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FULL PAPER

Filtration-histogram based texture analysis and CALIPER based pattern analysis as quantitative CT techniques in idiopathic pulmonary fibrosis: head-to-head comparison

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Objective To assess the prognostic performance of two quantitative CT (qCT) techniques in idiopathic pulmonary fibrosis (IPF) compared to established clinical measures of disease severity (GAP index).

Methods: Retrospective analysis of high-resolution CT scans for 59 patients (age 70.5 ± 8.8 years) with two qCT methods. Computer-aided lung informatics for pathology evaluation and ratings based analysis classified the lung parenchyma into six different patterns: normal, ground glass, reticulation, hyperlucent, honeycombing and pulmonary vessels. Filtration histogram-based texture analysis extracted texture features: mean intensity, standard deviation (SD), entropy, mean of positive pixels (MPPs), skewness and kurtosis at different spatial scale filters. Univariate Kaplan–Meier survival analysis assessed the different qCT parameters' performance to predict patient outcome and refine the standard GAP staging system. Multivariate cox regression analysis assessed the independence of the significant univariate predictors of patient outcome.

Results The predominant parenchymal lung pattern was reticulation (16.6% ± 13.9), with pulmonary vessel percentage being the most predictive of worse patient outcome (p = 0.009). Higher SD, entropy and MPP, in addition to lower skewness and kurtosis at fine texture scale (SSF2), were the most significant predictors of worse outcome (p < 0.001). Multivariate cox regression analysis demonstrated that SD (SSF2) was the only independent predictor of survival (p < 0.001). Better patient outcome prediction was achieved after adding total vessel percentage and SD (SSF2) to the GAP staging system (p = 0.006).

Conclusion: Filtration-histogram texture analysis can be an independent predictor of patient mortality in IPF patients.

Advances in knowledge: qCT analysis can help in risk stratifying IPF patients in addition to clinical markers.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia characterised by progressive lung fibrosis associated with a high mortality rate. IPF is diagnosed by a combination of clinical and radiological findings, which can obviate the need for a lung biopsy.[1] To date, there is a lack of adequate prognostication factors as patients with IPF display a significantly variable rate of disease progression.[2] Currently, the agreed-upon primary endpoint for clinical trials is the 12 month change in forced vital capacity (FVC)[3]; however, relying on FVC measurements for predicting patient outcome has

several drawbacks. Serial measurements are required as the baseline measurement change is more predictive of outcome.[4–6] In addition, FVC measurements are subject to variability between visits even though a decline of 5–10% can be a predictor of poor prognosis.[7,8] As such, there is an ongoing need for early disease outcome predictors to tailor patient management and for risk stratification purposes. High-resolution CT (HRCT) is the standard of choice for imaging IPF patients.[9] However, there is no widely acceptable radiological biomarker of disease severity even though it was found that the extent of honeycombing and reticulation is an independent predictor of mortality.[10] Previous studies, investigating the use of quantitative CT (qCT) to risk-stratify IPF patients instead of visual scoring found interesting results and identified new parameters with the potential to serve as prognostic biomarkers.[11,12] Several methods were proposed as a tool for qCT.[13] Texture analysis with computer-aided classification (computer-aided lung informatics for pathology evaluation and ratings, CALIPER) and histogram-based analysis are among the utilised methods.[14,15] These software tools are based on different technical approaches, and both have shown important applications in various clinical settings and in different chronic lung diseases. This study aims to compare the prognostic and synergistic value of two different qCT methods in a well-selected cohort of IPF patients compared to standard clinical measures of disease severity.

METHODS AND MATERIALS

Patients

The study was approved by the ethics board [London-Harrow Research Ethics Committee (REC reference 06/Q0505/22)], and all patients provided written informed consent. A series of full inspiration HRCT scans (full inspiration volumetric 1 mm slices, peak voltage 120 kVp, tube current modulation range 30–140 mA, B70 kernel) for 59 patients were selected from an original cohort of 113 patients prospectively recruited for comparison of fludeoxyglucose positron emission tomography (FDG PET), HRCT and pulmonary function tests (PFTs).[16] From the original cohort, we filtered and included in the analysis, only the scans acquired on the same scanner (VCT PET/64, GE Healthcare, Chicago, IL), following the same image acquisition protocol and without breathing artefacts on the HRCT. As a result, out of the total cohort, 54 patients were excluded: 25 were scanned with an HRCT protocol with variable slice thickness or sequential gaps in the acquisition. 15 patients had no lung kernel reconstruction and the remaining 14 patients had breathing artefacts that impaired the quality of the scans and affected image analysis. The scans were analysed with two separate software packages utilising different qCT techniques, CALIPER (IMBIO Lung Texture Analysis™ with CALIPER technology exclusively licensed from Mayo Clinic, Minneapolis) and filtration-histogram-based texture analysis (TexRAD, Feedback Medical Ltd, Cambridge). The CALIPER analysis was performed as previously described,[16] and an experienced radiographer checked the consistency of the images to be sure that the patterns seen at qCT corresponded to the abnormality seen on the CT images. The data set for patients included in our study was retrieved from the original cohort. Filtration-histogram-based texture analysis was performed by a radiologist with 6 years of experience in chest image analysis. IPF was diagnosed on radiological and clinical grounds after a multidisciplinary team (MDT) review, which included interstitial lung diseases (ILDs) trained radiologists, ILD respiratory physicians, specialist nurses, and a lung pathologist. All patients with symptoms of acute infection were excluded. The patients were categorised according to the well-established GAP classification[17] and the GAP stage was calculated in office during the initial visit and within 3 weeks from the HRCT. The GAP index ranges from 0 to 8, which corresponds to the best and worst prognosis, respectively. According to the GAP index, the patients were stratified into three stages (GAP stage I–III), which are identified as GAP stage I (GAP index 0–3), GAP stage II (GAP index 4, 5), and GAP stage III (GAP index 6–8).

Follow-up

The follow-up duration was from scanning to the date of death or 9 years, whichever occurred first. Patients were followed up by utilising patient charts, electronic databases, general practitioner records, or telephone interviews.

Quantitative CT texture (qCT-T) and pattern (qCT-P) analysis

DICOM images extracted from PACS were anonymised and transferred to the qCT-T analysis software. The CT images were viewed utilising the lung window (window: 1500, level: −600) and manual regions of interest (ROIs) were drawn covering the entire lung parenchyma, excluding large vessels and airways. The ROIs were drawn every 10 slices, equivalent to a thickness of 1 cm.

For each patient, heterogeneity within each ROI was evaluated using a filtration-histogram-based texture analysis technique as described previously.[18] Filtration step comprised of extracting and enhancing image features of different sizes and intensity variation, corresponding to the spatial scale filter (SSF), which ranged from SSF = 2–4 mm, where SSF2 corresponded to fine texture scale, SSF3 corresponded to medium texture scale and SSF4 corresponded to coarse texture scale. Following the filtration-step, quantification of texture using statistical and histogram-based parameters was undertaken at each derived image (SSF value) which comprised of the following: mean intensity [which reflects average brightness with filtration and mean lung attenuation (MLA) without filtration at SSF0)]standard deviation (SD, which reflects the width of the histogram or dispersion from the average), entropy (which reflects irregularity), mean of positive pixels (MPPs, which reflects average brightness of only positive pixel values), kurtosis (which reflects sharpness of the histogram distribution) and skewness (which reflects the asymmetry of the histogram distribution). Quantification of texture using the above metrics was also undertaken without filtration (SSF0, conventional CT image). For each patient, at each SSF value (0,2,3,4), a cumulative (volume) assessment of the texture results derived from multiple ROIs delineated across the multiple CT slices was computed.

The assessment of qCT-P was undertaken using CALIPER analysis software as described previously.[11] Briefly, each voxel from the HRCT data was categorised into patterns based on algorithmic identification. These patterns include, normal

parenchyma, hyperlucent, ground-glass opacification, honeycombing, reticulation and pulmonary vessels. Percentages of each pattern were computed utilising the whole lung volume as a reference. The combination of reticulation, honeycombing and ground-glass opacification, labelled as total parenchymal lung damage, was used to measure the overall disease burden.

Statistical analysis

Univariate Kaplan–Meier (KM) survival analysis assessed the ability of qCT-T, qCT-P, PFT, GAP scores, modified GAP scores and patient demographics to predict overall patient survival (Log-rank test evaluated the difference in the survival curves) based on median value as the cut-off for each parameter.

Modified GAP scoring

The best univariate survival predictors for qCT-T and qCT-P features based on the KM survival analysis were selected to modify the traditional GAP index. These predictors were binarised (based on the median value as a cut-off from the KM survival analysis) with a score of 0 for good prognosis, 1 for poor prognosis, and added to the existing GAP staging system. The two modified scores were GAP_qCT-T (GAP scores modified based on qCT-T) ranging from 0 to 9 and GAP_qCT-T_qCT-P (GAP scores modified based on qCT-T and qCT-P) ranging from 0 to 10. These two modified scores were further stratified into three stages as the following: the GAP_qCT-T stages were 0–3, 4–6 and 7–9, and the GAP_qCT-T_qCT-P stages were 0–4, 5–7 and 8–10 for stages I, II, and III respectively.

Multivariate cox regression analysis (Stepwise Forward Wald) assessed the independence and interactions (combinations/synergistic-value) of the significant univariate markers and provided the performance characteristics (hazard ratio, 95% confidence interval, *p*-value). Statistical analysis was carried out using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Macintosh, v. 26.0: IBM Corp.) with a $p < 0.05$ considered significant.

RESULTS

59 patients (age 70.5 ± 8.8 years) underwent qCT-T and qCT-P analysis. Within the study sample, 49 (83.1%) patients were males. At baseline, the average GAP index was 4.4 ± 1.75 (0–8); 17 patients (28.8%) were classified as GAP stage I, 24 patients (40.6%) were classified as stage II, and the remaining 17 patients (28.8%) were classified as stage III. One patient was excluded from the GAP analysis due to unobtainable PFT data. Values of FVC, forced expiratory volume in 1 s (FEV1), total lung capacity (TLC), carbon monoxide transfer coefficient (KCO), and the transfer factor for carbon monoxide (TLCO) are shown in Table 1. The mean ± SD follow-up period was 24.3 ± 22.3 months (range: 0–109.4); during this time, 30 (50.8%) patients died. The qCT-T and qCT-P analyses results are shown in Table 2; the predominant pattern was reticular lung, with an average percentage of 16.6±13.9% (0.3–74.5); on average, 70.45±17.3% (19.2–94) of lung parenchyma was deemed normal.

Table 1. PFTs obtained at baseline

PFTs (% Pred)	Value
FVC	72 ± 17.8 (37–122)
FEV1	74.9 ± 37.6 (31.8–112)
TLC	73.8 ± 37.6 (55–91)
KCO	78.6 ± 31.1 (34–118)
TLCO	45.2 ± 13.6 (14–79)
GAP index	4.4 ± 1.75 (0–8)

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; KCO, carbon monoxide transfer coefficient; PFT, pulmonary function test; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide.
Figures are expressed as mean ± standard deviation (range).

Univariate Kaplan–Meier survival analysis

The KM survival analysis was performed for all the clinical variables (PFTs and GAP) and the imaging-derived biomarkers (qCT-T and qCT-P) summarised in Table 3 with survival curves for the most significant markers displayed in Figure 1.

PFT

All the PFTs, with the exception of the TLC and KCO, were significant predictors of overall survival, with the FVC being the most significant ($p = 0.006$, Table 3, Figure 1).

qCT-texture analysis

Several filtration-histogram-based texture parameters predicted patient outcome (Table 3). Amongst the different texture filter scales, the fine texture scale (SSF2) was the best predictor of overall survival, where a higher SD, entropy and MPP, in addition to lower skewness and kurtosis, were associated with worse patient outcome ($p < 0.001$). SD at fine texture scale (SSF2) ≥652.85 identified poor prognostic patients (median survival: 17.5 months) from good prognostic patients (median survival: 80.9 months) ($p < 0.001$, Figure 1).

qCT-pattern

Amongst the qCT-P parameters, the total pulmonary vessel percentage was the best predictor of patient survival ($p = 0.009$). Patients with a value of ≥3.87% had a median survival of 17.2 months compared to >109.4 months in patients with a total pulmonary vessel of <3.87%.

Multivariate cox regression analysis

A multivariate cox regression analysis comprising of all the significant univariate predictors (PFT, qCT– lung patterns and qCT – texture features) of overall survival resulted in fine texture (SSF2) parameter quantified as SD being the only significant independent predictor of overall survival (hazard ratio: 16.9, 95% confidence interval: 3.6–79.6, $p < 0.001$, Table 4). Visual illustration of filtration-histogram and CALIPER-based qCT analysis for a patient with a poor prognosis is depicted in Figure 2.

Modified GAP scores

The KM survival analysis results of the traditional and modified GAP index after combining with the best qCT-T

Table 2. Quantitative CT parameters (pattern and texture) derived from HRCT

Parameter		Value
qCT - Lung-patterns		
Normal parenchyma (%)		70.45 ± 17.3 (19.2–94)
Normal parenchyma (cm3)		2975.8 ± 1270.8 (400.9–5600)
Hyperlucent (%)		4.8 ± 7.11 (0.00006–26)
Ground-glass (%)		6.6 ± 8.6 (0.04–50.6)
Reticular (%)		16.6 ± 13.9 (0.3–74.5)
Honeycomb (%)		1.5 ± 1.9 (0–7.4)
Parenchymal damage (%)		24.8 ± 18.4 (0.8–80.8)
Vessels (%)		4 ± 1.8 (0.9–9.7)
Vessels (cm3)		148.5 ± 43 (67.1–241)
qCT - Texture-features		
Without filtration	Mean-Intensity	−734 ± 72 [(−870) - (−475.5)]
	SD	239.3 ± 35.4 (135.3–315.8)
	Entropy	6.4 ± 0.2 (5.7–6.8)
	MPP	112.3 ± 21.7 (21.3–174.4)
	Skewness	1.9 ± 0.7 (0.5–4.2)
	Kurtosis	4.4 ± 4.0 (-0.5–23.3)
Fine-texture (SSF = 2 mm)	Mean-Intensity	−57.7 ± 21.8 [(−102.7) - (−16.6)]
	SD	638.5 ± 80.8 (422.7–771.8)
	Entropy	7.7 ± 0.2 (7.2–8)
	MPP	494.4 ± 80 (274–630.5)
	Skewness	0.9 ± 0.3 (0.3–1.6)
	Kurtosis	4.6 ± 2.1 (1.8–11.4)
Medium-texture (SSF = 3 mm)	Mean-Intensity	−116 ± 28.5 [(−171) - (−55.7)]
	SD	623.8 ± 64.4 (466.6–756.5)
	Entropy	7.7 ± 0.16 (7.2–8.0)
	MPP	472.8 ± 70 (270.3–603.9)
	Skewness	0.8 ± 0.25 (0.3–1.4)
	Kurtosis	4.0 ± 1.6 (1.6–7.7)
Coarse-texture (SSF = 4 mm)	Mean-Intensity	−179.2 ± 31 [(−236.6) - (−113.9)]
	SD	618.5 ± 53.6 (501.8–739)
	Entropy	7.7 ± 0.14 (7.3–8)
	MPP	448.7 ± 64.4 (263.6–579.4)
	Skewness	0.5 ± 0.24 [(−0.14) - (1.0)]
	Kurtosis	3.0 ± 1.0 (1.2–5.4)

MPP, mean positive pixels; SD, standard deviation; SSF, spatial scale of the filter.
Values are expressed as mean ± standard deviation (range).

parameter—SD at fine texture scale (GAP_qCT-T) and the best qCT-P parameter, total vessel percentage, (GAP_qCT-T_qCT-P) are presented in Figure 3. The GAP index was not statistically significant in predicting patient outcome ($p = 0.06$). Both iterations of the modified GAP scores outperformed the traditional GAP system and allowed for better outcome prediction (GAP_qCT-T_qCT-P, $p = 0.002$, GAP_qCT-T, $p = 0.006$). Using a median cut-off of ≥5, the GAP_qCT-T identified patients with poor prognosis with a median survival of 22.6 months. The GAP_qCT-T_qCT-P score demonstrated a better prediction of outcome. Using a median cut-off value of ≥6, the GAP_qCT-T_qCT-P identified poor prognostic

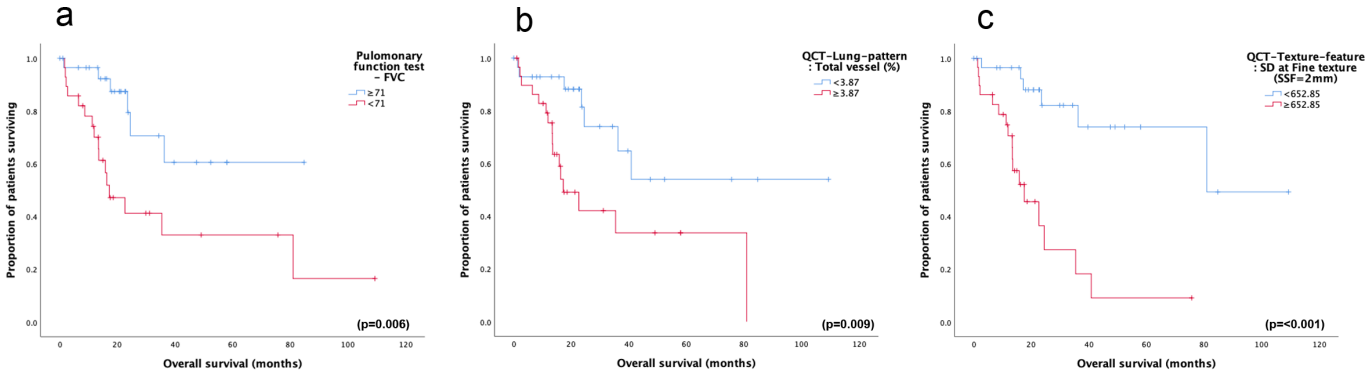
Table 3. Results of Kaplan–Meier survival analysis based on the median value as a cutoff to discriminate between good and poor prognostic groups

Parameter		Cutoff[a]	Median survival (months)		*p*-value
			<Cut-off	≥Cutoff	
Pulmonary function test (% Pred)					
FVC		<71	17.2	-	**0.006**
FEV1		<77	22.6	80.9	**0.030**
TLCO		<47	23.5	-	**0.015**
qCT – Lung-patterns					
Total vessel (%)		≥3.87	-	17.2	**0.009**
Total Vessel (cm^3)		≥142.41	-	22.6	**0.034**
Reticular (%)		≥13.92	80.9	17.2	**0.013**
Parenchymal damage (%)		≥20.90	80.9	22.6	**0.014**
qCT – Texture-features					
Without filtration	Mean-Intensity	≥−746.18	80.9	22.6	**0.011**
	SD	≥245.58	80.9	17.2	**<0.001**
	Entropy	≥6.45	80.9	17.5	**<0.001**
	MPP	≥111.11	80.9	35.4	0.756
	Skewness	<1.89	17.5	80.9	**<0.001**
	Kurtosis	<3.65	17.5	-	**<0.001**
Fine-texture (SSF = 2 mm)	Mean-Intensity	<−60.66	23.5	80.9	0.096
	SD	≥652.85	80.9	17.5	**<0.001**
	Entropy	≥7.68	80.9	17.2	**<0.001**
	MPP	≥503.41	80.9	17.2	**<0.001**
	Skewness	<0.95	22.6	-	**0.001**
	Kurtosis	<4.41	17.5	80.9	**<0.001**
Medium-texture (SSF = 3 mm)	Mean-Intensity	<−115.08	23.5	80.9	0.096
	SD	≥627.87	80.9	17.5	**0.001**
	Entropy	≥7.67	80.9	17.5	**<0.001**
	MPP	≥482.93	80.9	17.5	**0.002**
	Skewness	<0.72	17.5	-	**0.003**
	Kurtosis	<4.07	17.2	80.9	**<0.001**
Coarse-texture (SSF = 4 mm)	Mean-Intensity	<−178.17	23.5	80.9	0.113
	SD	≥616.24	80.9	17.5	**<0.001**
	Entropy	≥7.68	80.9	17.2	**<0.001**
	MPP	≥459.97	80.9	22.6	**0.003**
	Skewness	<0.47	35.4	40.8	0.577
	Kurtosis	<3.12	17.5	80.9	**0.001**

FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; MPP, mean positive pixels; SD, standard deviation; SSF, spatial scale of the filter; TLCO, transfer factor of the lung for carbon monoxide.
[a]Direction of the cut-off indicates a poor prognosis.

patients with a median survival of 17.53 months. For the two iterations of the modified GAP score, the median survival for the good prognostic patients (lower than the respective cut-off value) was not reached during the follow-up period. Based on the modified GAP scores, the patients were further stratified into low-, intermediate- and high-risk groups as discussed in the methods sections, and the results are presented in Table 5.

Figure 1. Kaplan–Meier survival analysis plots based on the median cut-off for the best predictors of survival from pulmonary function tests in addition to quantitative CT parameters (pattern and texture) as per Table 3. Forced vital capacity (a), total vessel percentage (b) and standard deviation quantified at fine texture scale, SSF2 (c) are presented. SSF, spatial scale filter.



DISCUSSION

Our study demonstrates that multiple qCT features can predict overall survival in IPF patients. qCT on its own or in combination with the GAP score can provide added value in the prognostication of IPF patients (better predict patient outcome) when compared to the GAP score on its own. Several previous studies suggest that the extent of fibrosis assessed quantitatively on HRCT is a strong predictor of outcomes in IPF.[15,19,20] Maldonado et al. in 2014 were amongst the first to evaluate an automated volumetric quantification tool for assessing specific parenchymal radiological features on HRCT. The authors demonstrated that percentage and total ILD changes were predictive of survival. Most recently, Jacob et al on a larger cohort of patients evaluated CALIPER against mortality; by applying a multivariate analysis, independent predictors of mortality were vessel-related structure component and honeycombing.[11,21,22] Our results are in agreement with the previously published literature highlighting the importance of vessels quantification as a prognostic tool, though this parameter was not an independent predictor of overall survival in our multivariate analysis. There is no obvious explanation for this discrepancy in our study compared to the previously published studies, but the difference in population or severity of disease and possible comorbidities, including older patients in our group, may have played a role. It is however also worth mentioning that what is referred to as pulmonary vessels by the computerised software represents the sum of pulmonary veins and arteries but also may include and capture other connected tubular structures, *i.e.* adjoining regions of fibrosis or small collapsed distal bronchial structures. As computer tools evolve and supervised machine learning progresses, it will be interesting to see the impact and understand differences related to the assessment of separate components of vessel-related structure and its ability to improve the prognostication of IPF patients.

In texture analysis, statistical calculations, including histogram-based summary statistics, are employed; Additionally, different types of image filtration can be performed to remove noise, enhance edges, and emphasise or extract certain features. Ultimately, several parameters, including the mean, median, histogram skew, and kurtosis of attenuation, have been shown to characterise texture features in IPF, reflect the extent of severity and correlate with visual scoring by experienced radiologists.[15] Different data extraction methods, from simple threshold measurements to texture metrics that capture morphology and regional heterogeneity, make the comparison among qCT-T studies difficult. To our knowledge, our study is the first to utilise a filtration-based histogram analysis technique in the analysis of IPF. However, it has been widely applied in a number of different oncological applications.[23–25] Many previous studies explored using histogram analysis to correlate with physiological parameters and outcome in idiopathic pulmonary fibrosis, showing that higher MLA, lower skewness and kurtosis were associated with poor pulmonary function.[26–28] These parameters were also associated with a worse outcome, as demonstrated by Ash et al and Best et al.[29,30] Our study shows comparative results with higher MLA, lower skewness, and kurtosis from conventional images (without filtration) linked to worse disease outcomes. Our study also demonstrated the filtration step's value, where at the different texture filter scales (fine, medium and coarse), higher SD, higher entropy, higher MPP, lower skewness, and lower kurtosis were associated with worse patient outcome. It is unclear why fine and medium texture scales were more significant than coarse texture parameters. We hypothesise that fine/medium texture scales are superior in capturing pathological lung patterns (*i.e.* honeycombing and reticulation) compared to coarse texture, which may reflect larger structures. Further confirmation in larger prospective studies, where tissue/histology may be available, is needed to validate our preliminary findings.

Amongst the different filter scales, the fine texture scale demonstrated the most significant difference between good and poor prognostic groups for the above texture metrics. qCT-based filtration-histogram texture analysis was the best univariate and independent predictor of overall survival. Adding the most significant texture marker (SD at fine texture scale) to the GAP score improved patient outcome prediction. However, a better patient outcome prediction was achieved after adding the best marker from each of the two qCT techniques, SD at fine texture scale and total vessel percentage, to the GAP staging system.

The UK National Institute for Health & Care Excellence current guidelines recommends antifibrotic treatment, with nintedanib or pirfenidone, for patients with an FVC between 50 and 80%.[31,32] Having additional biomarkers to predict disease

Table 4. Summary of multivariate cox regression analysis model comprising of the most significant univariate predictors of survival amongst pulmonary function test, QCT-lung patterns and QCT-texture features

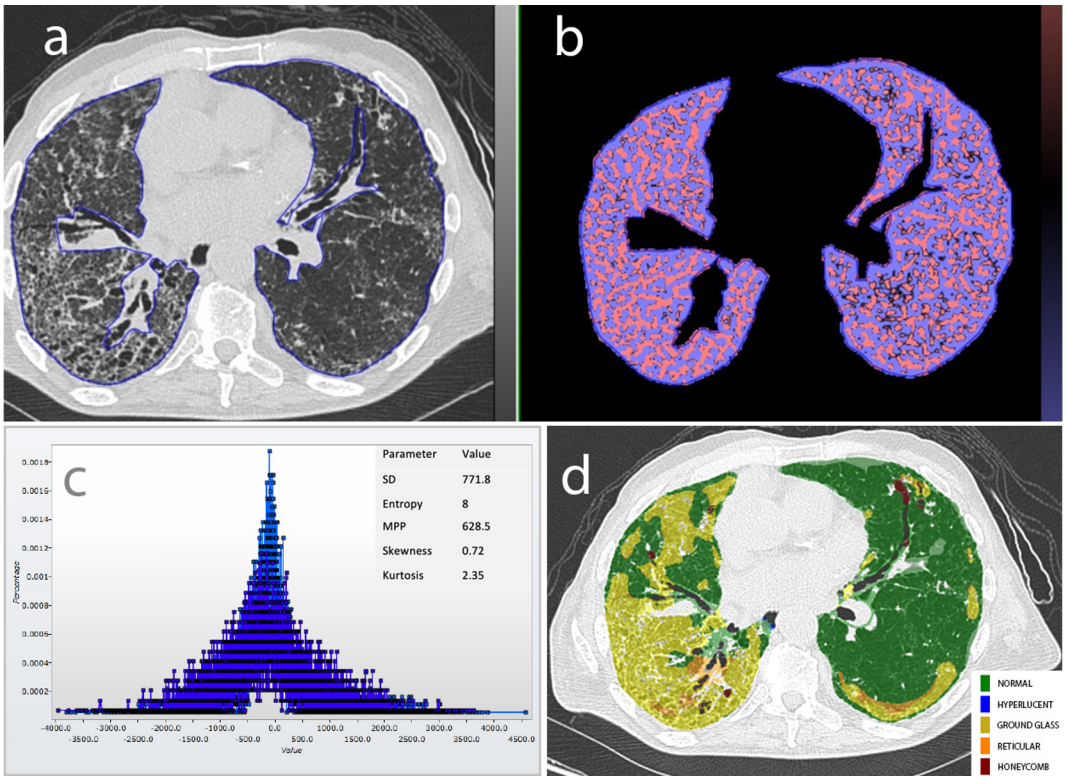
Parameter *included* in the model	**HR**	**95% CI**	***p*-value**
QCT-texture-feature Fine-texture (SSF = 2 mm), SD	16.9	3.6–79.6	<0.001
Parameters *not included* in the model		**Score**	*p*-value
Pulmonary function test			
FVC		0.622	0.430
FEV1		0.287	0.592
TLCO		0.036	0.851
QCT-lung patterns			
Total vessel (%)		0.014	0.907
Total vessel (cm^3)		0.622	0.430
Reticular (%)		2.816	0.093
Parenchymal damage (%)		0.677	0.411
QCT-texture-features			
Without filtration	Mean–intensity	0.351	0.554
	SD	0.174	0.676
	Entropy	0.076	0.783
	Skewness	0.093	0.760
	Kurtosis	0.114	0.736
Fine-texture (SSF = 2 mm)	Entropy	0.008	0.930
	MPP	0.001	0.979
	Skewness	0.901	0.342
	Kurtosis	0.093	0.760
Medium-texture (SSF = 3 mm)	SD	0.077	0.782
	Entropy	0.044	0.835
	MPP	0.084	0.773
	Skewness	1.471	0.225
	Kurtosis	0.505	0.477
Coarse-texture (SSF = 4 mm)	SD	0.046	0.830
	Entropy	0.046	0.830
	MPP	7.578	0.006
	Kurtosis	0.299	0.584

FEV1, forced expiratory volume in 1 s; HR, hazard ratio; MPP, mean positive pixels; SD, standard deviation; SSF, spatial scale of the filter; TLCO, transfer factor of the lung for carbon monoxide.

severity, particularly in patients with an FVC>80%, will provide additional prognostic implication that could facilitate the decision to initiate therapy earlier.[33] Based on our data, as shown in Table 5, we were able to reclassify many patients. Both modified GAP scores reclassified patients from high risk to lower risk categories. Additionally, adding the SD at fine texture scale and total vessel percentage reclassified more patients into the low-risk category despite their impaired lung function (FVC<80% predicted).

We recognise our study has some limitations, including the limited number of patients in our cohort, lack of long follow-up examinations, absence of correlation with visual CT and low-dose HRCT used for the analysis. Despite this, only patients scanned on the same scanner following the same imaging protocol were included in the analysis to keep the CT image acquisition parameters consistent. This may explain the partly diverse results in our study compared to others. It is notable that the lack of comparative studies in an IPF setting and the different methodology of texture-based algorithms, single slice *vs* volumetric measurements, low dose *vs* standard dose and slice thickness used can affect the reproducibility and routine application of these techniques in the clinical settings. We acknowledge this point as a potential issue, however, standardisation of protocols

Figure 2. CALIPER and filtration-histogram based texture analysis for a poor prognostic patient. Conventional axial CT slice with manually contoured ROIs across the whole lung (a) provides a visual representation of the disease extent. Filtered texture map at fine texture scale (SSF2) is shown (b) where the red and blue spots correspond to positive and negative filtered texture pixel values, respectively. Histogram analysis at the fine texture scale (SSF2) depicts the distribution of the filtered pixel intensity (c). Note the fine-filtered texture quantifiers – SD, entropy, MPP are elevated, whereas skewness and kurtosis are of low values. Selected axial CT slice with superimposed CALIPER lung pattern analysis for the same patient (d). CALIPER, computer-aided lung informatics for pathology evaluation and ratings; MPP, mean of positive pixel; SD, standard deviation; SSF, spatial scale filter.



across centres are becoming more and more frequent and technical improvements including faster scanners, will mitigate the problem related, respectively to different technical parameters and breathing artefacts.[34–36]

Furthermore, previous oncological studies have demonstrated good reproducibility for filtration-histogram-based texture analysis using multicentre clinical validation,[23,37] robustness to variation in image acquisition parameters[38,39] and good inter- and

Figure 3. Kaplan–Meier survival analysis plots based on the median cut-off for best predictors of survival based on GAP and modified GAP scores; (a) represents the GAP index alone, (b) represents the modified GAP index after the addition of the best qCT-texture after filtration (standard deviation quantified at fine texture scale, SSF2) and (c) represents the modified GAP index after the addition of the best qCT-texture after filtration (standard deviation quantified at fine texture scale, SSF2) and best qCT-pattern (total vessel percentage). Both iterations of the modified GAP scores outperformed the GAP index alone and allowed for a better outcome prediction. qCT, quantitative CT; SSF, spatial scale filter.

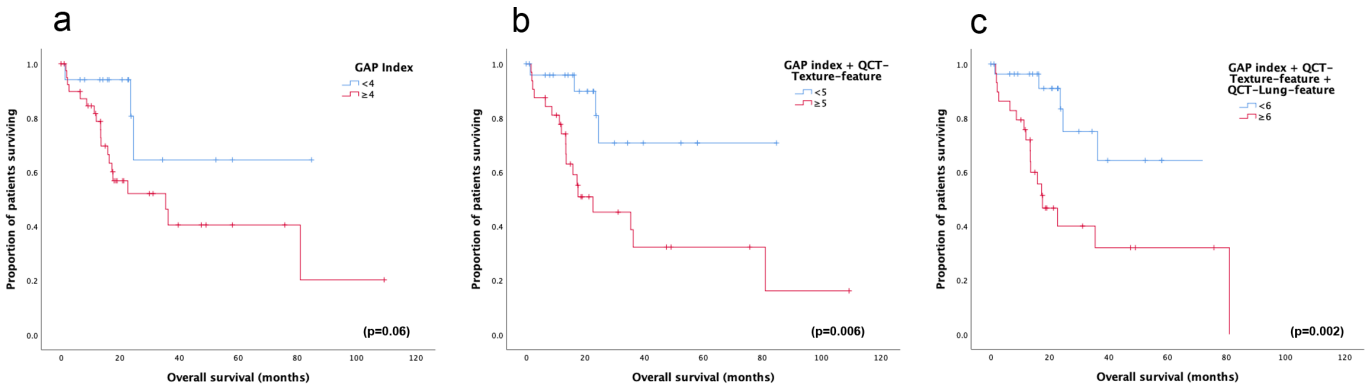


Table 5. Distribution of patients (expressed as n) according to the risk category as defined by GAP index, texture (fine texture quantified as standard deviation) and pattern (total vessel percentage) quantitative CT parameters (qCT-T, qCT-P) with their corresponding median survival (expressed in months)

	Low risk		Intermediate risk		High risk	
Scoring system	Patients (n)	Survival	Patients (n)	Survival	Patients (n)	Survival
GAP	17	-	24	36.2	17	17.2
GAP+qCTT	14	-	31	35.4	13	11.9
GAP+qCT-T+qCTP	23	-	23	35.4	12	11.2

intraoperator repeatability (good intraclass correlation from test–retest technique). Employing a volumetric qCT technique for the whole lung assessment, using the CALIPER pattern and filtration-histogram-based texture analysis, enabled us to capture parenchymal heterogeneity across the whole lung, which is key in the quantification of a diffuse disease condition like IPF. Future technical improvements of new software and more advanced machine learning techniques will create further exciting opportunities for prognostication and longitudinal studies. On the same note, we would like to highlight that this was a pilot, exploratory study, the results of which need to be validated in the future in a larger external/independent cohort. In this pilot study in the absence of an external, independent validation cohort, for KM survival analysis we used median value as a cut-off which results in equal proportion of patients above and below the cut-off. Median value as a cut-off is unbiased compared to other approaches to determine cut-off, *e.g.* receiver operating characteristics or lowest log-rank test *p*-value which introduce bias when employed in the same cohort.

Finally, we acknowledge the limitations of the GAP index to predict patient outcome; we trust that more integrative and evidence-based methods can provide a better understanding at baseline and follow-up for these patients.[40,41]

CONCLUSION

We have shown that qCT-P and qCT-T represent important IPF assessment tools, with the latter performing slightly better for survival prediction. Many other important clinical questions require an answer, including which patients to treat, when to start and stop treatment and who will primarily benefit from treatment. Further larger studies are needed, but it is becoming more apparent that quantitative CT has the potential to help clinicians in finding the right answers.

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COMPETING INTERESTS

B.G. is the co-inventor of the TexRAD texture analysis software used in this study and is a shareholder (owing to his inventorship and is not an employee) of Feedback Plc., a UK-based company which owns, develops, and markets the software. All the other authors certify having complete control over the study and results submitted. The remaining authors and authors institutions have no conflicts of interest.

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PATIENT CONSENT

All patients provided written informed consent.

ETHICS APPROVAL

The study was approved by the ethics board [London-Harrow Research Ethics Committee (REC reference 06/Q0505/22)].

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