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Association Between Pulmonary Vessel-Related Structures and Cryptogenic Fibrosing Alveolitis Using Derived Computed Tomography Among Chinese Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The aim of this study was to assess the association between pulmonary vessel-related structures and cryptogenic fibrosing alveolitis (CFA) in a drug trial in a Chinese population using derived computed tomography (dCT) to evaluate functional reduction and survival.

Material/Methods: Discovery and validation cohorts were chosen separately by fulfilment of drug trial entry criteria, and we enrolled 269 and 292 consecutive patients, respectively. CFA patients who had undergone imaging based on volumetric non-contrast CT at our hospital were subjected to pulmonary vessel-related structure (PVS) measures and dCT to forecast mortality and reduction in reduced forced vital capacity of CFA.

Results: The best forecaster of survival and reduction in terms of reduced forced vital capacity were found to be the dCT-generated outcomes in terms of PVS scores. Patients having less extensive disease highlighted the dCT outcomes through outperformance of CFA measures. When we used the cohort enhancement device, we found reduction in the requisite sample size of a CFA drug trial by 31% with the use of more than 5.0% dCT PVS score.

Conclusions: We found an association between CFA and PVS using dCT and it is far better than the results achieved so far by use of criterion standard measures. Additionally, reduction in the restrictive trial costs was also achieved by using cohort enhancement in a CFA drug trial setting, as PVS scores forced us to decrease the size of required CFA drug trial population by 30%. Interestingly, patients who had to take antifibrotic medication for longer periods had longer survival and less decreases forced vital capacity, as identified by PVS scores.

MeSH Keywords: Idiopathic Pulmonary Fibrosis • Multidetector Computed Tomography • Pulmonary Artery

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Background

Cryptogenic fibrosing alveolitis (CFA), which is a critical condition of assembling of activated fibroblasts within the lung-parenchyma, displays a dubious disease track, but with increasing prevalence [1,2] and it also leads to a sharp decrease in median patient survival, to less than 5 years [3–5]. However, reduced forced vital capacity (FVCl) is found to be the primary measure of results in CFA during a drug trial [6,7], as well as being reported to affect survival in several CFA cohorts [8,9].

A weak forecasting at baseline in CFA is important to lead the timely referral for lung transplantation and this information can be collected by characterization of indicators that are strongly associated with later stages of CFA [10]. In actual sense, cohort enhancement strategies used in CFA drug trail settings can decrease the sample sizes, and reduction in the restrictive costs with respect to the clinical trials can be achieved [11] by forecasting the patients prone to experience increased clinical events [12].

Recently, it has been observed that advanced computer algorithms-based CT analyses can better forecast survival from various fibrosing lung diseases in comparison to visual CT scores [13–15]. However, survival of CFA patients is strongly associated with quantification of pulmonary vessel-related structures (PVS) [15]. Still, forecasting of survival in CFA is unexplored across multicenter patient cohorts, and also with moderately affected patients through utilizing the quantification of PVS. The value of using of dCT imaging as a cohort enhancement device in CFA is also unclear.

Based on the above evidence, we designed this study to assess the association between PVS and CFA using derived computed tomography (dCT). During this process, we forecasted mortality using various function tests and visual and dCT scoring in CFA patients at various severity levels through a discovery cohort. A separate validation cohort for CFA was also examined. We also analysed whether specific variables of dCT, specifically PVS scores, were responsible for enhancement in CFA drug trail populations.

Material and Methods

Subjects

A multidisciplinary team of doctors diagnosed all the research subjects and collected non-contrast volumetric CT scanning reports. In the discovery cohort, all successive CFA patients who presented to our hospital between February 2008 and July 2012 were enrolled. However, for the validation cohort, all CFA patients presenting to our hospital between August 2012 and January 2015 were merged afterwards.

Pulmonary function test

As per established protocol [16], the cases in which pulmonary function examinations were executed within 3 months of the respective CT scan were chosen for analysis. According to Wells et al. [17], composite physiologic index (CPI) was calculated after assessment of various parameters *viz.* forced expiratory volume in one second, forced vital capacity and single breath carbon monoxide diffusing capacity corrected for hemoglobin concentration (DLco). Following the same work, plethysmographic lung volumes, spirometry, and diffusion capacity for carbon monoxide were also assessed. Additionally, gender-age-physiology (GAP) score and GAP index were calculated for both cohorts as per a previous report [18].

CT protocol

We used a 64-slice/256-slice/4-slice multiple-detector CT scanner purchased from Somatom Sensation 64 (Germany), Phillips (USA), and Siemens Volume Zoom (Germany) for CT scans followed by rebuilding of all images using B70 kernel purchased from Siemens (Germany) for high spatial frequency. We followed a previous report [19] for the purpose of visual CT scoring through percentage lobar basis by estimating the extent of total interstitial lung disease. We categorized the result of traction bronchiectasis as "severity" and "extent" scores. The first one was labelled as: none, mild, moderate, severe having respective points of 0, 1, 2, and 3 in a 19-point scale (score range=0–18) by taking the average of the extent of dilatation throughout the lobe and degree of airway dilatation within areas of fibrosis. The second one was labeled by summing up the numbers of segments of the lung (to a maximum of 3 segments per lobe) containing traction bronchiectasis and showing it on a 17-point scale (score range=0–16).

dCT evaluation

As per previous a report, we processed the data [20] using an augmented algorithm (Siemens B70) after applying a median filter. For this purpose, we used 3×3×3 voxel volume units. The lungs segmentation was then performed from the surrounding thoracic into the upper, middle, and lower areas of the lung using the carina as a reference point [21]. On the other hand, the airway was segmented with the help of continual 3D region growing, and related constituent analysis. Furthermore, for 15×15×15 voxel volume units, categorization based upon parenchymal tissue was applied on the basis of texture analysis, 3D morphology, and volumetric histogram signature mapping. On the basis of Eigen values of the Hessian matrix, an optimised multi-scale augmentation filter was used for the extraction of the pulmonary vessel. Subsequently, the second-order derivatives were also calculated in the sectors of each pulmonary voxel and then included in the Hessian matrix.

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Computation of this matrix leads to the probability of connection of an underlying voxel with a dense tubular structure; thus, vessel or vessel-related tubular structure representation was achieved [22]. After exclusion of vessels at the lung hilum, our pulmonary PVS score (dCT PVS) was expressed as a percentage of entire lung volume.

Evaluation-CT pattern

The scoring of CT variables was noted down visually and by dCT up to reticular pattern, honeycombing, and ground-glass opacification. The summation of the first 2 extents is represented as fibrosing extent, while the summation of all the 3 extents is termed as interstitial lung disease. However, in visual scores, quantification of traction bronchiectasis and severity extent cannot be excluded. dCT also quantified pulmonary PVS score (described above). dCT PVS scores were further subdivided as per the details of cross-sectional area and region of the structures and then showed as a percentage value of the 3 dCT-zonal volumes.

Statistical analysis

A total of 26 forecasters were used to study the desired association: (i) 5 visual scores; (ii) 5 CPI scores; (iii) 4 dCT scores; (iv), and 12 detailed PVS scores (3 total zonal PVS scores and the 3 cross-sectional areas [<10 mm^2, 10–20 mm^2, >20 mm^2] found in one of the upper, middle, or lower areas of the lungs). We considered death and longitudinal FVC trajectories to measure the clinical results. As per a previous report [23], we corrected the cut-off for statistical significance after comparing the forecaster variables. For this purpose, firstly, we plotted $-\log_{10}p$ values of each variable of 2 cohort sets on the x- and y-axes, respectively. Thus, we estimated the effective number of Eigen value-derived autonomous tests and then adjusted the significance by dividing it by 0.05.

Longitudinal analysis

Repeated function tests were performed longitudinally on the 2 cohorts. In each follow-up, the percentage FVC[=100×(FVC value/baseline FVC value)] was calculated and called the target variable. Baseline FVC value, sex, age at CT image, smoking status (ever *vs.* never), and interactions between time and sex were confounders. For this analysis lmer function from the R package lme4 was used [24], while the $-\log_{10}p$ values of the forecaster-by-time interaction were also presented for both cohort sets. We also calculated presence or absence of a 10% reduction in reduced forced vital capacity (FVCl) at 12 months for each subject. We used logistic regression analysis for mortality at 12 months by using glm function in R.

Survival analysis

Models based upon right-censored Cox proportional hazards were used for this purpose. CT imaging was used to measure time to death event or censoring. Sex, smoking status (ever *vs.* never) and age at CT imaging events were used for the correction of these models. The coxph function [25] was used for our analysis. As mentioned above, we plotted $-\log_{10}p$ values of the forecaster for the 2 cohort sets. Refinement in the C-index was calculated with respect to addition of powerful PVS measure to a confounders' adjusted model.

Power analysis

The effect of dCT PVS as an enhancement parameter was explored by conducting a power analysis through estimation of probable sample size omissions in the clinical trials by keeping 90% power and threshold of 0.05 (p-value) in a 2-sample *t* test. We kept the control group on antifibrotic medication, having an average reduction by 110 mL/year in FVCl during the CFA drug trial. We investigated 3 drug effects – 30%, 45%, and 60% effect – and it led to average annual reduction in respective FVCl as 77 mL, 60.5 mL, and 44 mL. We calculated the standard deviation in the cohort with DLco ≥35% so that we could derive the effect size (Cohen's d). We found a median absolute deviation of 229.82 when using a stable estimator. In the devalued design, the effect sizes (d) were 0.15, 0.23, and 0.29, respectively, while in the valued design, we found 3.9, 4.8, and 5.4 as dCT PVS thresholds retaining 75%, 55%, and 35% of subjects (with DLco ≥35%), respectively. We also found 230.3, 199.8, 197.3, respectively, as the standard deviation of annual reduction in FVCl. There values are clear indication of the effect of potency of each drug on corresponding effect and sample sizes.

Results

Baseline data

We have evaluated the capability of our dCT to aid cohort enhancement in a drug trial protocol. For this purpose, we analyzed the patients having percent-forecasted DLco range of 35%–85% in the discovery (n=180) and validation (n=206) cohorts. In addition to this primary analysis, we also performed 2 secondary analyses. In order to study the role of medication on CT in foretelling FVCl survival and reduction, we merged both the cohorts and then examined the patients with a DLco ≥35% in 2 ways: ones who had not received antifibrotic medication (n=213) and those who were received antifibrotics (n=165). This was the first case of the secondary analyses. In the second case, we evaluated the outcome of dCT devices in forecasting the various study measures in patients with critical condition

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Table 1. Comparison of subjects' characteristics in discovery and validations cohorts of CFA.

Subjects	Variables	Discovery cohort (n=269)	Validation cohort (n=292)	Cohort comparison
All CFA patients (DLco ≥35% predicted)	Median Age (in years)	68	70	0.13#
	Male/Female (ratio)	201/68	231/61	0.73#
	Alive/Dead (survival)	69/200	98/194	0.10#
	CPI	58.5±15.2	55.3±14.2	0.03
	% DLco (predicted)	39.2±14.5	41.5±16.7	0.04
	dCT interstitial lung disease (extent)	28.9±14.8	25.9±18.2	0.21
	%FVC (predicted)	72.4 ±19.2	78.4±21.1	0.004
	dCT PVS (score)	5.4±1.9	6.1±2.1	0.11
CFA patients (DLco <35% predicted)	dCT PVS (score)	5.1±1.4 (n=180)	5.3±1.6 (n=211)	0.09
	%FVC (predicted)	78.7±17.4 (n=168)	81.2±17.9 (n=168)	0.07
	dCT interstitial lung disease (extent)	22.1±13.7 (n=180)	21.3±15.2 (n=180)	0.36
	% DLco (predicted)	46.4±12.4 (n=180)	48.5±15.3 (n=180)	0.02
	CPI	52.2±10.1 (n=168)	50.2±11.1 (n=168)	<0.05

Data represent median values for patient age and mean values with standard deviations for dCT and lung function variables. Statistically significant differences between the 2 groups were calculated using the chi-square test for categorical independent variables (#) and the *t* test for continuous variables. FVC – forced vital capacity; DLco – diffusing capacity for carbon monoxide; CPI – composite physiologic index; PVS – pulmonary vessel-related structure.

of disease by examining the patients with a DLco <35% forecasted in both cohorts (n=91 for both sets). We found higher mean DLco for the patients with a DLco ≥35% forecasted in the validation cohort than those in other cohorts (Table 1).

Reduction in FVCl values

The strongest forecasters for reduction in FVCl values were dCT fibrosing extent and upper-area PVS, *i.e.,* dCT variables in both the entire discovery (n=197) and validation (n=213) cohort sets (Figure 1A). However, when our analyses were limited to DLco ≥35%, forecasters such as upper- and mid-area PVS subdivisions were found to be the best ones in the forecasting of reduction in FVCl values in both the discovery (n=142) and validation (n=173) cohorts (Figure 1B).

Survival analyses

The strongest forecasters of survival were CPI, total PVS, UA PVS, and DLco scores in complete examination in both the discovery (n=269) and validation (n=292) cohort sets (detailed data not shown). However, when our analyses were limited toDLco ≥35% forecasters such as total and upper-area PVS subdivisions, CPI, and DLco scores, and large PVS (>20 mm^2) in the mid- and upper-areas were found to be the most powerful ones in the forecasting of 1-year mortality in patients who had fulfilled the drug trial entry criteria (n=388) (detailed data not shown).

Mortality in one year

The strongest forecasters for mortality in one year were total PVS and upper- and mid-area PVS subdivisions, *i.e.,* dCT variables in both the entire discovery (n=244) and validation (n=258) cohort sets (detailed data not shown). However, when our analyses were limited to DLco ≥35% forecasters such as upper-area PVS subdivisions and visual traction bronchiectasis extent and severity were found to be the most powerful ones in the forecasting of 1-year mortality in both the discovery (n=161) and validation (n=181) cohorts (detailed data not shown).

Antifibrotic medication sub-analyses (never *vs.* ever)

The strongest forecasters of sub-analyses in patients who were had not received antifibrotic medication (DLco ≥35% forecasted) were UA PVS scores in both the discovery (n=139) and validation (n=74) cohort sets (detailed data not shown). However, in patients who received with antifibrotic medication (DLco ≥35% forecasted), the strongest forecasters were upper- and

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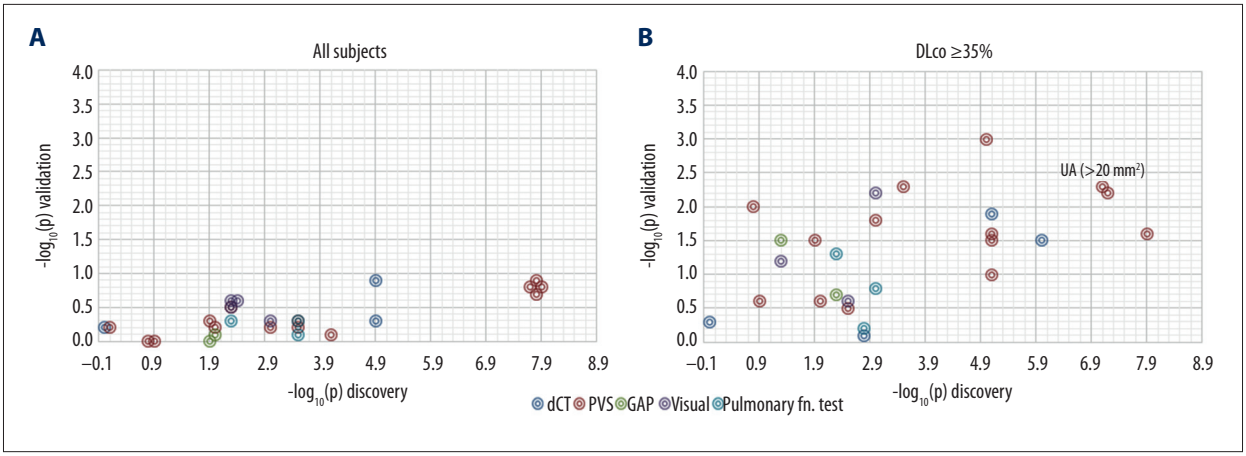

Figure 1. Scatter plots demonstrating -log10(p)-values for variables: dCT, PVS, GAP, visual and pulmonary functional (fn.) test in the discovery (x-axis) and validation (y-axis) cohorts. Graphs (**A, B**) represent all subjects and patients with a DLco ≥35% forecasted. DLco – diffusing capacity for carbon monoxide; CPI – composite physiologic index; UA – upper-area; PVS – pulmonary vessel-related structure.

mid-area PVS variables in the discovery (n=35) and validation (n=130) cohorts (detailed data not shown).

C-Index analyses

We compared the respective strengths of adjusted models that had forecasted the 1-year mortality with the help of the C-index for models containing dCT PVS subdivision scores, functional indices, and visual CT variables. We also adjusted these models for patient age, gender, and smoking status. In patients with a DLco ≥35% forecasted who had not received antifibrotics (n=185), the algorithm was rebuilt. On the other hand, when we examined the models individually in the merged 2 cohorts, we found that the models in dCT PVS subdivisions were far better than the models containing functional indices in forecasting 1-year mortality (Table 2). In the same table, we also found that the models in dCT PVS subdivisions have higher C-index values than models containing CPI, FVC, and DLco in the merged cohort, when C-index was used to compare the adjusted Cox mortality models. We also observed increase in the model C-index due to addition of a mid- or upper-area PVS subdivision score to the model having functional index (Table 3).

Subjects with severe disease

The strongest forecasters for survival were CPI and DLco in the subjects having severe disease (DLco <35% forecasted; n=173) (detailed data not shown). However, there was no strong forecasting of reduction in FVCl or 1-year mortality in all these cases (DLco <35% forecasted). The same result was observed in the subjects who received antifibrotic medication and were sub-analyzed (n=30) (detailed data not shown). However, lower-area PVS subdivision forecasted reduction in FVCl in subjects (DLco <35% forecasted) who never received antifibrotics and were sub-analyzed (n=142). We also found a strong relationship between upper-area PVS subdivisions with 1-year mortality and survival in these cases (detailed data not shown).

Cohort adornment using dCT PVS variables

The goal of our study was to analyze the effect of dCT imaging in cohort enhancement of CFA drug trials. To achieve this, we calculated the possible savings to a CFA drug trial resulting from cohort enhancement of all the subjects, using various dCT total PVS variables (Table 4). Therefore, we modelled 3 possible effect sizes on reduction in FVCl (30%, 45%, and 60% reduction in FVCl) using CFA patients with a DLco ≥35% forecasted. We analysed at cohort enhancement using 3 dCT PVS variables corresponding to 75% (dCT PVS=4.1% of the lung), 55% (dCT PVS=4.9% of the lung), and 35% (dCT PVS=5.6% of the lung) of the original CFA subjects at each drug effect size. If we restrict a clinical trial cohort to CFA patients having dCT PVS variable of 4.9% of the lung (or even higher), we can easily reduce the sample size by 28% to identify the same drug treatment (Table 4). Additionally, in this case, we also found that half of all CFA subjects were included. We found a model C-index for the dCT PVS variable of 4.9% in the discovery cohort of patients with a DLco ≥35% forecasted and not on antifibrotics (n=139) was 0.70 for survival and 0.76 for 1-year mortality. We further examined the effect of medication in all the subjects with a DLco ≥35% forecasted with a PVS >4.9% (n=195) so that we can exclude the possibility of dCT PVS variable of 4.9% as identification of non-medicated patients. We observed increased life expectancy in this subpopulation due to use of antifibrotic medication (detailed data not shown).

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Table 2. C-indices values for adjusted models containing dCT, functional and visual CT variables.

Variables	Discovery cohort (n=139)		Validation cohort (n=74)		Combined cohort (n=213)	
	Survival	Mortality*	Survival	Mortality*	Survival	Mortality*
dCT PVS	0.71	0.76	0.65	0.70	0.69	0.76
UA PVS	0.71	0.78	0.63	0.72	0.70	0.77
UA[1]	0.70	0.77	0.57	0.60	0.67	0.76
UA[2]	0.71	0.77	0.60	0.71	0.70	0.77
UA[3]	0.70	0.77	0.65	0.73	0.67	0.76
MA PVS	0.70	0.74	0.65	0.68	0.70	0.71
MA[1]	0.65	0.68	0.59	0.55	0.64	0.67
MA[2]	0.67	0.71	0.60	0.63	0.68	0.70
MA[3]	0.70	0.76	0.65	0.67	0.68	0.71
LA PVS	0.59	0.61	0.61	0.65	0.63	0.68
LA[1]	0.53	0.53	0.50	0.50	0.55	0.62
LA[2]	0.56	0.59	0.55	0.58	0.59	0.62
LA[3]	0.62	0.61	0.62	0.74	0.64	0.68
GAP index	0.68	0.64	0.68	0.78	0.64	0.70
GAP score	0.59	0.54	0.35	0.43	0.50	0.61
CPI	0.65	0.68	0.68	0.64	0.68	0.70
FVC	0.65	0.68	0.63	0.65	0.65	0.70
DLco	0.61	0.59	0.67	0.64	0.64	0.66
dCT fibrosing extent	0.67	0.72	0.68	0.76	0.68	0.75
Visual fibrosing extent	0.60	0.59	0.59	0.60	0.61	0.64
dCT interstitial lung disease extent	0.68	0.72	0.60	0.68	0.68	0.71
Visual interstitial lung disease extent	0.62	0.64	0.60	0.57	0.62	0.65
dCT honeycombing extent	0.51	0.53	0.47	0.70	0.51	0.62
Visual honeycombing extent	0.60	0.54	0.50	0.68	0.57	0.63
Traction bronchiectasis extent	0.62	0.71	0.60	0.64	0.61	0.67
Traction bronchiectasis severity	0.59	0.63	0.62	0.70	0.62	0.68

In all study patients with a DLco ≥35% not receiving antifibrotic medication. All models were adjusted for patient age, gender, smoking status (never *vs.* ever) and CT reconstruction algorithm. GAP – gender, age and physiology (score and index); CPI – composite physiologic index; FVC – forced vital capacity; DLco – diffusing capacity for carbon monoxide; UA – upper-area; MA – middle-area; LA – lower-area; PVS – pulmonary vessel-related structure, * in one year; [1] (<10 mm^2); [2] (10–20 mm^2); [3] (>20 mm^2).

Discussion

In this study we have demonstrated that dCT variables such as dCT PVS can 2 separate disease end-points: discovery and validation cohorts with CFA. The first end-point is survival and the second end-point is FVCl in one year; therefore, we found an augmented effect size in CFA subjects with less severity of disease. Additionally, we have also demonstrated that PVS scores can be used in cohort enhancement of CFA subjects. We found reduction in CFA drug trial sample size by 28% when the patients

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Table 3. Change in C-index values for adjusted models with the addition of dCT pulmonary vessel-related structure subdivisions.

Variables	Functional indices		
	CPI	FVC	DLCO
dCT PVS	0.049	0.056	0.074
UA PVS	0.044	0.049	0.070
UA[1]	0.030	0.024	0.050
UA[2]	0.039	0.044	0.066
UA[3]	0.037	0.040	0.063
MA PVS	0.037	0.050	0.059
MA[1]	0.013	0.022	0.027
MA[2]	0.023	0.031	0.040
MA[3]	0.040	0.044	0.056
LA PVS	0.008	0.016	0.016
LA[1]	0.008	–0.001	0.001
LA[2]	0.006	0.003	0.005
LA[3]	0.023	0.029	0.035

In all study patients with a DLco ≥35% not receiving antifibrotic medication (n=213). All models were adjusted for patient age, gender, smoking status (never *vs.* ever) and CT reconstruction algorithm. GAP – gender, age and physiology (score and index); CPI – composite physiologic index; FVC – forced vital capacity; DLco – diffusing capacity for carbon monoxide; UA – upper-area; MA – middle-area; LA – lower-area; PVS – pulmonary vessel-related structure; * in one year; [1] (<10 mm^2); [2] (10–20 mm^2); [3] (>20 mm^2).

were selected using dCT PVS variable of over 4.9%. These patients also have an enhanced life expectancy and decreased rate of FVCl when taking antifibrotic medicated in comparison to the condition when they were not receiving antifibrotics.

Radiologists have used existing computer algorithms to analyze CT imaging in CFA by designating and evaluating the CT parenchymal pattern library and then acknowledged visually [26]. Besides, the association of PVS with prognostication has been explored properly; hence, our work will lead to its proper quantification. We know that PVS measures the quantification of pulmonary arteries and veins, but without avoiding the measure related, to study the connection between tubular structures of adjoining regions of fibrosis. Therefore, our dCT PVS-based quantification protocol is the first representation of its kind that has no imminent measurement variation, and hence eventually strongly forecasts the mortality in CFA. In the future, with the evolution and progress in different new computer devices and machine learning processes, we expect growth in and dependency on our protocol.

However, CPI and DLco functional tests were found to the best forecasters of survival in CFA patients with critical condition of disease (DLco <35% forecasted). Thus, we can forecast a major basis of mortality in patients with critical condition of disease, even without measuring the comprehensive right heart catheter, and hence pulmonary hypertension will remain speculative. One shortcoming of this result is that it will decrease the ability to treat patients with mild disease. Our results are the first evidence of usage of traction bronchiectasis as a forecaster of mortality through quantifying FVCl. Furthermore, the capability of the visual traction bronchiectasis score in forecasting of FVCl may lead radiologists to use automation of traction bronchiectasis measurement, and that will, eventually, be the future of CFA analyses. Upper-area PVS were found to be the best forecaster of mortality in most analyses, while lower-area PVS lacked strong signals; therefore, PVS provides selective evaluation in discrete lung subunits.

We were also being successful in reducing the cost of modern drug trials in CFA by using dCT as a cohort enhancement device. Additionally, the use of dCT PVS scores may allow particular selection of CFA patients, which will finally lead to more rapid FVCl through savings in follow-up and trial size and hence presents itself as cost-effective protocol. The major limitation

Table 4. Impact of cohort enriching a CFA drug trial study population.

Reduction in FVCd		dCT PVS variable (% of population)			
		0 (100)	4.1 (75)	4.9 (55)	5.6 (35)
30% effect	Size	2508	2458	1806	1753
	Size difference (%)	0 (0)	50 (2)	702 (28)	752 (30)
45% effect	Size	981	961	706	687
	Size difference (%)	0 (0)	20 (2)	275 (28)	294 (30)
60% effect	Size	629	616	453	440
	Size difference (%)	0 (0)	13 (2)	176 (28)	189 (30)

FVCd – forced vital capacity decline.

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of our protocol is that, due to other computed analysis, it requires non-contrast volumetric imaging through use of appropriate algorithms. In our dCT scan, we used edge-enhancing algorithms in most of the CT scans and that will be responsible for the misclassification of ground-glass opacities, honeycombing, or even reticulation. In order to avoid this, we have avoided use of the Siemens B80 algorithm, which is the most severely edge-enhanced one. There is another limitation in our study, as dCT PVS measures predominantly include cryptogenic fibrosing alveolitis, but in patients with extensive fibrosis, it also includes reticular densities and peribronchial fibrosis. Hence, exact quantification of the contribution of associated perivascular fibrosis in overall variable strength may not be possible by using our protocol. However, the robustness of our measure is quite good in the upper-area of the lung, and PVS scores strongly forecasted the survival, even where the fibrosing extent is least in CFA, and hence established its utility across independent patient populations. Our study has another advantage over other possible drug trial setting due to a longer follow-up period.

Use of our dCT protocol needs several preparatory steps such as a high-quality CT scan, and severe edge-enhancing algorithms should be specifically avoided; therefore, a desired scanner algorithm must be used to rebuild the CT. Besides, to decrease the image noise and to ensure optimal parenchymal characterisation, CT data must be pre-processed prior to computer analysis. Another important factor with dCT is that an entire CT test in it takes no more than 60 seconds without compromising with quality control of segmentation accuracy. We also expect that our dCT PVS protocol will be used in multicenter studies, as it can forecast mortality across CT algorithms, even in the validation cohort.

Conclusions

Our dCT protocol of CFA accurately forecasts the survival and mortality with FVCl in subjects with mild disease through quantification of PVS. Additionally, dCT PVS scores can select particular CFA subjects who cannot skip their mortality in drug trials or respond to antifibrotic medication. Therefore, our protocol-generated dCT PVS scores may play an important role in the reduction of restrictive costs of current CFA trials by drug trial cohort enhancement.

Conflict of interest

None.

References:

1. Agabiti N, Porretta MA, Bauleo L et al: Idiopathic Pulmonary Fibrosis (IPF) incidence and prevalence in Italy. Sarcoidosis Vasc Diffuse Lung Dis, 2014; 31: 191–97
2. Nezhad AJ, Kooshali MHY: Lung cancer in idiopathic pulmonary fibrosis: A systematic review and meta-analysis. PLoS One, 2018; 13: e0202360
3. Yunt ZX, Chung JH, Hobbs S et al: High-resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: Relationship to survival. Respir Med, 2017; 126: 100–4
4. Daccord C, Maher TM: Recent advances in understanding idiopathic pulmonary fibrosis. F1000Res. 2016; 5: pii: F1000 Faculty Rev-1046
5. Raghu G, Collard HR, Egan JJ et al: Fibrosis. AEJACoIP. An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis – evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med, 2011; 183: 788–824
6. Reichmann WM, Yu YF, Macaulay D et al: Change in forced vital capacity and associated subsequent outcomes in patients with newly diagnosed idiopathic pulmonary fibrosis. BMC Pulm Med, 2015; 15: 167
7. Kimura M, Taniguchi H, Kondoh Y et al: Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. Respiration, 2013; 85: 456–63
8. Latsi PI, du Bois RM, Nicholson AG et al: Fibrotic idiopathic interstitial pneumonia: The prognostic value of longitudinal functional trends. Am J Respir Crit Care Med, 2003; 168: 531–37
9. King TE, Safrin S, Starko KM et al: Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. Chest, 2005; 127: 171–77
10. Oldham JM, Noth I: Idiopathic pulmonary fibrosis: Early detection and referral. Respir Med, 2014; 108: 819–29
11. Fernández Fabrellas E, Peris Sánchez R, Sabater Abad C, Juan Samper G: Prognosis and follow-up of idiopathic pulmonary fibrosis. Med Sci (Basel), 2018; 6: pii: E51
12. Soo E, Adamali H, Edey A: Idiopathic pulmonary fibrosis: Current and future directions. J Clin Radiol, 2017; 72: 343–55
13. Obert M, Kampschulte M, Limburg R et al: Quantitative computed tomography applied to interstitial lung diseases. Eur J Radiol, 2018; 100: 99–107
14. Jacob J, Bartholmai BJ, Rajagopalan S et al: Automated quantitative computed tomography versus visual computed tomography scoring in idiopathic pulmonary fibrosis: Validation against pulmonary function. J Thorac Imaging, 2016; 31: 304–11
15. Jacob J, Bartholmai B, Rajagopalan S et al: Mortality prediction in idiopathic pulmonary fibrosis: Evaluation of computer-based CT analysis with conventional severity measures. Eur Respir J, 2017; 49: 1601011
16. Quanjer PH: Standardized lung function testing. Eur Respir J-Suppl, 1993; 6: 1–100
17. Wells AU, Desai SR, Rubens MB et al: Idiopathic pulmonary fibrosis: A composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med, 2003; 167: 962–69
18. Ley B, Ryerson CJ, Vittinghoff E et al: A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med, 2012; 156: 684–91
19. Hansell DM, Bankier AA, MacMahon H et al: Fleischner Society: Glossary of terms for thoracic imaging. Radiology, 2008; 246: 697–722
20. Maldonado F, Moua T, Rajagopalan S et al: Automated quantification of radiological patterns forecasts survival in idiopathic pulmonary fibrosis. Eur Respir J, 2014; 43: 204–12
21. Hu S, Hoffman EA, Reinhardt JM: Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. IEEE Trans Med Imaging, 2001; 20: 490–98
22. Shikata H, McLennan G, Hoffman EA, Sonka M: Segmentation of pulmonary vascular trees from thoracic 3D CT images. Int J Biomed Imaging, 2009; 2009: 636240
23. Li J, Ji L: Adjusting multiple testing in multilocus analyses using the eigenvalues of a correlation matrix. Heredity (Edinb), 2005; 95: 221–27
24. Bates D, Machler M, Bolker B, Walker S: Fitting linear mixed-effects models using lme4. Journal of Statistical Software, 2015; 67: 1–48
25. R Core Team: R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2018
26. Salisbury ML, Lynch DA, van Beek EJ et al: Idiopathic pulmonary fibrosis: The association between the adaptive multiple features method and fibrosis outcomes. Am J Respir Crit Care Med, 2017; 195: 921–29

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