Weak to no correlation between quantitative high-resolution computed tomography metrics and lung function change in fibrotic diseases

Yixuan Zou[1], Xuefeng Hou[1], Neha Anegondi[2], Mohammadreza Negahdar[3], Dorothy Cheung[4], Paula Belloni[4], Alex de Crespigny[2] and Alexandre Fernandez Coimbra[2]

[1]Product Development Data Sciences, Genentech, Inc., South San Francisco, CA, USA. [2]Clinical Imaging Group, Genentech, Inc., South San Francisco, CA, USA. [3]Artificial Intelligence, Genentech, Inc., South San Francisco, CA, USA. [4]Clinical Science, Genentech, Inc., South San Francisco, CA, USA.

Corresponding author: Yixuan Zou (zou.yixuan@gene.com)

Abstract

Background Identifying systemic sclerosis (SSc) and idiopathic pulmonary fibrosis (IPF) patients at risk of more rapid forced vital capacity (FVC) decline could improve trial design. The purpose of the present study was to explore the prognostic value of quantitative high-resolution computed tomography (HRCT) metrics derived by Imbio lung texture analysis (LTA) tool in predicting FVC slope.

Methods This retrospective study used data from patients who were not treated with investigational drugs with and without background antifibrotic therapies in tocilizumab phase 3 SSc, lebrikizumab phase 2 IPF, and zinpentraxin alfa phase 2 IPF studies conducted from 2015 to 2021. Controlled HRCT axial volumetric multidetector computed tomography scans were evaluated using the Imbio LTA tool. Associations between HRCT metrics and FVC slope were assessed through the Spearman correlation coefficient and adjusted R^2 in a linear regression model adjusted by demographics and baseline clinical characteristics.

Results A total of 271 SSc and IPF patients were analysed. Correlation coefficients of highest magnitude were observed in the SSc study between the extent of ground glass, normal volume, quantification of interstitial lung disease, reticular pattern, and FVC slope (−0.25, 0.28, −0.28, and −0.33, respectively), while the correlation coefficients observed in IPF studies were in general <0.2. The incremental prognostic value of the baseline HRCT metrics was marginal after adjusting baseline characteristics and was inconsistent across study arms.

Conclusion Data from the SSc and IPF studies suggested weak to no and inconsistent correlation between quantitative HRCT metrics derived by the Imbio LTA tool and FVC slope in the studied SSc and IPF population.

Introduction

Interstitial lung disease (ILD) causes progressive scarring of the lung tissue through inflammation and fibrosis [1]. The most common form of ILD is idiopathic pulmonary fibrosis (IPF), a chronic and ultimately fatal ILD characterised by progressive worsening of dyspnoea and irreversible loss of lung function [2]. Systemic sclerosis (SSc) is a rare chronic disease characterised by diffuse fibrosis in the skin and internal organs including the lungs. ILD consisting of scattered foci of fibroblast proliferation accounts for 33% of deaths in SSc patients [3]. In both SSc and IPF, lung fibrosis is associated with substantial mortality [4]. Change in forced vital capacity (FVC) is most widely accepted as a surrogate for mortality and is the key clinical end-point in clinical trials to measure disease progression in IPF [2, 5, 6] and in SSc [7–10].

High-resolution computed tomography (HRCT) has a key role in diagnosing ILD [11]. The prognostic value of different quantitative HRCT metrics in disease progression in ILDs was shown by various studies. One retrospective study showed quantification of vessel-related structures (VRS) strongly correlated with survival and FVC decline in IPF patients [12]. A systematic review identified the extent of disease on HRCT scan as the only variable that independently predicted both mortality and ILD progression measured by FVC in SSc-ILD [13]. In contrast, DENTON *et al.* [14] showed very weak evidence of correlation between a greater extent of fibrotic ILD at baseline and FVC decline in the SSc-ILD population from the SENSCIS trial evaluating nintedanib in SSc-ILD. Overall, the utility of different quantitative HRCT metrics in predicting FVC decline has not been studied across multicentre patient cohorts or in patients with different ILDs (*e.g.* IPF *versus* SSc-ILD), and statistical methods were not consistently used to quantify the association between baseline HRCT metrics and FVC decline, which makes the comparison between different studies very challenging.

As FVC is a commonly used clinical end-point in ILD trials, building prognostic models for FVC may facilitate identification of patients that are more likely to progress and therefore can potentially reduce sample size and shorten the trial duration. Our goal was to evaluate the prognostic value of quantitative HRCT metrics derived by lung texture analysis using the Imbio lung texture analysis (LTA) tool (Imbio LLC, Minneapolis, MN, USA) in predicting FVC slope in a tocilizumab phase 3 study in SSc (FocuSSced), a lebrikizumab phase 2 study in IPF (RIFF) and a zinpentraxin alfa phase 2 study in IPF (PRM-151–202).

Methods

Trial designs

This study retrospectively examined the prognostic value of HRCT metrics in predicting FVC decline. Screening and/or longitudinal FVC and HRCT data from participants with SSc or IPF in three prospective clinical trials, FocuSSced (www.clinicaltrials.gov identifier NCT02453256) [15], RIFF (www.clinicaltrials.gov identifier NCT01872689) [16] and PRM-151-202 (www.clinicaltrials.gov identifier NCT02550873) [17] conducted from 2015 to 2021 were analysed retrospectively. Only patients (n=271) who were not treated with investigational drugs (*i.e.* tocilizumab in FocuSSced, lebrikizumab in RIFF and zinpentraxin alfa in PRM-151-202) and had baseline HRCT scans and FVC measurements were included. The key inclusion/exclusion criteria are summarised in table 1. The details of the sample size determination could be found in the study manuscripts [15–17]. The phase 3 FocuSSced (n=210) study evaluated the effects of tocilizumab in patients with SSc utilising the percentage of predicted forced vital capacity (FVC % pred) and FVC change from baseline at week 48 as secondary end-points with pulmonary fibrosis determined by HRCT scans as an exploratory end-point. Only the placebo arm from the FocuSSced study was included in the analysis, and the study did not allow the use of any antifibrotic therapy. Approximately 65% of patients had HRCT-defined ILD, with 77% of participants having >10% total lung involvement as assessed by quantification of interstitial lung disease (qILD) [18]. The phase 2 RIFF study enrolled patients with IPF

TABLE 1 Study overview				
	Tocilizumab phase 3 in SSc (FocuSSced)	**Zinpentraxin alfa phase 2 in IPF (PRM-151-202)**	**Lebrikizumab phase 2 in IPF (RIFF) cohort A**	**Lebrikizumab phase 2 in IPF (RIFF) cohort B**
Population	SSc	IPF	IPF	IPF
Study design	Double-blinded, placebo-controlled	Double-blinded, placebo-controlled	Double-blinded, placebo-controlled	Double-blinded, placebo-controlled
Double-blinded treatment duration	48 weeks	28 weeks	52 weeks	52 weeks
Key inclusion/exclusion criteria	Age ⩾18 years Diagnosis of SSc FVC ⩽55% pred D_{LCO} ⩽45% pred No background IPF therapy allowed	Age 40–80 years 50% pred⩽FVC⩽90% pred 25% pred⩽D_{LCO}⩽90% pred 6MWD ⩾150 m Background IPF therapy allowed	Age ⩾40 years 40% pred⩽FVC⩽100% pred 25% pred⩽D_{LCO}⩽90% pred 6MWD ⩾100 m No background IPF therapy allowed	Age ⩾40 years 40% pred⩽FVC⩽100% pred 25% pred⩽D_{LCO}⩽90% pred 6MWD ⩾100 m Tolerated dose of pirfenidone
Trial registration (www.clinicaltrials.gov) and reference	NCT02453256 [15]	NCT02550873 [17]	NCT01872689 [16]	NCT01872689 [16]

SSc: systemic sclerosis; IPF: idiopathic pulmonary fibrosis; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance.

into two cohorts (n=505): 1) cohort A was designed to evaluate the safety and efficacy of the investigational drug lebrikizumab as a monotherapy and had two arms, the lebrikizumab arm and the placebo arm; 2) cohort B was designed to evaluate the safety and efficacy of lebrikizumab as a combination with pirfenidone and had two arms, the lebrikizumab plus pirfenidone arm and the pirfenidone-only arm. It studied the annualised rate of FVC % pred decline over 52 weeks following lebrikizumab administration with quantitative lung fibrosis score on HRCT as an exploratory end-point. Only the placebo arm in cohort A and the pirfenidone arm in cohort B from the RIFF study were included in the analysis. Cohort A did not allow the use of any antifibrotic therapy, while cohort B required a tolerated dose of pirfenidone as an inclusion criterion. The inclusion of the pirfenidone arm in cohort B in our prognostic analysis was to better understand the prognosis of FVC progression with the background use of antifibrotic therapy to guide trial design when an antifibrotic therapy is allowed. The zinpentraxin alfa phase 2 study (PRM-151-202) enrolled 117 patients with IPF and evaluated change in FVC % pred from baseline to week 28 after treatment and examined HRCT metrics as secondary end-points. Only the placebo arm from the PRM-151-202 study was included in the analysis. The study allowed the use of concurrent antifibrotic therapy, and 82% of the placebo patients were on current antifibrotic therapy at baseline.

As reported in each study publication [15–17], protocols were approved by each centre's institutional review board/ethics committee and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization E6 Guidelines for Good Clinical Practice. All participants and/ or their legally authorised representatives provided written informed consent.

Computed tomography scans and quantitative evaluation

HRCT scans for the studies were acquired using multiple scanners (Siemens, Philips, Toshiba, GE). Only axial volumetric multidetector computed tomography (CT) scans taken in the supine position with slice thickness of 1.25 mm were included for the analysis and evaluated using the Imbio LTA tool. The fully automated LTA tool applies advanced computer vision to transform a standard CT scan into a detailed map and provides quantification of the lung textures that are key to identifying ILD and other fibrotic conditions. Patterns scored volumetrically by the LTA algorithm included ground-glass opacities, reticular pattern and honeycombing, hyperlucent, normal lung, and VRS [19]. The ground-glass opacities, reticular pattern, and honeycombing were summed to represent the ILD extent in the lung as qILD. All parenchymal pattern volumes were expressed as a percentage of the lung, after correcting for total lung volume calculated by the LTA tool.

Statistical analysis

Statistical analyses were performed by using R version 4.0.3 or above (R Foundation for Statistical Computing, Vienna, Austria). Baseline data were summarised as mean±SD for continuous variables, or n (%) for discrete variables. The Spearman correlation coefficient was calculated to quantify the association between the continuous variables as it requires no assumptions on the data distribution and is not sensitive to outliers. The correlations between FVC and HRCT metrics at baseline were assessed. The prognostic value of the baseline HRCT metrics was evaluated in a stepwise approach: 1) the univariate correlation between baseline HRCT metrics and FVC slope calculated from simple linear regression between FVC measurements and visit days was assessed using Spearman correlation coefficient; and 2) the additive prognostic value was assessed using the adjusted determination of coefficient (adjusted R^2) from a multiple linear regression model adjusted by baseline FVC, age, gender and height with the FVC slope as the response variable.

Results

Subjects

The baseline characteristics of each study arm are summarised in table 2. The baseline FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) were much higher, while ILD extent assessed by qILD was lower in the FocuSSced placebo arm compared to other study arms, which may suggest that SSc patients have less lung disease severity at baseline than IPF patients. Among the three IPF study arms, PRM-151-202 placebo arm had lower FVC and qILD, but higher D_{LCO} than the RIFF cohort A placebo arm and RIFF cohort B pirfenidone arm. The disease progression as measured by FVC and D_{LCO} are visualised in supplementary figures S1 and S2.

Correlation between FVC and HRCT metrics at baseline

A forest plot showing the Spearman correlation between HRCT metrics and FVC at baseline are shown in figure 1. A greater extent of qILD, VRS, reticular pattern, and ground glass were weakly correlated with a lower FVC at baseline, while a smaller extent of normal lung volume and hyperlucency were weakly correlated with a higher FVC at baseline. Honeycombing was not shown to be correlated with FVC at baseline.

TABLE 2 Patients' clinical characteristics and high-resolution computed tomography metrics at baseline.				
	FocuSSced placebo	PRM-151-202 placebo	RIFF cohort A placebo	RIFF cohort B PFD
Patients	88	39	38	106
Concurrent IPF therapy at baseline				
Yes	0/88 (0)	32/39 (82)	0/38 (0)	106/106 (100)
No	88/88 (100)	7/39 (18)	38/38 (100)	0/106 (0)
Sex				
Female	75/88 (85)	10/39 (26)	6/38 (16)	17/106 (16)
Male	13/88 (15)	29/39 (74)	32/38 (84)	89/106 (84)
Age (years)	50±12	68±7	70±7	69±7
	50 (23–73)	67 (52–80)	70 (54–84)	69 (50–83)
Race				
American Indian or Alaska Native	3/88 (3.4)	0/39 (0)	0/38 (0)	0/106 (0)
Asian	7/88 (8.0)	0/39 (0)	4/38 (11)	4/106 (3.8)
Black or African American	3/88 (3.4)	0/39 (0)	0/38 (0)	1/106 (0.9)
Native Hawaiian or other Pacific Islander	0/88 (0)	0/39 (0)	0/38 (0)	1/106 (0.9)
Other	1/88 (1.1)	0/39 (0)	0/38 (0)	3/106 (2.8)
Unknown	0/88 (0)	0/39 (0)	0/38 (0)	2/106 (1.9)
White	74/88 (84)	39/39 (100)	34/38 (89)	95/106 (90)
Height (cm)	163±9	174±9	171±10	172±8
	162 (146–186)	175 (150–191)	170 (156–201)	173 (153–191)
Weight (kg)	67±16	87±13	87±19	86±15
	65 (44–131)	87 (63–112)	83 (58–150)	86 (42–127)
BMI (kg·m^{-2})	25.1±5.3	28.8±3.4	29.3±5.0	29.1±4.4
	23.8 (18.3–44.9)	28.0 (22.2–36.4)	28.7 (21.1–47.4)	28.8 (17.5–42.9)
Ground glass (%)	3±6	14±13	14±13	19±17
	1 (0–31)	11 (1–67)	9 (3–72)	14 (1–84)
Honeycomb (%)	0.65±2.50	0.35±0.89	0.90±1.37	0.52±1.70
	0.05 (0.00–21.80)	0.15 (0.00–5.54)	0.42 (0.01–6.27)	0.17 (0.00–16.78)
Hyperlucent (%)	3.69±7.79	1.23±1.97	1.53±3.12	1.16±2.31
	1.00 (0.00–47.39)	0.59 (0.01–10.57)	0.37 (0.00–16.29)	0.24 (0.00–12.03)
qILD (%)	5±7	19±14	24±16	26±18
	3 (0–35)	15 (2–81)	19 (7–87)	20 (6–93)
Normal volume (%)	91±10	80±14	75±16	74±18
	94 (52–100)	84 (19–95)	80 (13–93)	79 (7–94)
Reticular pattern (%)	1.7±3.8	4.4±2.6	8.5±10.5	5.6±3.9
	0.7 (0.0–32.8)	3.6 (1.0–14.6)	5.8 (0.9–57.4)	4.4 (0.9–21.5)
Vessel volume (%)	2.14±0.80	5.29±1.81	5.15±1.61	5.44±2.08
	1.98 (1.06–5.80)	4.91 (2.52–11.18)	4.81 (2.68–8.75)	5.06 (2.24–13.02)
D_{LCO} (mL·min^{-1}·mmHg^{-1})	17.7±4.9	13.1±3.7	4.2±1.0	4.2±1.2
	17.2 (8.6–32.3)	13.5 (6.5–21.2)	3.9 (2.4–6.7)	4.1 (2.0–8.5)
D_{LCO} (% pred)	77±19	43±10	43±9	43±11
	76 (35–149)	43 (22–69)	42 (26–65)	42 (20–76)
FVC (mL)	2976±783	2758±657	2870±712	2863±691
	2940 (1430–6210)	2610 (1670–4470)	2812 (1491–4655)	2831 (1321–4573)
FVC (% pred)	83±15	67±11	74±12	71±14
	87 (53–115)	66 (47–89)	75 (47–97)	71 (44–98)
6MWD (m)	Not available	458±118	490±153	535±169
		450 (183–725)	457 (299–975)	504 (118–990)

Data are presented as n, n/N (%), mean±SD or median (range). PFD: pirfenidone; IPF: idiopathic pulmonary fibrosis; BMI: body mass index; qILD: quantification of interstitial lung disease; D_{LCO}: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; 6MWD: 6-min walk distance.

Correlation between baseline HRCT metrics and FVC slope

Across all HRCT metrics, the univariate correlation with FVC slope was weak to no with inconsistent directionality among all four study arms (figures 2 and 3). Specifically, in terms of directionality, in the PRM-151-202 placebo arm, the correlation between the extent of vessel volume, qILD, and ground glass and FVC slope was positive, while the correlation between normal volume and FVC slope was negative, but for the remaining three study arms the correlation between these HRCT metrics and FVC slope was in an opposite direction. The correlation between the extent of reticular pattern with FVC slope was positive
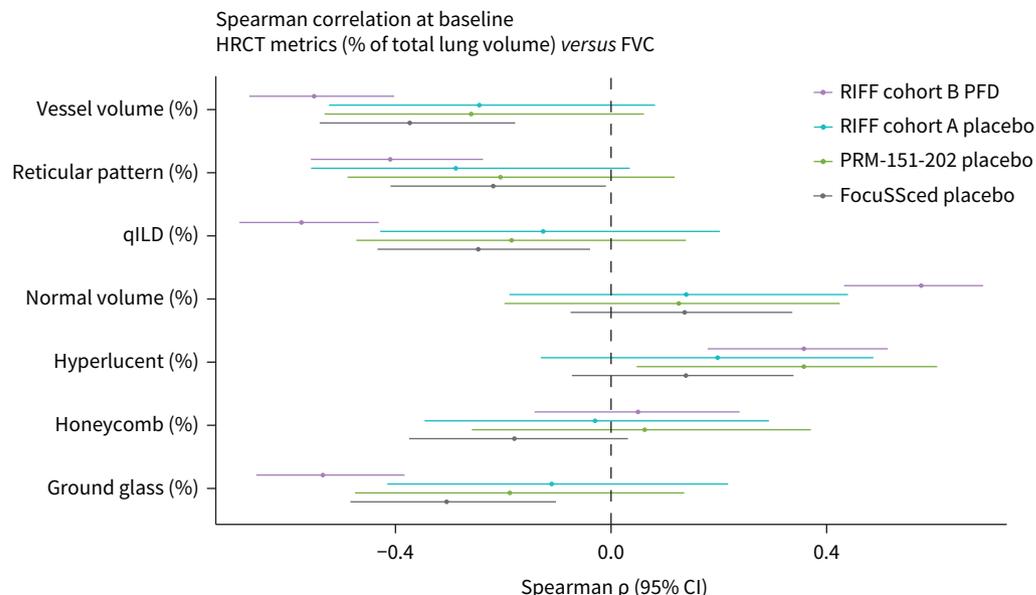
FIGURE 1 Forest plot for the Spearman correlation coefficient with 95% confidence intervals between forced vital capacity (FVC) and high-resolution computed tomography (HRCT) metrics at baseline. qILD: quantification of interstitial lung disease; PFD: pirfenidone.

in the RIFF cohort A placebo arm, but was negative in the other three study arms. The correlation between the extent of hyperlucency and FVC slope was positive in the RIFF cohort B pirfenidone arm, but was negative in the other three study arms. For the extent of honeycombing, the correlation with FVC slope was negative in RIFF cohort B pirfenidone arm and FocuSSced placebo arm, but was positive in the other two study arms. In terms of the magnitude of correlation, correlation coefficients of highest magnitude were observed in the FocuSSced placebo arm between the extent of ground glass, normal volume, qILD, reticular pattern, and FVC slope (−0.25, 0.28, −0.28, and −0.33, respectively), while the correlation coefficients observed in other three study arms were in general <0.2 (figure 3). Overall, the 95% confidence intervals of the correlation coefficients were highly overlapping, and the magnitude of the correlation coefficients suggested there was weak to no correlation between different quantitative HRCT metrics and FVC slope.
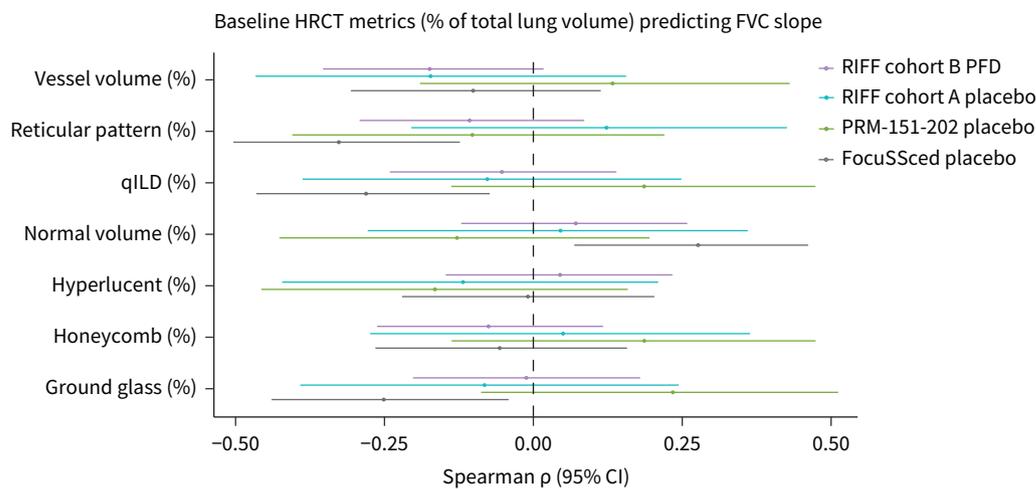

FIGURE 2 Forest plot for the Spearman correlation coefficient with 95% confidence intervals between forced vital capacity (FVC) and high-resolution computed tomography (HRCT) metrics. qILD: quantification of interstitial lung disease; PFD: pirfenidone.
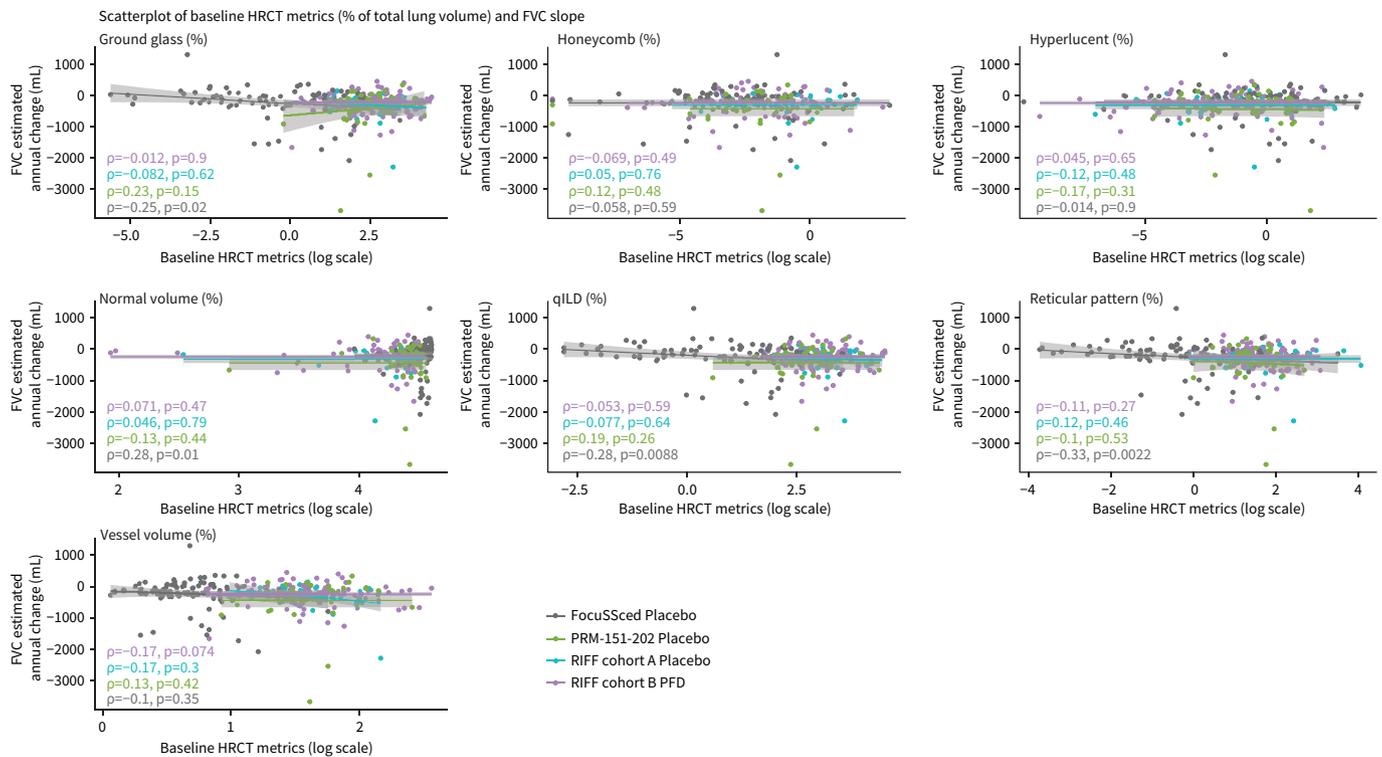
FIGURE 3 Scatterplot with a smooth line using a generalised additive model between baseline high-resolution computed tomography (HRCT) metrics and forced vital capacity (FVC) slope. The shaded area represents 95% confidence interval of the smooth line. qILD: quantification of interstitial lung disease; PFD: pirfenidone.

As shown in figure 4, the incremental prognostic value of the baseline HRCT metrics on top of the demographics and clinical characteristics in predicting FVC slope was inconsistent across study arms, and the magnitude of the prognostic effect was very marginal (adjusted R^2 mostly <0.2). Specifically, while the extent of vessel volume had the highest adjusted R^2 value among all baseline HRCT metrics in the FocuSSced placebo arm (adjusted $R^2=0.09$) and the RIFF cohort A placebo arm (adjusted $R^2=0.16$), the extent of reticular pattern and hyperlucency had the highest adjusted R^2 in the PRM-151-202 placebo arm (adjusted $R^2=0.13$) and the RIFF cohort B pirfenidone arm (adjusted $R^2=0.13$), respectively.

Discussion

We have shown that the baseline HRCT metrics had weak to no association with FVC slope using data from randomised controlled trials in patients with SSc or IPF. Weak to no correlation was seen with inconsistent directionality between HRCT metrics and FVC slope across different studies, while the 95% confidence intervals of the Spearman correlation coefficients were overlapping. Highest correlation coefficients, but of small magnitude, were observed in the FocuSSced placebo arm between the extent of ground glass, normal volume, qILD, reticular pattern, and FVC slope (−0.25, 0.28, −0.28, and −0.33, respectively). There was no consistent prognostic value of any HRCT metrics after adjusting baseline demographic and clinical characteristics.

Multiple studies attempted to develop prognostic models to predict FVC decline in ILD patients using quantitative HRCT metrics. Similar to what is presented in this study, data from 288 placebo SSc-ILD patients in the SENSCIS trial only showed very weak evidence of correlation between a greater extent of fibrotic ILD at baseline and a greater decline in FVC % predicted at week 52 (r −0.09, 95% CI −0.2–0.03) [14]. Two other studies [12, 20] concluded that a greater extent of fibrotic ILD or VRS on HRCT was associated with a higher rate of ILD progression measured by FVC. However, the study by JACOB *et al.* [12] only showed that VRS was statistically significant associated with FVC decline, but the magnitude of the correlation was not given by any correlation coefficient, whereas in the study by KHANNA *et al.* [20], the degree of lung fibrosis was dichotomised with 25% lung involvement as an arbitrary cut-off, and a larger FVC change from baseline was reported in patients with a higher degree of fibrosis on HRCT scans. The
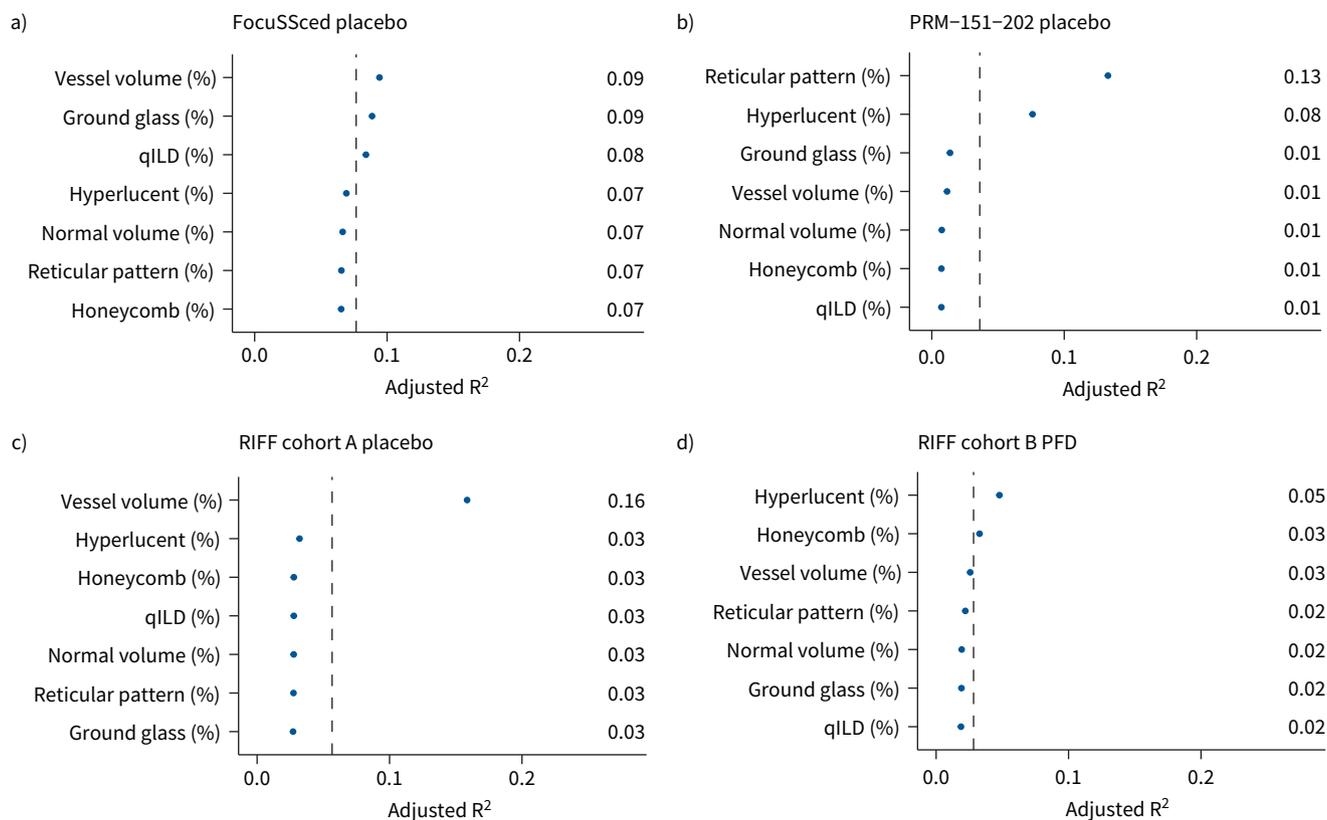
FIGURE 4 Adjusted R^2 of high-resolution computed tomography (HRCT) metrics in predicting forced vital capacity (FVC) slope after adjusting baseline clinical characteristics. a) Tocilizumab phase 3 in systemic sclerosis (SSc) (n=86); two patients were not included in the analysis as they did not have post-baseline measurements; b) zinpentraxin alfa phase 2 in idiopathic pulmonary fibrosis (IPF) (n=39); c) lebrikizumab phase 2 in IPF cohort A (n=38); d) lebrikizumab phase 2 in IPF cohort B (n=106). Each HRCT metric was sorted based on their adjusted R^2 level. The dashed line is the adjusted R^2 from the base model, and each dot represents the adjusted R^2 from the base model with the added HRCT metric. Base model: FVC slope ~ baseline FVC + sex + age + height; added model: FVC slope ~ baseline FVC + sex + age + height + HRCT. qILD: quantification of interstitial lung disease; PFD: pirfenidone.

discrepancies between the findings of these two studies and our work are likely due to differences in the study population, study design, and statistical methodology. In another observational study, JACOB *et al.* [12] showed significant but weak Pearson's correlation (r −0.42) between annualised FVC change and absolute VRS change in IPF patients not receiving antifibrotic therapy. However, the clinical utility of this finding is probably limited as the VRS change was assessed from two CT scans with a mean interval ~1 year, it cannot be used to predict FVC progression over a similar period of time and therefore cannot be considered as a prognostic factor on its own.

Compared to that which has been reported in the literature, our analyses have the following strengths: 1) the data we used were from randomised controlled clinical trials with pre-defined assessments, which ensured the data quality of FVC measurements and HRCT scans; 2) different populations were examined (*e.g.* patients with and without antifibrotic medication, SSc and IPF patients) to support the generalisability of our findings; 3) consistency of findings between studies was assessed to validate our conclusions; and 4) a comprehensive evaluation of HRCT metrics that were not limited to the extent of ILD (qILD) and VRS that were more commonly studied in the literature.

There were a few limitations to our study. The analyses were conducted retrospectively, so the findings should be considered exploratory and will need to be confirmed in future studies with a prospective analysis plan. Even though the inclusion of different populations could be considered as a strength of our study, the heterogeneity of the study patients (*i.e.* SSc *versus* IPF) may have complicated the interpretation of the study results, along with the heterogeneity of study design elements including trial duration, inclusion/exclusion criteria, permit of the background antifibrotic therapies, *etc.*

In conclusion, little evidence of correlation was found between the HRCT metrics derived by Imbio LTA at baseline and FVC slope in patients from the tocilizumab phase 3 study in SSc, lebrikizumab phase 2 study in IPF and zinpentraxin alfa phase 2 study in IPF who did not receive the investigational drug. Correlation was weak to none with inconsistent directionality between HRCT metrics and FVC slope across different studies, and nor was the added prognostic value of baseline HRCT metrics consistent when the multiple linear regression model was adjusted by baseline FVC, age, gender and height. In summary, these findings suggested that FVC progression in patients with SSc or IPF may be independent of the severity of fibrotic-related lung texture on HRCT as assessed by Imbio LTA at baseline. The clinical utility of using these HRCT metrics for patient enrichment to reduce the study size or covariate adjustment in SSc and IPF studies to improve the precision of treatment estimation may be very limited. Due to limited mortality data in the studies and lack of end-of-study HRCT scans, the prognostic value of HRCT of survival and the surrogacy of HRCT metrics in place of FVC in SSc and IPF remains to be evaluated in the future with larger and longer studies with multiple HRCT scans.

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