e-Lung computed tomography biomarkers are associated with outcomes in fibrotic interstitial lung diseases

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e-Lung CT biomarkers provide prognostic information outperforming standard tools in ILD and provide a robust objective means of quantifying fibrosis extent over time. e-Lung can be used to improve the care of patients in routine clinical practice. https://bit.ly/4qFWiMv

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Abstract

Background The e-Lung weighted reticulovascular score (WRVS) is an automated computed tomography biomarker that quantifies interstitial lung disease (ILD) severity and is associated with prognosis in patients with idiopathic pulmonary fibrosis (IPF). The aims of the present study were to evaluate WRVS as a prognostic factor in patients with non-IPF ILD.

Methods The test cohort comprised patients from the Open Source Imaging Consortium and the validation cohort, patients recruited to the prospective German CoWorker ILD registry. Associations between baseline and serial WRVS with future forced vital capacity (FVC) decline and survival were tested.

Results Median survival was 7.1 and 6.1 years in the test (n=302) and validation (n=378) cohorts, respectively. Baseline WRVS was associated with mortality in test (hazard ratio (HR) 1.11, 95% CI 1.08–1.14; p<0.001, C-index 0.75) and validation (HR 1.12, 95% CI 1.09–1.15; p<0.001, C-index 0.72) cohorts. A threshold WRVS of ⩾15% was associated with mortality in both cohorts (HR 4.77, 95% CI 3.11–7.31; p<0.001, C-index 0.71, and HR 3.49, 95% CI 2.48–4.91; p<0.001, C-index 0.63 for test and validation cohorts, respectively). After adjustment for FVC, age and sex, baseline WRVS was associated with future FVC decline or death in test (OR 1.13, 95% CI 1.06–1.21; p<0.001, C-index 0.72) and validation (OR 1.18, 95% CI 1.11–1.25; p<0.001, C-index 0.72) cohorts. A rise in WRVS of 3% on serial computed tomography was associated with mortality in both test (HR 5.69, 95% CI 2.77–11.70; p<0.001, C-index 0.75) and validation cohorts (HR 1.99, 95% CI 1.09–3.65; p=0.026, C-index 0.57).

Conclusion In patients with non-IPF ILD, the e-Lung WRVS biomarker is associated with mortality and FVC decline when applied to baseline high-resolution computed tomography scans replicating previous studies in IPF. Patients with an increase in WRVS of 3% on serial computed tomography scans have significantly increased risk of mortality.

Introduction

The fibrotic interstitial lung diseases (ILDs) are a group of conditions of differing aetiologies having a common final pathway of parenchymal lung architectural destruction leading to respiratory failure and

reduced life expectancy [1]. While some patients with non-idiopathic pulmonary fibrosis (IPF) fibrotic ILDs can be stabilised with treatment, others experience progressive pulmonary fibrosis (PPF) with a disease behaviour akin to that of IPF [2], where in the appropriate clinical setting, the only curative treatment option is lung transplantation [3].

The management of patients with non-IPF ILD is often targeted at the underlying disease pathogenesis, with antifibrotic treatment introduced when PPF has ensued [4, 5]. Risk stratification of patients based on likelihood of progression is central to optimal care as identification of PPF at the earliest possible opportunity is key to the best patient outcomes. The diagnosis of PPF relies in part on disease progression as identified by radiologists on computed tomography (CT) [5], but progression can be challenging to identify [6], and assessing the extent of fibrosis on CT is affected by interobserver variability [7].

Artificial intelligence (AI) approaches have shown promise in non-IPF ILD although the majority of the published literature to date has focused on predictive biomarkers with less data to support the application of AI to the serial evaluation of CT scans [8]. Deep-learning approaches have been shown to improve the identification of usual interstitial pneumonia (UIP) and are discriminatory for survival [9–11], and the pulmonary vasculature as defined by pulmonary vessel volume and vessel related structures has also been shown to hold prognostic information [12, 13]. The weighted reticulovascular score (WRVS) (e-Lung; Brainomix, Oxford, UK) is an automated biomarker that quantifies reticular abnormalities and pulmonary vascular structures on CT. The WRVS from a baseline CT scan has been demonstrated to be associated with future disease progression in IPF [14] with a threshold level of 15% being strongly associated with subsequent 52-week forced vital capacity (FVC) decline [15]. In patients with IPF, a rise in WRVS of $\geqslant$3% is associated with poorer outcomes and increased risk of death [14].

Whether e-Lung WRVS is also a prognostic factor in non-IPF ILD has not previously been studied, and so we set out to conduct a prognostic factor study [16], to evaluate the performance of e-Lung in test and validation cohorts of patients with non-IPF ILD. We additionally aimed to evaluate the sensitivity of e-Lung to change in disease extent when applied to serial CT scans using previously validated thresholds.

Methods

Clinical and CT data

The test cohort comprised consecutive patients with non-IPF ILD from the Open Source Imaging Consortium (OSIC) accessed in May 2022. OSIC is a General Data Protection Regulation secure not-for-profit organisation with CT scans and matched clinical data contributed by clinical, academic and pharmaceutical industry partners. The OSIC Data Repository has central institutional review board (IRB) and multiple institution IRB approvals. Patients were eligible for the study if they had a diagnosis of non-IPF ILD as designated by the contributing site and had at least one non-contrast enhanced volumetric thoracic CT with slice thickness $\leqslant$2.5 mm. Additional data included patient demographics and survival time from the date of the CT to time of death, lung transplantation or censoring. In patients for whom serial CT scans were available (6–18 months from baseline), serial change of e-Lung biomarkers was evaluated against survival measured from the date of the second CT scan.

The validation cohort comprised consecutive patients prospectively enrolled to the CoWorker registry of fibrotic ILD in Heidelberg, Germany. This registry has been used previously to validate several definitions of progressive fibrosing ILD with between 30% and 50% of patients meeting criteria for progression depending on the definition applied [17].

e-Lung automated CT biomarker evaluation

e-Lung automatically segments the lung parenchyma on CT scans leveraging multiclass neural network (CNN) methods based on the two-dimensional UNet architecture (supplementary methods) [14]. It then identifies and measures various lung patterns and structures using imaging characteristics such as shape and intensity. Unlike traditional methods for automated disease quantification that rely on manually crafted features, CNNs represent a type of deep-learning technology. The reticulovascular score biomarker (RVS), calculated as a percentage of lung volume, is determined automatically by detecting all voxels in the lung area that resemble branching vessel-like structures or linear features with similar density to pulmonary vessels reflecting reticulation (figure 1). The WRVS is calculated by summing these voxels with a weighting that considers their relative positions within the lungs. This weighting mechanism, based on Euclidian distance from the outer lung boundary, prioritises the outer regions of each lung, considering that peripheral fibrotic conditions are often linked with a poorer prognosis [9]. The final WRVS is quantified as a ratio of peripheral lung volume, expressed as a percentage.

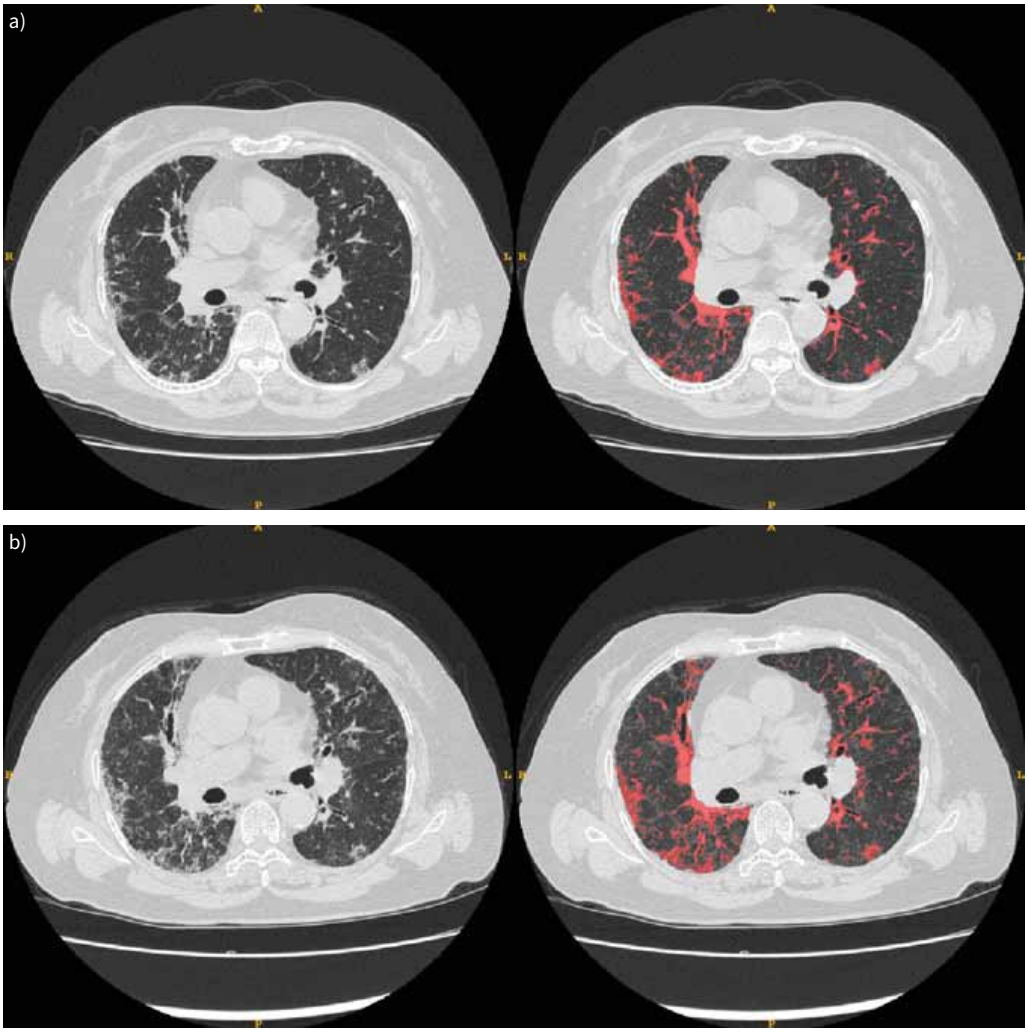

FIGURE 1 Example of a patient from the Open Source Imaging Consortium with a) baseline and b) follow-up computed tomography scans, 50 weeks apart. The left-hand side of each panel shows the original high-resolution computed tomography scan and the right-hand side demonstrates the e-Lung segmented reticulovascular structures. The weighted reticulovascular score for a) the baseline scan is 20.1% and b) the follow-up scan is 27.2%.

Statistical methods

Cohort characteristics are presented using mean±SD or median (interquartile range (IQR)) for continuous variables, and number and percentage for binary and categorical variables.

To assess the value of WRVS as a prognostic factor we sought to understand its relationship to future outcomes, including transplant-free survival, and 12-month FVC decline.

To model relationships between biomarkers and transplant-free survival, we used Cox regression, censoring at the last known follow-up time point. To assess the strength of relationships we report hazard ratios (HRs) with 95% confidence intervals. Where different predictors are being compared, but are quantified using different units, the hazard ratio is not directly comparable, and therefore we additionally report the Harrell C-index. For binary variables, relationships were plotted graphically using Kaplan–Meier curves.

To assess relationships between biomarkers and 12-month FVC decline and between serial CT changes and outcome, we used two different approaches depending on the cohort. In the OSIC cohort, serial FVC and CT time points closest to 1 year were used to determine change from baseline. The Heidelberg cohort

had a more irregular follow-up schedule. For serial CT analysis, CT scans closest to 1 year were analysed where the time interval between scans was 6–24 months. We used a mixed-effects model to estimate the levels of FVC at 12 months based on serial measurements. This model included a second-degree polynomial of time as a fixed effect to capture the nonlinear trajectory of FVC decline, which is often observed in the study population. We used a random coefficients approach where both the intercept (baseline FVC) and the slope (rate of decline) were allowed to vary for each patient, identified by a unique patient identifier. This approach accounts for subject-specific variability and handles unbalanced data. To assess model performance, we visually inspected the fitted individual trajectories against the observed FVC measurements. The model was then used to extrapolate FVC values for each patient at 12 months, and these predicted values were used to calculate the decline from baseline. For FVC, clinically significant decline was ⩾10% [18]. If patients died before 12 months, they were included as decliners. The outcome was then used in a logistic regression model to determine odds ratios for predictive biomarkers. Baseline WRVS was dichotomised at a 15% threshold, based on previous work [14, 15]. In sensitivity analyses, we ran the same models with FVC decline defined as an absolute reduction in FVC of ⩾5% over 12 months.

Univariable and multivariable Cox regression determined relationships between change in CT biomarkers and outcome. The previously validated change in WRVS of 3% absolute change [14] was assessed against survival, using univariable and multivariable Cox regression analyses.

Results

The test cohort from the OSIC database comprised 302 patients with non-IPF diagnoses: 31 (10%) with fibrotic hypersensitivity pneumonitis, 89 (29%) with connective tissue disease related ILD (CTD-ILD) and 182 (60%) with unclassifiable fibrotic ILD (uILD). The specific diagnosis was made by multidisciplinary team discussion or by an expert pulmonology or rheumatology physician in 296 (98%) of patients. Of these, 89 (29.5%) died or underwent lung transplant during the follow-up period. The overall median (IQR) transplant-free survival was 7.1 (3.2–9.5) years. Patient demographics from the test cohort are shown in table 1. 131 (43%) patients underwent serial CT. Median time between baseline and follow-up scan was 54 weeks (range 29–76 weeks).

Patient characteristics in the validation cohort (n=378) are shown in table 1. This group comprised 157 (42%) patients with fibrotic hypersensitivity pneumonitis, 93 (25%) patients with CTD-ILD, 64 (17%) patients with uILD, 57 (15%) patients with idiopathic nonspecific interstitial pneumonia and seven (1.9%) patients with fibrotic interstitial lung abnormality. All patients were assigned a final ILD diagnosis after multidisciplinary team discussion. 135 (36%) patients underwent serial follow-up CT. Median (IQR) time between baseline and follow-up scan was 56 (45–71) weeks. Survival data were missing in 25 (5%) patients and 144 patients died or underwent lung transplant during the follow-up period. FVC decline outcome could not be calculated in 60 patients. Sensitivity analyses confirmed that there were no differences in baseline demographics for those with missing outcome (supplementary table S1). Overall median (IQR) transplant-free survival was 6.1 years (1.8–inestimable) years.

TABLE 1 Characteristics of test and validation cohorts

	OSIC test cohort	Heidelberg validation cohort
Patients	302	378
Male	165 (55)	209 (55)
Age years	64.80±12.10	67.0±11.5
Baseline FVC % pred	82.60±21.7[#]	72.8±20.2
Baseline D_{LCO} % pred	Not available	47.35±16.96[¶]
Ever-smoker	167 (59)[#]	212 (58)[+]
WRVS % at baseline	12.7±6.96	11.7±5.4
Patients with serial CT	131 (43)	135 (36)
Time between baseline and follow-up CT weeks	54 (49–60)	56 (45–71)
Survival years	7.1 (3.2–9.5)	6.1 (1.8–inestimable)[§]
Follow-up time in survivors years	3.5 (2.0–5.4)	4.5 (2.7–6.0)

Data are presented as n, n (%), mean±SD or median (interquartile range). OSIC: Open Source Imaging Consortium; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; WRVS: weighted reticulovascular score; CT: computed tomography. [#]: 18 patients missing data; [¶]: 37 patients missing data; [+]: 11 missing data; [§]: 60 patients missing survival or follow-up FVC data.

Test (OSIC) cohort results

Associations between baseline CT parameters and survival in test cohort

Baseline CT WRVS was numerically marginally more strongly associated with mortality (HR 1.11, 95% CI 1.08–1.14; p<0.001, C-index 0.75) than baseline FVC % predicted (HR 0.97, 95% CI 0.96–0.98; p<0.001, C-index 0.74). Baseline WRVS remained independently associated with mortality when adjusted for baseline FVC, age and sex (1.07, 95% CI 1.04–1.10; p<0.001, C-index 0.80).

Associations between baseline CT parameters applying binary thresholds and survival in test cohort

Patients with WRVS ⩾15% at baseline CT were at significantly increased risk of mortality (HR 4.77, 95% CI 3.11–7.31; p<0.001, C-index 0.71) (figure 2), and the prognostic significance was retained when adjusted for baseline FVC, age and sex (HR 2.91, 95% CI 1.78–4.76; p<0.001, C-index 0.80). In those with WRVS <15%, 98%, 89% and 82% of patients were alive at 1, 3 and 5 years, respectively, compared to 89%, 48% and 30%, respectively, in those with WRVS ⩾15%.

Associations between baseline CT parameters and future 12-month FVC decline or death in test cohort

In 219 (73%) patients, baseline and follow-up FVC was available (median time between baseline and follow-up FVC 51 weeks, range 28–70 weeks). After adjusting for baseline FVC, age and sex, there was a significant association between baseline WRVS and subsequent FVC decline (10% relative decline in volume) or death at 12 months (OR 1.13, 95% CI 1.06–1.21; p<0.001, C-index 0.72). Similarly, the WRVS was strongly associated with absolute decline in FVC of >5% after adjusting for baseline FVC, age and sex (OR 1.08, 95% CI 1.03–1.15; p=0.004, C-index 0.65).

Associations between serial change CT parameters and outcomes in test cohort

Annualised change in WRVS% from baseline was associated with mortality, adjusted for age and sex and independent of annualised FVC change (HR 1.16, 95% CI 1.10–1.22; p<0.001, C-index 0.76). An increase in the WRVS by ⩾3% identified patients with greater than five times increased risk of death (HR 5.69, 95% CI 2.77–11.70; p<0.001, C-index 0.75) (figure 3), which remained significant when adjusting for baseline FVC, age and sex (HR 4.91, 95% CI 2.34–10.34; p<0.001; C-index 0.80).

Patients with an increase in WRVS of ⩾3% had a mean±SD absolute reduction in FVC volume of 409±317 mL, compared to a mean±SD increase of 3±341 mL in those without. The range of WRVS change on serial CT and its relationship with FVC change is shown in supplementary figures S2 and S3.

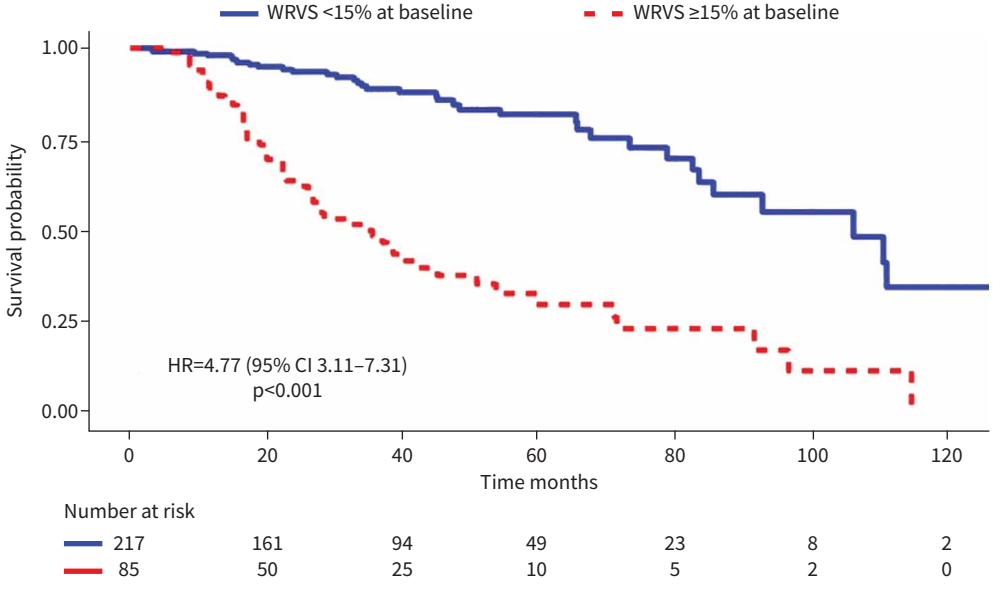

FIGURE 2 Survival probability for patients in the Open Source Imaging Consortium test cohort stratified by a weighted reticulovascular score (WRVS) of <15% or ⩾15%. HR: hazard ratio.

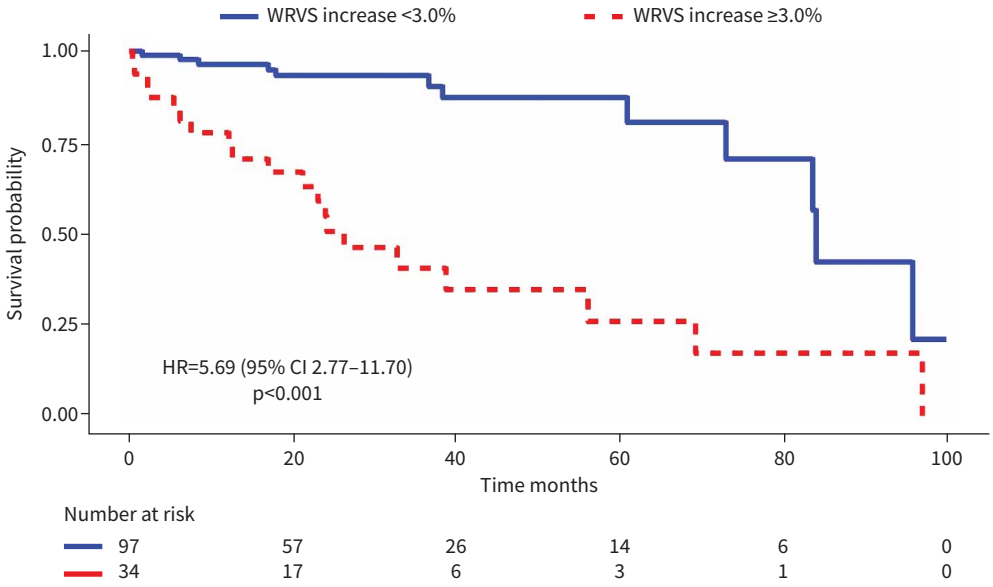

FIGURE 3 Survival probability for patients in the Open Source Imaging Consortium test cohort stratified by a change in weighted reticulovascular score (WRVS) of <3% or ⩾3%. HR: hazard ratio.

Validation (Heidelberg) cohort results

Associations between baseline CT parameters and survival in validation cohort

Baseline CT WRVS was more strongly associated with mortality (HR 1.12, 95% CI 1.09–1.15; p<0.001, C-index 0.72), as compared to FVC % predicted (HR 0.98, 95% CI 0.97–0.99; p<0.001, C-index 0.61), diffusing capacity of the lung for carbon monoxide (D_{LCO}) (HR 0.97, 95% CI 0.95–0.98; p<0.001, C-index 0.68), and Gender, Age, Physiology (GAP) score (HR 1.53, 95% CI 1.38–1.69; p<0.001, C-index 0.71). Baseline WRVS remained independently associated with mortality when adjusted for baseline FVC, age and sex (1.14, 95% CI 1.10–1.18; p<0.001, C-index 0.75), and separately when adjusted for D_{LCO} (HR 1.09, 95% CI 1.05–1.13, p<0.001, C-index 0.72) and GAP score (HR 1.08, 95% CI 1.05–1.11; p<0.001, C-index 0.74).

Associations between baseline CT parameters applying binary thresholds and survival in validation cohort

Patients with WRVS ⩾15% at baseline CT were at significantly increased risk of mortality (HR 3.49, 95% CI 2.48–4.91; p<0.001, C-index 0.63) (figure 4), with prognostic significance retained when adjusting for baseline FVC, age and sex (HR 3.16, 95% CI 2.09–4.76; p<0.001, C-index 0.75), and separately when adjusted for D_{LCO} (HR 2.11, 95% CI 1.39–3.20; p<0.001, C-index 0.70) and GAP score (HR 2.14, 95% CI 1.48–3.11; p<0.001, C-index 0.72).

Associations between baseline CT parameters and 12-month FVC decline or death in validation cohort

In the validation cohort, 318 patients had follow-up FVC or died within 1 year. After adjustment for baseline FVC, age and sex, baseline WRVS was associated with subsequent FVC decline (10% relative decline in volume) or death at 12 months (OR 1.18, 95% CI 1.11–1.25; p⩽0.001, C-index 0.72). Similarly, when defining FVC decline as ⩾5% absolute reduction in % predicted, there was a strong association between WRVS and outcome after adjusting for baseline FVC, age and sex (OR 1.13, 95% CI 1.06–1.21; p<0.001, C-index 0.82).

Associations between serial change in CT parameters and outcome in validation cohort

An increase in annualised WRVS was significantly associated with mortality (HR 1.10, 95% CI 1.00–1.22; p=0.043, C-index 0.56. An increase in WRVS of ⩾3% on serial CT was significantly associated with adverse outcome compared to WRVS change of <3% (HR 1.99, 95% CI 1.09–3.65; p=0.026, C-index 0.57) (figure 5), which remained significant when adjusting for baseline FVC, age and sex (HR 2.22, 95% CI 1.20–4.01; p=0.01, C-index 0.67). Patients with an increase in the WRVS of ⩾3% had a mean±SD absolute reduction in FVC volume of 119±239 mL, compared to mean±SD change of 0±388 mL in those without.

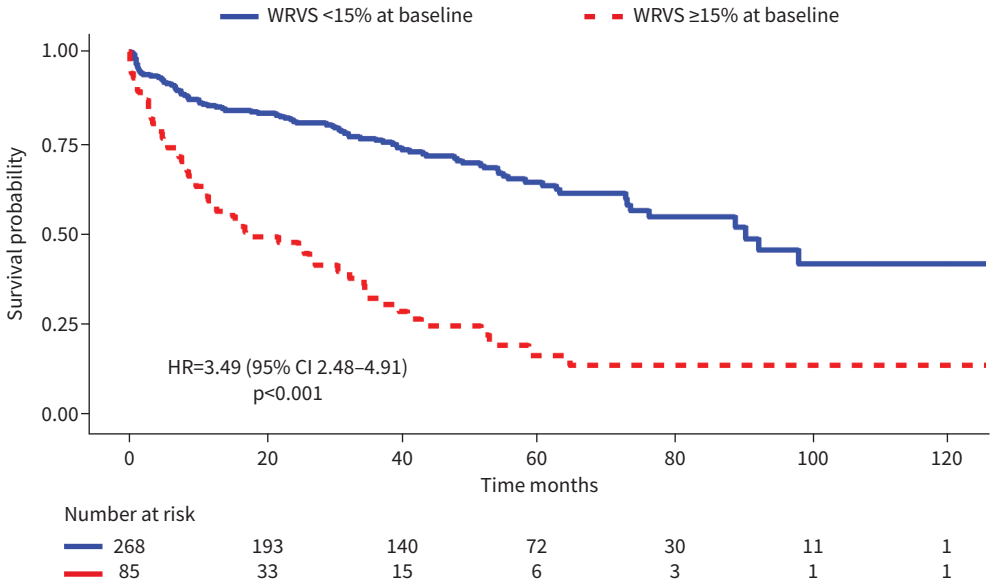

FIGURE 4 Survival probability for patients in the Heidelberg validation cohort stratified by a weighted reticulovascular score (WRVS) of <15% or ⩾15%. HR: hazard ratio.

Discussion

Identification and management of PPF represents a significant challenge in clinical practice [5]. Predicting disease course and identifying factors associated with future progression are crucial for improving prognosis and individualising treatment plans [19]. Our study demonstrates that the use of an automated tool to quantify pulmonary fibrosis from routinely performed baseline CTs allows for risk assessment and timely identification of disease progression. In both test and independent validation cohorts, baseline values of the e-Lung WRVS CT biomarker were a strong prognostic factor for disease progression, in terms of both future lung function decline over the subsequent 52 weeks, and mortality. Additionally, we were able to validate an imaging-based threshold for percentage parenchymal changes that are linked to a

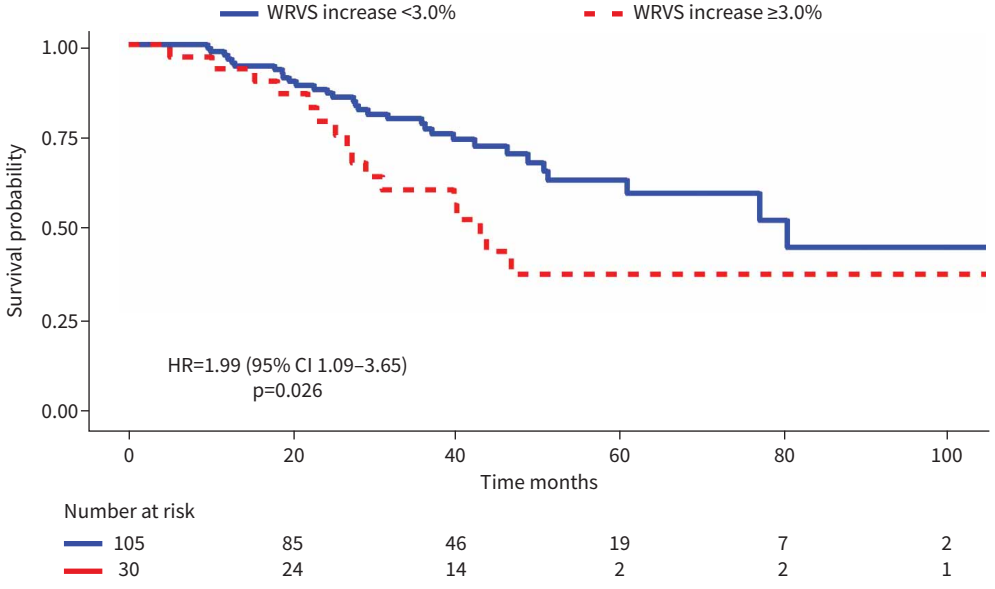

FIGURE 5 Survival probability for patients in the Heidelberg validation cohort stratified by a change in weighted reticulovascular score (WRVS) of <3% or ⩾3%. HR: hazard ratio.

poorer prognosis, as a WRVS ⩾15% proved to be strongly associated with an increased mortality risk. Interestingly, this is the same numeric threshold previously validated in patients with IPF, potentially due to the shared pathobiology between IPF and PPF, particularly when the burden of disease is predominantly peripheral and subpleural in a UIP-like distribution. While integration of UIP status is beyond the scope of this study, we have previously demonstrated that WRVS is prognostic independently of UIP status, suggesting that the extent of disease is more important than the pattern of fibrosis [20].

A number of previous studies have shown a relationship between automated CT biomarkers and adverse outcome both at baseline [21–25] and over serial CT in patients with IPF and PPF [26, 27]. The e-Lung WRVS biomarker uses a novel approach to quantify ILD severity by focusing on the segmentation and measurement of linear structures in a three-dimensional plane using a CNN-based approach without relying on radiologist-labelled regions of interest on an axial plane. This may offer advantages, for example in patients where progression is defined by increased volume and coarseness of reticulation, but where total parenchymal involvement is stable [27].

There is a growing appreciation of the concept that the vasculature plays an important role in the pathogenesis and progression of pulmonary fibrosis, and imaging-based algorithms including e-Lung have previously leveraged this anatomic compartment to prognosticate [14, 22, 23, 28–30]. Our study adds further support to this.

It is acknowledged that confidently separating pulmonary vessels from reticular opacities in the periphery of the lung is not readily done using quantitative or visual methods, as the two structures merge imperceptibly [31]. On this basis, the WRVS is an automated quantitative biomarker that deliberately aims to segment peripheral reticular and vascular structures as a biomarker for lung fibrosis. The peripheral weighting is applied to reflect the known additional prognostic significance provided by fibrotic lung disease located in subpleural regions [9]. We have further validated WRVS as an accurate quantitative measure of pulmonary fibrosis through an analysis of the imaging substudy of the INBUILD clinical trial of nintedanib in PPF. We found that the WRVS was sensitive to fibrosis progression and to the therapeutic impact of nintedanib and that its performance mirrored quantitative lung fibrosis, a quantitative CT tool widely used in ILD clinical trials [32, 33].

In this study, we demonstrate that the WRVS is sensitive to progression on CT and replicate the previous value of 3% [30]; this threshold for change identified patients with IPF at risk of future mortality. It is possible that the minimum clinically important difference for WRVS change is <3%; this is subject to ongoing study. While direct comparisons were not performed in this study, it is considered unlikely that even an expert reader can reliably identify such subtle alterations on a volumetric CT scan of a patient with fibrotic lung disease.

An automated imaging-based biomarker which can both risk-stratify patients for progression at baseline CT and sensitively and objectively identify progression on serial CT is of potential clinical value. It is estimated that approximately half of patients with fibrotic ILD develop PPF [34], and so identifying patients for closer monitoring is an imperative, as the earliest introduction of antifibrotic therapy is associated with the best patient outcomes [4] Currently, the assessment of fibrosing ILD progression primarily relies on subjective visual estimation of CT which is affected by interobserver variability [7] or lung function parameters, particularly FVC and diffusing capacity for carbon monoxide (D_{LCO}), both of which are influenced by effort dependency or intralaboratory variability [35].

Our study has certain limitations. The data were analysed retrospectively, and the validation cohort comprised patients from a single centre, which may have introduced selection bias and resulted in potential loss to follow-up. As a result, there was missing data in this cohort, but a sensitivity analysis shows that there was no difference in baseline demographics, disease severity or imaging biomarkers in those without follow-up data, minimising the likelihood this represents a source of bias. CT scans analysed in this study followed strict inclusion criteria. Images acquired outside of dedicated lung centres may not meet these high standards, potentially raising questions surrounding the generalisability of the data generated. However, it is an important mitigating factor that the test cohort comprised patients and scans from a real-world consortium, and by definition therefore a wide variety of institutions, healthcare settings, scanner manufacturers and acquisition parameters. e-Lung has been shown to prognosticate regardless of these factors in previously published sensitivity analyses [30]. In this study, we elected to focus on the detection and quantification of reticulation and vascular structures within fibrotic lungs. Imaging features of ILD are diverse and include other parenchymal abnormalities, such as ground-glass opacities. These were not considered in this study and are the subject of separate ongoing studies. Due to the nature of this

study, it was not possible to conduct an analysis regarding a potential difference in patients' response to therapy; this should be the subject of future research. While we did not formally evaluate whether pulmonary arterial hypertension might have been a relevant confounder, the linkage between WRVS and FVC decline makes it likely the mortality signal identified relates to fibrosis progression. However, it is possible that that pre-clinical features of pulmonary vascular remodelling are detected by e-Lung and so understanding the role of the vasculature in IPF prognosis is of importance and the focus of separate studies. Finally, D_{LCO} % predicted values were only available in the validation cohort and not in the test cohort, and so it was only possible to perform a comparison of the prognostic performance of WRVS with D_{LCO} in the validation cohort.

In summary, we have shown that when applied to baseline, routinely performed HRCT scans, e-Lung WRVS is an independent prognostic factor in a diverse cohort of patients with non-IPF fibrotic ILD and can identify patients at risk of future PPF and mortality. Progression of the e-Lung WRVS biomarker is more strongly associated with future mortality than FVC decline. These data support the further evaluation of e-Lung as a potential tool to assist decision making in the clinical care of patients with fibrotic ILD and could be incorporated into future clinical trials.

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Provenance: Submitted article, peer reviewed.

Ethics statement: The Open Source Imaging Consortium Data Repository has Central institutional review board (IRB) and multiple institution IRB approvals. The CoWorker registry of fibrotic ILD in Heidelberg, Germany has local ethical approval.

Author contributions: K. Abbasi Dezfouli, A. Devaraj, C. Fernandez, O. von Stackelberg, C.P. Heussel, G.W.J. Harston, P.M. George and M. Kreuter conceived the study. F.A. Ottink, C. Rennison-Jones, W. Bou-Zeid and O. Joly performed the imaging biomarker analyses. S. Gerry performed the statistical analyses. All authors drafted the manuscript and approved the final version.

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