the extent of fibrosis. Therefore, the prognostic value of variation in the extent of emphysema is overpowered/confounded in univariate analysis because the highly variable extent of associated pulmonary fibrosis is not taken into account. On multivariate analysis however (Table 6), visual emphysema (on a four-point scale) was independently predictive of mortality when analysed against and adjusted for CALIPER ILD extent. Neither isolated nor admixed emphysema extents were predictive of survival following correction for global disease extent (using DLco).

Outcome adjusted for summed models of disease severity

On univariate mortality analyses, summed CALIPER ILD extent and visual emphysema extent (CILDemph) and summed visual ILD extent and visual emphysema extent (VILDemph) both strongly predicted outcome (Table 7). CILDemph and VILDemph also demonstrated strong linkages with with DLco (R^2=0.43, p<0.0001 and R^2=0.45, p<0.0001 respectively)[Supplementary Table 3].

When separately adjusting for disease severity (using CILDemph, VILDemph and DLco), the presence of emphysema did not independently predict mortality (Table 7), with results maintained in patients with severe disease (DLco<35% predicted)[Supplementary Table 4].

As separate contributors to severity, emphysema and fibrosis both had added linkage to mortality. However, once the total extent of disease was summed (as a combined fibrosis and emphysema score), it was immaterial (in terms of predicting mortality) whether the total extent of disease was due to pulmonary fibrosis alone or a combination of pulmonary fibrosis and emphysema. As well as there being no evidence that CPFE was greater than the sum of its parts in predicting mortality, no link to more progressive disease (as judged by greater mortality for a given extent of disease) was identified in CPFE following correction for the combined effects of emphysema and ILD. The multivariate analysis was possible only because there was very little difference in the total extent of disease whether or not emphysema was present and no collinearity between the total extent score and the presence or absence of emphysema was present.

DISCUSSION

Our study has shown that in a large consecutive IPF patient cohort, using a combination of visual emphysema analysis and computer-based ILD quantitation, neither the presence nor the extent of emphysema impacts survival following correction for baseline disease severity. For the first time, we have demonstrated the opposing effects on pulmonary volumes and gas transfer when emphysema lies primarily admixed within areas of fibrosis. We have furthermore demonstrated the inverse relationship that exists between admixed emphysema and traction bronchiectasis, a validated CT marker of fibrosis.

In past evaluations of IPF patients with emphysema, analysis has concentrated on those CPFE patients in whom emphysema is extensive. In the CPFE study by Cottin et al [7] patient selection rested on the recollection by clinicians of patients with concomitant emphysema and fibrosis. The possibility that a significant proportion of these cases had unusually extensive emphysema is suggested by the finding that 30/61 (49%) patients in their study [7] had an obstructive ventilatory defect (FEV1/FVC <70% predicted) compared to the current study where only 2/101 (2%) patients with emphysema demonstrated an obstructive defect. Studies have also defined non-validated emphysema extent thresholds such as >10% of the lung in their CPFE inclusion criteria. [4, 10] In the current study only 35/105 (33%) of CPFE patients had an extent of emphysema >10% of the lung.

There is little evidence that cohort-wide estimations of the phenomenon of CPFE and its impact have been adequately studied. It would seem logical that once

population based assessments of emphysema have been made in IPF across the range of disease severity, as was the aim of the current study, questions relating to useful thresholds for emphysema extent could subsequently be addressed. Indeed whilst emphysema thresholds per se may have value, greater importance may lie with delineating the predominant pathology in any single patient, namely deciding whether emphysema is more extensive in the lungs than fibrosis. In this regard, technological advances used in the current study, that were not available to prior investigations describing CPFE, may help improve the characterization of both emphysema and fibrosis extent. In addition to the utilization of automated CT quantitation which can improve on visual CT evaluation of ILD extent,[20, 22] we utilized volumetric CT acquisitions which allow the visual quantitation of emphysema and visual and computer-based quantitation of ILD across the entire lung volume, rather than at sampled interspaced levels.

In line with previous reports, in our study, IPF did not progress at a faster trajectory when emphysema co-existed. [4, 12] Instead prognosis in CPFE was more heavily aligned with baseline disease severity. The continued discordance in fundamental outcome measures such as mortality between CPFE reports [4, 7, 10, 12] argues for a pressing need for a definition, which doesn't currently exist, of what constitutes CPFE. An international initiative to agree on a CPFE definition is clearly warranted to curtail a real danger that future studies in CPFE cannot be integrated.

Our study findings provide further confirmation of the unique functional profile that occurs when emphysema co-exists with IPF. [4, 7, 10, 13, 18] Emphysema preserves lung

volumes, limiting the utility of FVC to act as an index to adjust for baseline disease severity in CPFE. CPI is negated in CPFE as it only measures the functional impact of fibrosis and not emphysema. It is DLco that represents the cardinal functional index in CPFE patients as it reflects the contribution of both interstitial fibrosis and emphysema to the reduction of gas exchange. The strength of DLco as a measure of disease severity in CPFE was confirmed by the strikingly similar results in our study when DLco and indices reflecting cumulative pulmonary damage (summed visual or CALIPER ILD and visual emphysema extents) were used to control for baseline disease severity. In turn the similarities in analyses between morphological scores and DLco validated our chosen methodological approach of combining quantitative and visual CT measures.

The clinical observations of the current study were made more robust by the utilization of independent methods of scoring ILD extent. Integrating automated and visual analysis is valuable, for example in our analyses, we selected those variables for which CALIPER is a strength (precision in delineating ILD extent) and those variables for which expert visual judgments are a requisite (distinguishing admixed emphysema from honeycomb cysts). Had a strategy of utilizing only automated scores been adopted in the current study, the distinct functional effects of admixed emphysema would not have been discovered. Whilst subjective and, increasingly, automated scoring have their proponents, the best model may be a combination of both modalities. A recent study by Araki et al[25] in a large Framingham Heart study cohort elegantly highlighted the constraints that can result when relying solely on an automated method of quantitation of interstitial lung abnormalities (ILA's). The

subtle differentiation of minor fibrotic changes as is seen in respiratory bronchiolitis, from abnormalities that are more compatible with early IPF such as sub-pleural reticular abnormalities are as yet not possible with automated systems and such analyses can be enhanced by the addition of visual ILA characterization.

Most studies evaluating emphysema in IPF have been hampered, as previously described, by limitations in the CT quantitation of fibrosis and emphysema extents. [4, 10, 15, 26] Automated quantitation studies meanwhile have been hampered by small sample sizes, [8, 27-30] and the challenges of distinguishing emphysema from honeycomb cysts or traction bronchiectasis. The challenge of separating emphysema from honeycombing by a computer tool remains unmet and was the reason for the reliance on visual emphysema scores for emphysema quantitation and characterization in the current study analyses.

Uniquely, we have identified that pure and admixed emphysema are associated with distinct functional consequences. Admixed emphysema preserved lung volumes including FVC and VA, in contrast to isolated emphysema. Emphysema is typically associated with air-trapping as a result of airway narrowing and collapse on expiration as bullous spaces fail to deflate. [31] In areas of fibrosis however, contraction of the interstitial connective tissue framework can pull open small airways, [32] visible on CT as traction bronchiectasis, [33] thereby allowing the ventilation of emphysematous airspaces with a consequent preservation of FVC and VA. In our analyses, a reduction in DLco values was primarily related to the extent of ILD and not admixed emphysema. The destruction of capillary beds in areas of isolated

emphysema are thought to inhibit gas transfer (DLco), by reducing the blood volume within the lungs. However in areas of admixed emphysema, vascular destruction may be a consequence of both fibrotic and emphysematous processes. Emphysema had a greater impact on Kco than the ILD extent scored visually or by CALIPER, reproducing previous findings.[1] However preservation of alveolar volume by admixed emphysema did influence the gas transfer coefficient, which is synonymous with DLco/VA.

The severity of traction bronchiectasis, a cardinal morphological measure of disease severity in IPF,[20, 34] was found to inversely relate to the extent of emphysema (admixed) in the present study in keeping with a previous report. [35] Whilst traction bronchiectasis enables bullae to remain ventilated, the emphysema-induced parenchymal damage that precedes interstitial fibrosis may limit the degree to which airways can be pulled open by a contracted and fibrosed connective tissue scaffold, when compared to areas of fibrosis without admixed emphysema. The relative reduction in ILD extent in CPFE patients compared to IPF patients in the current study are in accordance with previous results [4] and may reflect earlier recognition of symptoms of dyspnea, in a patients IPF disease course as emphysema reduces a patients functional reserve.

The PVV was shown to be reduced by 6% in IPF patients with emphysema and may reflect alveolar and capillary destruction in emphysema[36] resulting in reduced vascularity quantified by CALIPER within regions of emphysematoid lung. It has also been suggested that the high negative intrathoracic pressures required for

inspiration in patients with fibrosis may exert a pull on pulmonary vessel walls, and thereby result in an increase in the PVV. Consequently, when emphysema co-exists with fibrosis, a relative reduction in intrathoracic pressures may result in a slight reduction in the PVV when compared to patients with fibrosis alone.

In our study, when correcting for the visual extent of emphysema and at thresholds of >5% and >10% visual emphysema, smoking status had an independent effect on pulmonary function impairment. Specifically, a positive smoking history elevated FVC and reduced Kco by 6%, results which are very similar to that noted in a contemporaneous study evaluating the effects of smoking and emphysema in scleroderma.[37] However a report by Wells et al [1] demonstrated that after correcting for the presence of emphysema, smoking status had no independent effect on pulmonary function impairment. Though a smoking history would at first appear at odds with FVC elevation and Kco retardation the effects might simply reflect a link with emphysema secondary to smoking. As visual evaluation of a CT may only capture a proportion of the emphysema present within the lungs, the emergence of a statistically significant smoking history may indicate that emphysema extent has been underestimated by visual scores; a phenomenon that appears greatest at extremes of emphysema extent.

There were some limitations to the current study. Histopathological proof of an IPF diagnosis was lacking in the majority of patients, but all cases were reviewed according to current diagnostic and treatment guidelines [19] in what is now the accepted standard of an MDT setting. Distinguishing admixed emphysema from

honeycomb cysts is associated with poor inter-observer agreement, [38] and may have limited the reliability with which the emphysema extent was visually characterized. However the negative correlations between the admixed emphysema scores and the FEV1/FVC ratio, indicate that for the most part, honeycomb cysts were not being misclassified as emphysema.

In conclusion, we have demonstrated that it is baseline disease severity that determines outcome in a patient with IPF and that co-existing emphysema does not have an additional negative impact on outcome. We have demonstrated that DLco, by capturing the effects of both interstitial damage and emphysema is the optimal measure of disease severity when emphysema co-exists with fibrosis. Our study has also highlighted the physiological subtleties that develop when emphysema is both isolated from and admixed within areas of fibrosis.

Declaration of Interests

Dr. Jacob reports personal fees from Boehringer Ingleheim.

BJB, RK, SR report a grant from the Royal Brompton Hospital during the conduct of the study; another from Imbio, LLC, was outside the submitted work; and all have a patent: SYSTEMS AND METHODS FOR ANALYZING IN VIVO TISSUE VOLUMES USING MEDICAL IMAGING DATA licensed to Imbio, LLC.

TMM has, via his institution, received industry-academic funding from GlaxoSmithKline R&D, UCB and Novartis and has received consultancy or speakers fees from Apellis, Astra Zeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, GlaxoSmithKline R&D, Lanthio, InterMune, ProMetic, Roche, Sanofi-Aventis, Takeda and UCB.

Dr. Renzoni reports personal fees from Roche, personal fees from Boehringher, personal fees from Takeda, outside the submitted work.

Dr. Wells reports personal fees from Intermune, personal fees from Boehringer Inlgeheim, personal fees from Gilead, personal fees from MSD, personal fees from Roche, personal fees from Bayer, personal fees from Chiesi, outside the submitted work.

Dr. Walsh reports personal fees from Boehringer Ingleheim, personal fees from Roche, outside the submitted work.

Dr. Hansell reports personal fees from AstraZeneca, grants and personal fees from Intermune, personal fees from Boehringer Inlgeheim, personal fees from Sanofi, personal fees from Glaxo Smith Klein, personal fees from Roche, outside the submitted work.

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Variable Units are percentage unless stated	Group 1 No emphysema (n=167 unless stated)	Group 2 Visual Emphysema (n=105 unless stated)	Group Comparison
Median Age (years)	67	66	=0.05*
Male/female (ratio)	126/41	85/20	=0.29*
Survival (alive/dead)	49/118	22/83	=0.15*
Never/ever-smokers (ratio)	82/85	14/91	<0.0001*
Pack year history (years)	21.0 ± 14.6 (80)	35.0 ± 24.2 (84)	<0.0001^
Lung Cancer prevalence	1.2	9.5	=0.001*
FEV1 % predicted	67.7 ± 19.3 (149)	75.5 ± 17.8 (101)	=0.002^
FVC % predicted	62.9 ± 19.1 (149)	76.8 ± 19.1 (101)	<0.0001^
FEV1/FVC % predicted	108.4 ± 8.8 (149)	100.0 ± 12.8 (101)	<0.0001^
DLco % predicted	36.7 ± 13.4 (150)	35.6 ± 12.0 (97)	=0.52^
Kco % predicted	74.8 ± 17.5 (150)	61.5 ± 18.6 (97)	<0.0001^
TLC% predicted	59.0 ± 14.3 (143)	70.2 ± 15.7 (96)	<0.0001^
CPI	57.0 ± 11.7 (146)	52.4 ± 10.5 (92)	=0.001^
CALIPER ILD extent	29.3 ± 18.5	21.9 ± 16.2	=0.001^
Visual ILD extent	49.3 ± 17.7	44.0 ± 18.8	=0.02^
Visual TxBx	7.6 ± 3.2	6.5 ± 3.2	=0.008^

Table 1. Characteristics of IPF patients with and without emphysema. Variables examined include: patient demographic details and measures of pulmonary function indices, CALIPER and visually scored CT parameters. Data represent mean values with standard deviations unless otherwise stated. Significant differences between mean ranks of the two groups were calculated using the Chi-Square test for categorical independent variables (*) and the T test for continuous variables (^). FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, Kco=carbon monoxide transfer coefficient, TLC=total lung capacity, CPI=composite physiologic index, ILD=interstitial lung disease, TxBx=traction bronchiectasis, NS=not significant.

	Pulmonary function test	CT Pattern	Beta Coefficient	95% Confidence Interval	P value	Model R^2
Visual ILD and emphysema evaluation	FVC	Emphysema	0·48	0·28, 0·68	<0·0001	0·38
		ILD extent	-0·49	-0·60, -0·38	<0·0001	
	DLco	Emphysema	-0·34	-0·45, -0·22	<0·0001	0·49
		ILD extent	-0·49	-0·55, -0·42	<0·0001	
	Kco	Emphysema	-0.88	-1.06, -0.70	<0·0001	0.44
		ILD extent	-0.42	-0.53, -0.42	<0·0001	
	CPI	Emphysema	-0.02	-0.12, 0.09	0.76	0·47
		ILD extent	0·44	0·37, 0·50	<0·0001	
CALIPER ILD and visual emphysema evaluation	FVC	Emphysema	0.31	0.13, 0.49	0.001	0·52
		ILD extent	-0.67	-0·77, -0·57	<0·0001	
	DLco	Emphysema	-0·44	-0·56, -0.32	=0·0001	0·44
		ILD extent	-0·49	-0·56, -0·41	<0·0001	
	Kco	Emphysema	-0.91	-1.10, -0.71	<0·0001	0.33
		ILD extent	-0.23	-0.35, -0.11	0·0002	
	CPI	Emphysema	0.09	-0.02, 0.19	0.10	0·50
		ILD extent	0·47	0·41, 0·54	<0·0001	

Table 2. Relationships between pulmonary function indices (FVC, DLco, Kco and CPI) and visual and CALIPER interstitial lung disease extents and visual emphysema extent calculated using multivariate linear regression. The table is similar to Table 6, but instead of evaluating thresholds of emphysema, total emphysema extent was analysed in each model. All CT variables were calculated as a percent of total lung volume. In all models, adjustment was made for patient age, gender and smoking status (never vs ever). CT= Computed tomography, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, Kco= carbon monoxide transfer coefficient, CPI=composite physiological index, ILD=interstitial lung disease.

PFT	CALIPER ILD extent (percent)	Visual emphysema threshold	Smoking status (never vs ever)	Equation R^2
FVC	-0.7 (-0.8,-0.6) p<0.0001	7.7 (3.8,11.7) p=0.0001	5.2 (1.5,8.9) p=0.006	0.53
DLco	-0.5 (-0.5,-0.4) p<0.0001	-5.0 (-7.9,-2.0) p=0.001	-0.0 (-2.7,2.7) p=0.99	0.36
Kco	-0.2 (-0.3,-0.1) p=0.005	-13.5 (-18.4,-8.7) p<0.0001	-4.8 (-9.3,-0.3) p=0.04	0.20
CPI	0.5 (0.4,0.5) p<0.0001	-0.1 (-2.5,2.2) p=0.92	-1.5 (-3.7,0.7) p=0.18	0.49
FVC	-0.7 (-0.8,-0.6) p<0.0001	9.0 (4.2,13.9) p=0.0003	5.9 (2.3,9.5) p=0.001	0.52
DLco	-0.5 (-0.5,-0.4) p<0.0001	-10.3 (-13.7,6.9) p<0.0001	-0.5 (-2.0,3.0) p=0.70	0.41
Kco	-0.2 (-0.3,-0.1) p=0.001	-23.4 (-29.0,-17.9) p<0.0001	-4.4 (-8.5,-0.3) p=0.04	0.31
CPI	0.5 (0.4,0.5) p<0.0001	-1.9 (-0.9,4.8) p=0.19	-1.9 (-4.1,0.2) p=0.07	0.49
FVC	-0.7 (-0.8,-0.6) p<0.0001	10.2 (4.7,15.7) p=0.0003	6.1 (2.5,9.7) p=0.001	0.52
DLco	-0.5 (-0.5,-0.4) p<0.0001	-11.7 (-15.6,-7.8) p<0.0001	-0.3(-2.3,2.8) p=0.83	0.41
Kco	-0.2 (-0.3,-0.1) p=0.002	-25.2 (-31.5,-18.9) p<0.0001	-5.2 (-9.3,-1.0) p=0.02	0.29
CPI	0.5 (0.4,0.5) p<0.0001	-2.2 (-1.1, 5.4) p=0.91	-1.9 (-4.0,0.2) p=0.08	0.49

Table 3. The independent effects of CALIPER ILD extent and thresholds of visual emphysema on various pulmonary function indices (FVC, DLco, Kco, CPI). In all models adjustment was made for patient age, gender and smoking status (never vs ever). Emphysema extent thresholds that were examined included: >0% visual emphysema (white), >5% visual emphysema (light grey), >10% visual emphysema (dark grey). CALIPER ILD extent was quantified as a percentage of the lung; emphysema was categorized as presence above the relevant threshold; smokers were categorized as never or ever smokers. PFT=pulmonary function test, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, Kco=carbon monoxide transfer coefficient, ILD=interstitial lung disease.

PFT	CT Pattern	Beta Coefficient	95% Confidence Interval	P value	Model R^2
FVC	Isolated Emphysema	0.20	-0.22, 0.63	0.35	0·38
	Admixed Emphysema	0.73	0.36, 1.11	=0.0002	
	ILD extent	-0·51	-0·62, -0·39	<0·0001	
	Smoking status	6.30	1.88, 10.71	0.005	
DLco	Isolated Emphysema	-0·51	-0·75, -0·27	<0·0001	0·50
	Admixed Emphysema	-0.19	-0.40, 0.03	0.09	
	ILD extent	-0·50	-0·57, -0·43	<0·0001	
	Smoking status	-0.11	-2.64, 2.43	0.94	
Kco	Isolated Emphysema	-1.01	-1.39, -0.63	<0·0001	0.44
	Admixed Emphysema	-0.79	-1.12, -0.45	<0.0001	
	ILD extent	-0.43	-0.54, -0.32	<0·0001	
	Smoking status	-5.70	-9.68, -1.41	0·005	
VA	Isolated Emphysema	0.15	-0.16, 0.46	0.35	0·38
	Admixed Emphysema	0.48	0.20, 0.76	=0·001	
	ILD extent	-0·43	-0.52, -0·35	<0·0001	
	Smoking status	3.86	0.60, 7·11	=0.02	

Table 4. Associations between subtypes of emphysema (percentage of the lung comprising emphysema separate to or admixed with fibrosis) and various lung function indices (FVC, DLco, Kco and VA) examined using multivariate linear regression. For example, only isolated emphysema and not admixed emphysema was associated with DLco in a combined model. All models were adjusted for baseline visual interstitial lung disease (ILD) extent as a percentage of the lung, age, gender and smoking status (never vs ever). ILD and emphysema extents were calculated as a percent of total lung volume. PFT=pulmonary function test, CT= Computed tomography, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, Kco= carbon monoxide transfer coefficient, VA=alveolar volume.

	CT Pattern	Beta Coefficient	95% Confidence Interval	P value	Model R^2
Visual	Emphysema extent	-0.06	-0.09, -0.03	<0.0001	0·51
	Honeycombing	0.10	0.07, 0.12	<0.0001	
	ILD extent	0·06	0·05, 0·08	<0·0001	
Visual	Isolated Emphysema	-0.07	-0.13, -0.01	0.02	0.51
	Admixed Emphysema	-0.06	-0.11, -0.00	0.04	
	Honeycombing	0.10	0.07, 0.12	<0.0001	
	ILD extent	0·06	0·05, 0·08	<0·0001	
CALIPER	Emphysema extent*	-0.10	-0.14, -0.07	<0.0001	0·36
	Honeycombing	0.84	0.64, 1.05	<0·0001	
	ILD extent	0·06	0·04, 0·07	<0·0001	

Table 5. Visually and CALIPER scored CT determinants of traction bronchiectasis severity evaluated using multivariate linear regression. For example visually scored emphysema extent, ILD extent and honeycombing extent all expressed as a percentage of the lung were all independently associated with traction bronchiectasis severity. All models were adjusted for patient age, gender and smoking status (never vs ever). *Emphysema was only quantified visually. CT= Computed tomography, ILD=interstitial lung disease.

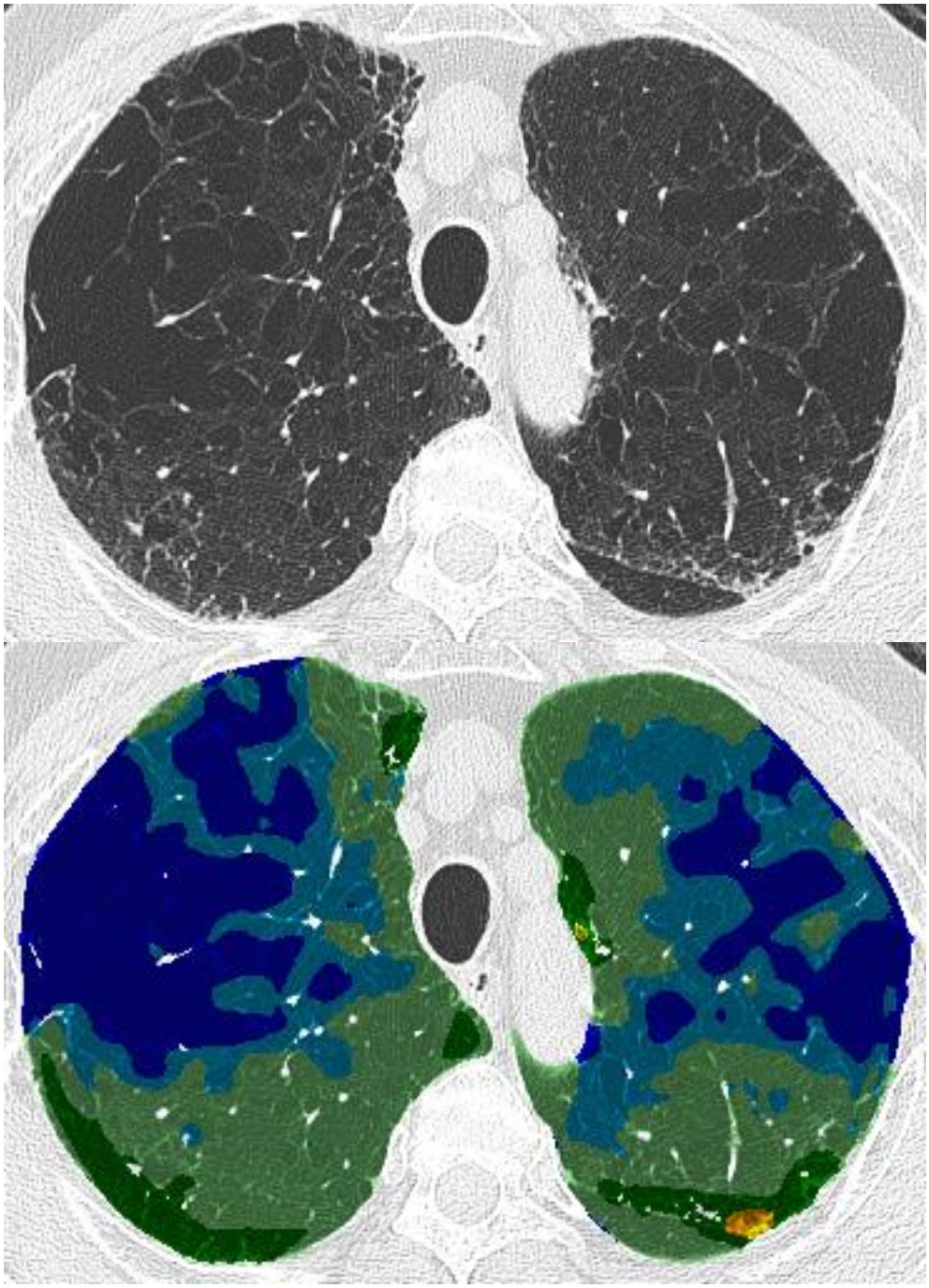
Baseline variables	Hazard ratio	P Value	95.0% Confidence Interval	
			Lower	Upper
Visual Emphysema (continuous)	1.01	0.18	1.00	1.02
Visual Emphysema (categorical)	1.10	0.17	0.96	1.25
Visual Emphysema (presence)	1.18	0.26	0.89	1.56
Visual ILD extent	1.03	<0.0001	1.02	1.04
CALIPER Emphysema	1.00	0.84	0.98	1.03
CALIPER ILD extent	1.03	<0.0001	1.03	1.04
CILDemph	1.03	<0·0001	1.03	1.04
VILDemph	1.02	<0.0001	1.02	1.03
FVC	1.07	<0·0001	1.06	1.08
DLco	1.04	<0·0001	1.03	1.05
CPI	1.07	<0.0001	1.05	1.08

Table 6. Univariate CALIPER and visually derived CT variables and pulmonary function indices predictive of mortality using Cox proportional hazards regression models. Visual emphysema was scored as a continuous variable, as a 4-point categorical variable (0=no emphysema, 1=0-5% emphysema, 2=5-15% emphysema, >15% emphysema) and as a binary, absence-presence variable. ILD=interstitial lung disease, CILDemph=summed total of CALIPER ILD extent and visual emphysema extent, VILDemph= summed total of visual ILD extent and visual emphysema extent, FVC=forced vital capacity, DLco=diffusing capacity for carbon monoxide, CPI=composite physiologic index.

Patient subset	Baseline severity and emphysema models	Hazard ratio	P Value	95.0% Confidence Interval	
				Lower	Upper
All patients	Visual Emphysema categorical	1.23	=0.006	1.06	1.43
	CALIPER ILD extent	1.04	<0·0001	1.03	1.04
	Visual Emphysema categorical	1.13	0.09	1.08	1.31
	Visual ILD extent	1.03	<0·0001	1.02	1.04
Model 1	CILDemph	1.03	<0.0001	1.03	1.04
	Visual Emphysema presence	0.93	0.67	0.68	1.29
Model 2	VILDemph	1.03	<0.0001	1.02	1.03
	Visual Emphysema presence	0.94	0.73	0.68	1.30
Model 3	DLco	0.94	<0·0001	0.93	0.95
	Visual Emphysema presence	0.98	0.93	0.71	1.37
Model 1	CILDemph	1.03	<0·0001	1.03	1.04
	Visual Emphysema categorical	0.91	0.20	0.78	1.05
Model 2	VILDemph	1.03	<0.0001	1.02	1.04
	Visual Emphysema categorical	0.88	0.11	0.75	1.03
Model 3	DLco	0.94	<0.0001	0.93	0.95
	Visual Emphysema categorical	0.97	0.68	0.83	1.13

Table 7. Multivariate Cox proportional hazards regression models. In an examination of all patients in the cohort (n=272), baseline ILD extent scored using CALIPER and visual assessment were separately evaluated in models against visual emphysema extent. Visual emphysema was scored as a 4-point categorical variable (0=no emphysema, 1=0-5% emphysema, 2=5-15% emphysema, >15% emphysema). In a separate subanalysis of patients with severe/end stage disease (n=130/272), two morphological measures of baseline disease severity were analysed. The first represented the combination of visual emphysema scores with CALIPER-derived ILD extent: CILDemph (Model 1) and the second represented the combination of visual emphysema scores with visually-derived ILD extent: VILDemph (Model 2). A third measure of baseline disease severity was a functional severity measure: DLco (Model 3). To evaluate whether the presence of emphysema had any impact on outcome

after adjusting for total baseline disease severity, all three models were separately evaluated alongside the presence of emphysema and the four-point categorical emphysema score. All models were adjusted for patient age, gender and smoking status (never vs ever).



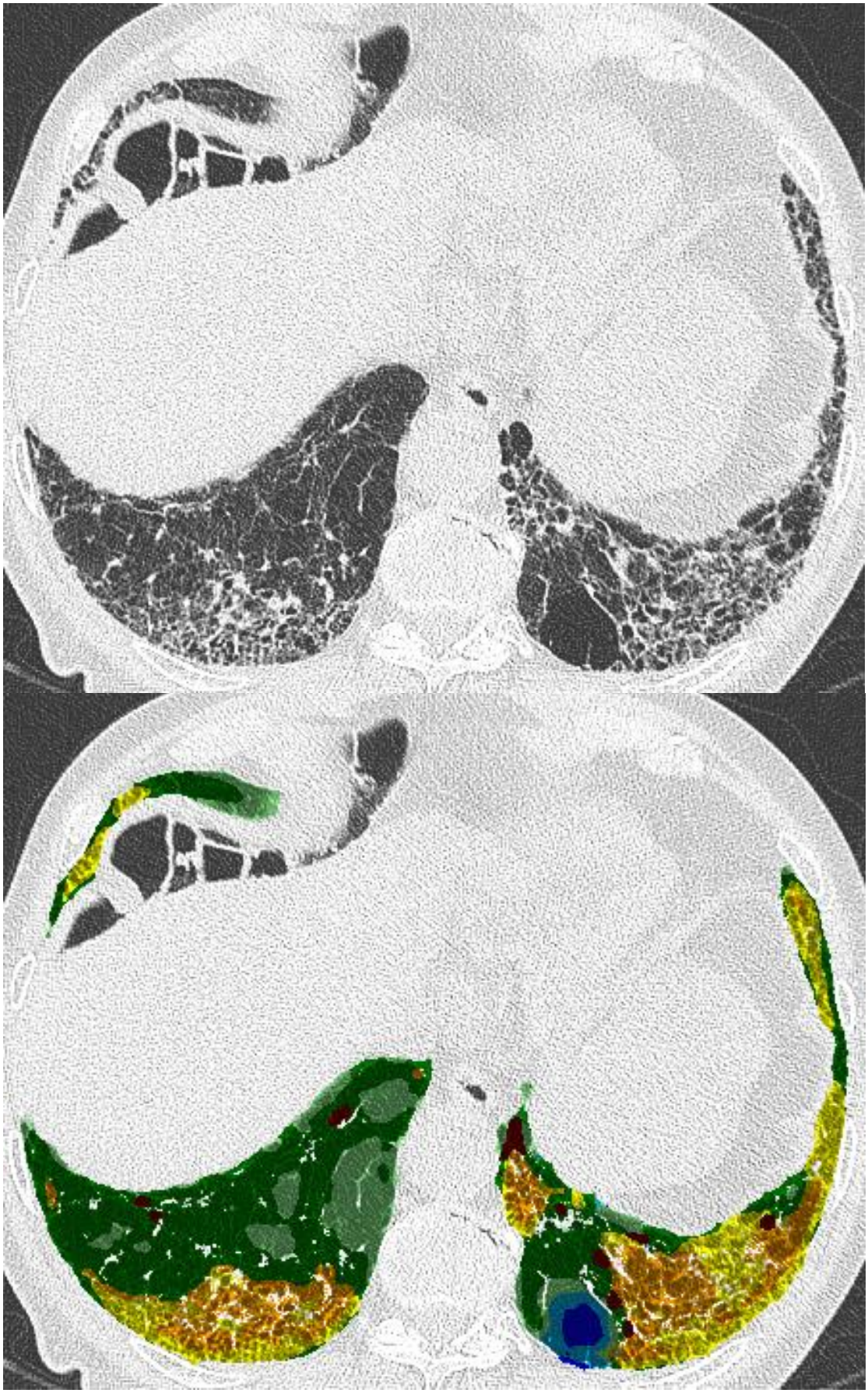


Figure 1. Axial CT images and colour overlay images demonstrating quantitation of parenchymal patterns by CALIPER in a 71-year-old male ex-40-pack-year smoker diagnosed with IPF. CT images (a+c) demonstrate severe emphysema in the upper lobes, and fibrosis characterized primarily by reticular pattern and traction bronchiectasis in the lower lobes, with an emphysematous bulla in the left lower lobe. On visual scoring, 40% of the lung was characterized as emphysema, whilst 31% was identified as interstitial lung disease. The CALIPER overlay images (b+d) outline emphysema (light and dark blue) in the upper lobes, quantified as 23% of the lung volume. The sum of ground glass opacities (yellow), reticular pattern (orange) and honeycombing (brown) constitute total interstitial lung disease extent which was quantified as 7.5% of the lung. CALIPER defines light and dark green areas as normal lung.

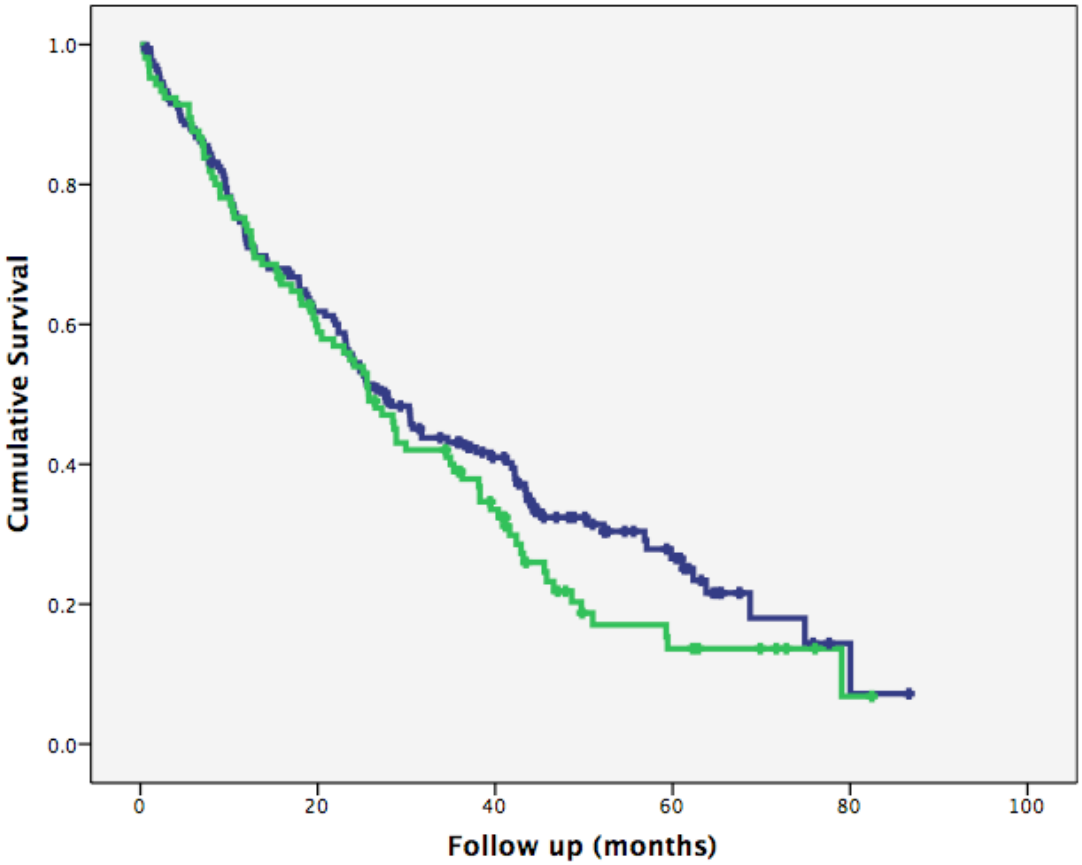


Figure 2a. Kaplan Meier survival curves were not found to be significantly different in outcome between IPF patients without any visually scored emphysema on CT (blue; n=167, restricted mean survival=36.5±2.3), and IPF patients with emphysema scored visually on CT (green; n=105, restricted mean survival=32.0±2.5). Log rank test p=0.20.

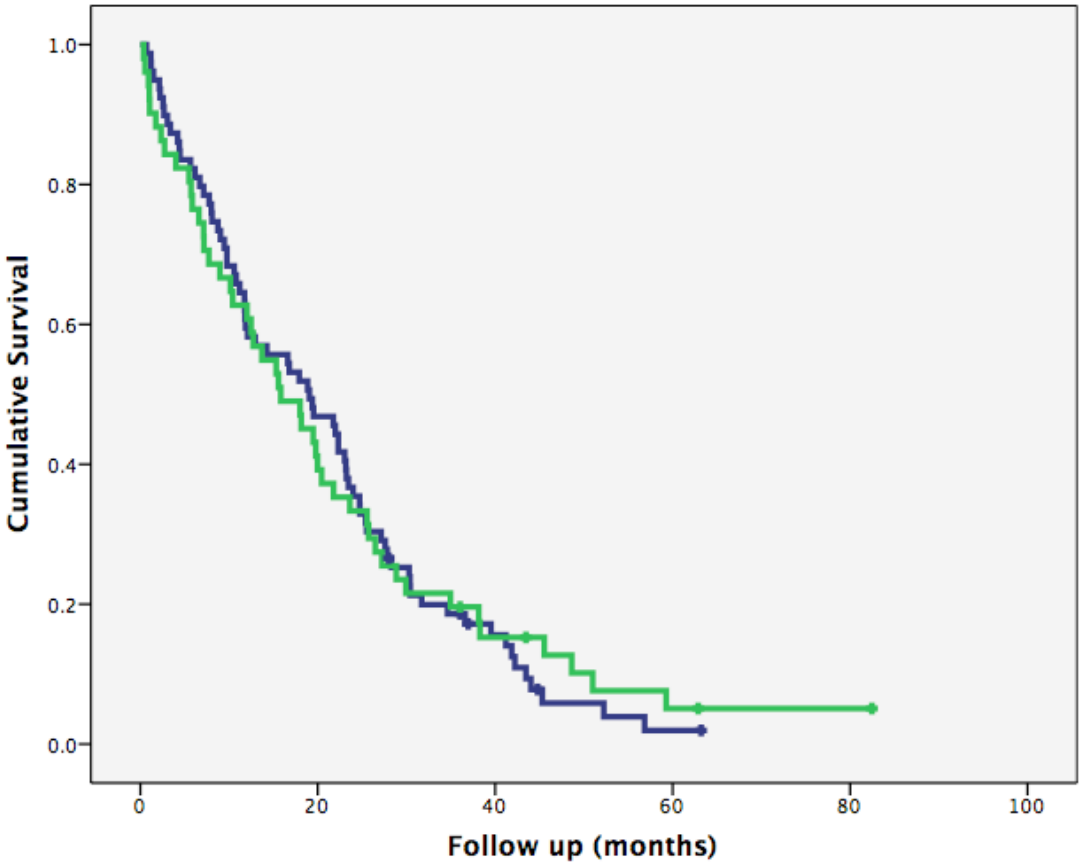


Figure 2b. Kaplan Meier survival curves were not found to be significantly different in outcome between IPF patients with a baseline DLco<35 without any visually scored emphysema on CT (blue; n=79, restricted mean survival=20.9±1.8), and IPF patients with emphysema scored visually on CT (green; n=51, restricted mean survival=21.8±2.9). Log rank test p=0.84.

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