Deep-learning CT imaging algorithm to detect UIP pattern in patients with SSc-ILD: association with disease progression and survival

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Key messages:

- A quarter of SSc-ILD patients were classified as having an 'intermediate probability of UIP'
- A higher UIP probability is associated with greater disease progression and worse survival
- These relationships are independent of demographics and baseline disease severity

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ABSTRACT

Objectives: Interstitial lung disease (ILD) is the most common cause of death in patients with systemic sclerosis (SSc), although disease behavior is highly heterogenous. While a usual interstitial pneumonia (UIP) pattern is associated with worse survival in other ILDs, its significance in SSc-ILD is unclear. We sought to assess the prognostic utility of a deep-learning HRCT algorithm of UIP probability in SSc-ILD.

Methods: Patients with SSc-ILD were included if HRCT images, concomitant lung function tests, and follow-up data were available. We used the Systematic Objective Fibrotic Imaging analysis Algorithm (SOFIA), a convolution neural network algorithm which provides probabilities of a UIP pattern on HRCT images. These were converted into the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)-based UIP probability categories. Decline in lung function was assessed by mixed-effect model analysis and relationship with survival by Cox proportional hazards analysis.

Results: 522 patients were included in the study. 19.5% were classified as UIP not in the differential, 53.5% as low probability of UIP, 25.7% as intermediate probability of UIP, and 1.3% as high probability of UIP. A higher likelihood of UIP probability expressed as PIOPED categories was associated with worse baseline FVC, as well as with decline in FVC (-0.08 (-0.14- -0.02), p=0.008), and worse 15-year survival (HR:1.88 (1.30-2.71), p=0.001), both independently of age, gender, ethnicity, smoking history, and baseline FVC.

Conclusion: Higher probability of a SOFIA-determined UIP pattern is associated with more advanced ILD, disease progression, and worse survival, suggesting that it may be a useful prognostic marker in SSc-ILD.

INTRODUCTION

Interstitial lung disease (ILD) is the main cause of morbidity and mortality in patients with Systemic Sclerosis (SSc). However, great variability exists in individual trajectories; while ILD remains limited in some patients, over a third of patients have progressive ILD, resulting in worsening breathlessness, and premature death. Recent data suggest that early treatment in patients at high-risk of progression protects against the development of fibrosis (1). Accurate tools that predict future disease progression, early in the disease course, are urgently needed.

The most common histopathological pattern in SSc-ILD, seen in over two-thirds of patients, is nonspecific interstitial pneumonia (NSIP). Histologically, NSIP is identified by a uniform distribution of interstitial changes, characterised by expansion of alveolar interstitium through inflammation and fibrosis. A usual interstitial pneumonia (UIP) pattern can also be seen, although much less frequently. In contrast to NSIP, UIP is characterised by regional heterogeneity, with areas of seemingly normal lung adjacent to areas of established fibrosis with fibroblastic foci, rare in NSIP, and microscopic honeycomb changes, absent in NSIP (2). While it is now recommended that all patients with SSc have a chest high resolution computed tomography (HRCT), surgical lung biopsies are rarely performed as a histological

pattern of UIP was not associated with a significantly worse survival than NSIP in an under-powered cohort (3).

There are no data that convincingly address the relationship between radiological pattern and mortality in SSc-ILD, the majority of studies are small and have not been appropriately adjusted for confounders. In a study of 359 patients with connective tissue disease-ILD, 207 with SSc-ILD, although an HRCT UIP pattern was associated with a higher risk of death than NSIP on univariable analysis, this was not independent of demographic variables (4). HRCT UIP was associated with higher mortality in 33 Japanese SSc-ILD patients, classified as either 'CT-UIP' (n=15) or 'CT-inconsistent with UIP' (n=18), however, no multivariable analyses were reported (5). Another study of Japanese SSc-ILD HRCT (n=48) found that there was no significant difference in survival with or without a UIP pattern (6).

These previous studies utilised traditional visual-based assessment of HRCT pattern, which is known to have high levels of interobserver variability and poor reproducibility. Computer-based assessment of HRCT pattern on the other hand can detect and capture subtle UIP-like features. The Systematic Objective Fibrotic Imaging analysis Algorithm (SOFIA) is a deep convolutional neural network, developed and validated in idiopathic fibrotic lung disease, to identify the probability of a UIP pattern (7). In 504 patients in the Australian IPF Registry, SOFIA UIP probabilities were predictive of transplant-free survival, independently of disease severity (HR:1.06 (1.04-1.08), $p<0.0001$) (8).

Computer-based analysis of HRCT images has outperformed visual-based assessments in different settings (9-12) but has not been extensively evaluated in SSc-ILD. We investigated whether SOFIA can significantly add to conventional prognostic biomarkers in SSc-ILD.

METHODS

Study population

Consecutive patients with a diagnosis of SSc-ILD presenting at the Royal Brompton Hospital Interstitial Lung Disease Unit from January 1990 to December 2019, were considered for this study. Diagnoses were made as per contemporaneous guidelines (13, 14). Approval was obtained from the Royal Brompton and Harefield hospitals institutional ethics committee (IRAS: 234527, REC: 18/LO/1392). Baseline was defined as the date of HRCT. Patients were only included in the study if lung function measurements within 6 months of baseline were available. Lung function measurements were performed in a single lab, including FVC and DLCO levels, as previously reported (15). Echo-reported Pulmonary Artery Systolic Pressure (PASP) within 1 year of baseline was recorded. All-cause mortality was collected until death, transplant, loss to follow-up, or end of study period (31/07/2023).

SOFIA

The SOFIA algorithm was run as previously described (8). The input is a four-HRCT slice montage, with an output of a set of continuous numbers, each representing a probability of each of the four UIP diagnosis categories, whose sum is 1.0. The SOFIA-determined UIP

probability scores were then converted into Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED)-based probability categories: UIP not included in the differential (0-4%); low probability of UIP (5-29%); intermediate probability of UIP (30-69%); high probability of UIP (70-94%); and pathognomonic for UIP (95-100%), originally developed for categorical estimation of probability of pulmonary embolus (16).

Statistical analysis

Analyses were performed using STATA15.1 (StataCorp, USA). Survival analysis was performed using proportional Cox regression. Confounders added in all multivariable analyses included age, gender, ethnicity, smoking history (ever/never), and baseline lung function to adjust for disease severity. Proportionality of the hazard function over time was assessed using Nelson-Aalen cumulative hazard plots (17), and linearity of the proportional-hazards assumption of each covariate over time by analysis of Schoenfeld residuals. Cumulative hazards were reasonably linear for at least 15 years, so this interval was selected for the survival analyses (Figure S1 in the Supporting Information). We found FVC violated the proportional hazard assumption, as the effect on survival was modest initially and started to increase after approximately two years. Accordingly, in the adjusted survival models, an interaction term between FVC and time >2 years was added (18).

The relationships between UIP probability and lung function measures were assessed by Spearman's correlation, and between PIOPED categories and lung function quartile by Kruskal-Wallis test. The relationship between SOFIA likelihoods and disease progression was assessed using change in FVC, based on its established primacy as a marker of ILD progression in clinical practice and SSc-ILD trials. Quantified using linear mixed-effects analysis, which accounts for variations in test intervals, using FVC (L) as the outcome measure with subject as a random effect and time from baseline and confounding variables as fixed effects. A p-value of <0.05 was considered significant.

RESULTS

Study population

A total of 736 eligible SSc-ILD patients were identified from our databases. Of these 214 were excluded because of unavailable/poor quality HRCT images, lung function, or follow-up data, leaving 522 patients included in the study (Figure 1). The baseline demographic and clinical characteristics of the study population are shown in Table 1.

SOFIA probabilities

When the PIOPED categories were applied, 19.5% of patients were classified as 'UIP not included in the differential', 53.5% as 'low probability of UIP', 25.7% as 'intermediate probability of UIP', and only 1.3% classified as 'high probability of UIP'. None of the HRCT scans were classified as 'pathognomonic for UIP' (Table 2).

The seven patients classified as 'high probability of UIP' were pooled with those classified as 'intermediate probability' for all further PIOPED analyses.

Relationship with disease severity

Formal visual scoring of the extent of fibrosis on HRCT was not performed, instead, lung function indices were used as measures of disease severity.

There was a significant inverse correlation between SOFIA-determined UIP probability and more severe lung function impairment, FVC (Rho=-0.33,) and DLCO (-0.48) ($p<0.0001$ for both). The distribution of PIOPED UIP probabilities was therefore examined according to FVC and DLCO quartiles, with higher PIOPED UIP pattern probabilities observed with decreasing baseline lung function quartiles, i.e. more severe disease impairment (Table 3).

Relationship with disease progression

On linear mixed-effect model analysis, SOFIA PIOPED categories were significantly associated with decline in FVC on univariable analysis (coefficient (95% CI): -0.35 (-0.45- -0.24), $p<0.001$), and in a multivariable model including age, gender, ethnicity, smoking history, and baseline FVC (-0.08 (-0.14- -0.02), $p=0.008$). A similar association was seen when the multivariable model included DLCO instead of FVC (-0.10 (-0.19- -0.01), $p=0.02$).

See also Supplementary Data S1 for results examining UIP probability as a continuous variable.

Relationship with survival

Within 15 years of follow-up there had been 287 deaths, corresponding to 55% of the study population. On univariable analysis, age, gender, ethnicity, smoking history, and measures of baseline lung function were associated with survival (Table 4). Compared to the PIOPED catergory of 'UIP not included in the differential ', an 'intermediate/high UIP probability' was also associated with worse 15-year survival (HR:2.11 (95%CI:1.49-2.98), $p<0.001$), while there was no signifcant difference in the patients with a 'low probability of UIP' (HR:1.26 (0.91-1.73). Median survival in the 'intermediate/high UIP probability' group was 6.75 years (95%CI: 3.01-15.01) compared to 12.32 (5.72-19.53) years in the 'low probability of UIP', and 14.59 (7.18-23.01) years in the category of 'UIP not in the differential'.

The association of the 'intermediate/high UIP probability' group with worse survival remained significant on multivariable analysis adjusting for age, gender, ethnicity, smoking history, and baseline FVC (HR:1.88 (1.30-2.71), $p=0.001$) (Figure 2). However, on inclusion of baseline DLCO instead of FVC, the relationship was no longer significant (HR:1.15 (0.79-1.69), $p=0.46$).

Similar results were seen when baseline PASP≥40 was included in the multivariable analysis, although with trends only bordering on significance for the analysis including FVC (Supplemental Table S1).

DISCUSSION

This study investigates the prognostic utility of the deep-learning CT imaging algorithm SOFIA in patients with SSc-ILD. The probability of a UIP pattern was low in most patients, in keeping with the known low prevalence of UIP in SSc-ILD, where fibrotic NSIP is known to predominate (2, 19). None of the patients in this study had a UIP probability sufficiently high to be classified as 'pathognomonic for UIP', and only a handful were classed as having a 'high probability of UIP'. However, a quarter of patients were categorised as having an 'intermediate probability of UIP', and this was associated with greater SSc-ILD progression as determined by FVC decline, and a significantly shorter survival. Computer-based assessment of HRCTs can objectively analyse and quantify disease, capturing the probability of a UIP pattern as a continuous variable, providing a more detailed reflection of more subtle UIP-like features which may be overlooked with visual based assessment.

In interpreting these observations, it is important to stress that SOFIA, an unsupervised deep learning algorithm, does not base the definition of 'UIP probability' on CT markers of UIP used routinely in radiological practice. The SOFIA algorithm was trained against human observation by skilled radiologists (7). However, unsupervised AI integrates all available CT information, including, potentially, variables that cannot be identified or quantified using human observers (20). In principle, this might include subtle CT signs of lung senescence or the processing of intricate small vessel abnormalities that can be quantified objectively but not by eye (11), along with other unrecognised variables. This is an important caveat because if, as discussed below, NSIP evolves to UIP in some SSc-ILD patients, it is likely that an admixture of NSIP and UIP will be designated as indicative of an intermediate probability of UIP, with concurrent NSIP features reducing UIP likelihood. We suggest that this may partially explain the low prevalence of 'high probability of UIP' in our study whilst also accounting for the prognostic importance of an 'intermediate probability of UIP'.

Early treatment in SSc-ILD patients at high-risk of progression protects against the development of fibrosis or slows progression (1, 21), hence the need for accurate tools that predict ILD progression in SSc. There are therapeutic options available to treat SSc-ILD patients including immunosuppressants and antifibrotic agents. However, the decision to initiate treatment and its timing are often difficult. In particular the timing of treatment with the antifibrotic nintedanib is difficult, as the drug can be associated with significant side effects and does not lead to an improvement of symptoms, although it slows disease progression. In the UK, antifibrotic treatment can only be prescribed in non-IPF patients once it has been shown that progression has occurred despite optimal traditional therapy, which usually includes immunosuppression. This delay in treatment until progression has been observed is far from ideal, as progression of fibrotic disease is irreversible, thus leaving the patient with further loss of lung function and worsened symptoms and quality of life. Timing of referral for lung transplant is equally complex. Our study suggests that a machine-

learning algorithm to identify UIP pattern applied to baseline imaging data of patients with SSc-ILD provides valuable prognostic information in addition to established baseline clinical predictors. This may aid in earlier patient selection for initiation of anti-fibrotic treatment and in the timing of initial lung transplant referral in selected patients.

Increasing probability of a UIP pattern on HRCT had prognostic significance in this cohort of SSc-ILD patients, independently of the demographic variables age, gender, ethnicity, and smoking history. The association between a higher probability of a UIP pattern and worse survival was maintained when baseline FVC was included in the analysis. However, this association was lost when baseline DLCO was included in the model. This could be explained by the fact that DLCO reflects both parenchymal and vascular involvement, while FVC more specifically reflects the severity of the ILD. Concomitant pulmonary vascular involvement is a frequent and difficult to diagnose complication in SSc-ILD (22), and is itself one of the main causes of early death in SSc patients (23, 24). Although our analysis did not substantially change after adjusting for a PASP>40 mmHg on echocardiogram, echocardiography provides an inaccurate estimate of the presence of pulmonary hypertension. Vascular abnormalities occur well before the development of clinically evident pulmonary hypertension, through a variety of pathways including inflammatory and fibrotic pre- and post-capillary changes (25), which are not easy to identify. Vascular abnormalities with close connections with fibroblastic foci, characteristic of UIP but not NSIP, have been described, with fibroblastic foci forming an interconnected reticulum, closely intertwined with an extensive and abnormal vascular network (26, 27). Alternatively, we cannot exclude that DLCO may be a better marker of baseline ILD severity than FVC.

CT changes suggestive of a UIP pattern may be associated with more severe disease, occurring later in the disease course. The evolution of a fibrotic NSIP into a UIP pattern has been described in the idiopathic setting (28) and in rheumatoid arthritis-ILD (29). In 127 SSc patients undergoing lung transplant, histopathological examination revealed that 87% of the explanted lungs were characterised by a UIP pattern, a far greater proportion than seen in the general SSc-ILD population. Nineteen of the patients with a UIP pattern at the time of transplant, also had histology performed from previous surgical lung biopsies, of which eight showed a different pathology at the two time-points. These data suggest that a UIP pattern occurs in more severe ILD in SSc (30). However, the fact that the SOFIA algorithm is associated with FVC decline, even after adjusting for FVC or DLCO in the multivariable model, suggests that increasing likelihood of a SOFIA UIP pattern has prognostic implications that are independent of baseline ILD severity.

It has recently been suggested that primary UIP (IPF) and secondary forms of UIP, most commonly encountered in fibrotic hypersensitivity pneumonitis and ILD associated with rheumatoid arthritis, might usefully be grouped as a stand-alone biologic entity, based on shared pathogenetic pathways and strikingly similar rapidity of progression, as judged by mortality and serial pulmonary function decline (31). The authors highlighted UIP in SSc-ILD as a possible exception to this rule, based on a lack of differences in outcomes in underpowered SSc-ILD cohorts. The unsupervised deep-learning SOFIA algorithm, identifying the likelihood of UIP, has previously provided striking prognostic separations in suspected IPF and in a broader cohort of non-IPF fibrotic ILDs (8). The current study suggests that similar prognostic separations exist in SSc-ILD, underpinning the AI

identification of UIP likelihood across the range of fibrotic ILDs as potentially indicative of a distinct biologic entity.

The association between disease severity and an increasing likelihood of UIP in SSc-ILD merits further discussion. The association may in part represent a higher likelihood of progression as UIP likelihood increases, with linkage to disease severity for that reason alone. However, it is also conceivable that NSIP evolves towards UIP in selected patients, especially when ILD is more severe. This may, at first seem counterintuitive: in idiopathic disease, there are data indicating that in IPF, a UIP pattern is present histologically even in early disease (32), and is also present in a subset of patients with ILAs (33). Epidemiologic data suggest that airborne injury, sometimes long before IPF is diagnosed, may result in an IPF predilection (34). Airway injury is evident in SSc-ILD, even in early ILD (35, 36). We suggest that airway injury in a pre-existing ILD other than IPF, in this case SSc-ILD, may have a similar role to previous extrinsic airway insults documented in epidemiologic studies, in promoting evolution to UIP.

Our study has some limitations. In order to achieve the large cohort utilised in this study it was necessary to use a wide recruitment window of 20 years. There have been changes in referral patterns during the study period, with a shift in recent times towards more frequent referral of severe SSc-ILD patients, while patients with less severe ILD are managed locally. Also, the Royal Brompton Hospital is a tertiary specialist respiratory center and therefore the cohort may not be representative of more general SSc-ILD population, as more severe cases are referred for assessment and treatment. Another unavoidable limitation of our study is the inability to adjust for treatment differences. Treatment regimens in SSc-ILD are too variable to allow categorical sub-analysis during longer term follow-up. There is a major variability in the choice, timing, and duration of treatment with large modifications often made due to side effects or non-efficacy.

In summary, this study has demonstrated the prognostic utility of the deep-learning algorithm SOFIA in SSc-ILD. Despite not being a common feature in SSc-ILD, higher SOFIA-determined probability of a UIP pattern on HRCT was associated with more severe disease, greater likelihood of SSc-ILD progression, and reduced survival. Incorporation of automated machine-learning algorithms in the work up of patients with SSc-ILD has the potential to significantly improve our prognostic ability and to therefore provide greater certainty as to which patients are more likely to progress in the future. If confirmed by future prospective studies, automated analysis of HRCT scans could be utilised clinically to improve prognostication in SSc-ILD, and aid identification of patients at risk of future disease progression who would benefit from prompt initiation of treatment.

	N=522
Age at baseline	53.7 (23.8-78.4)
Gender (Female)	389 (74.5)
Ethnicity (European)	360 (69.0)
Smoking (Never)	311 (60.5)
Cutaneous involvement (diffuse)*	147 (38.1)
Autoantibodies#	
ATA	193 (40.9)
ACA	34 (7.2)
Others	131 (27.8)
Baseline lung function	
DLCO% predicted	41.9 (31.9-54.5)
FVC% predicted	74.2 (57.8-88.9)

Table 1. Study population demographics.
Data are presented as; age: mean (range), all other data are presented as median (interquartile range), or number (percentage value) as appropriate. *n=386, # n=472. ACA: anti-centromere antibodies, ATA: anti-topoisomerase antibodies, DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity

	UIP probability	N	%
UIP not included in the differential	0-4%	102	19.5
Low probability of UIP	5-29%	279	53.5
Intermediate probability of UIP	30-69%	134	25.7
High probability of UIP	70-94%	7	1.3
Pathognomonic for UIP	95-100%	0	0

Table 2. PIOPED classification.

The number of patients classified into each PIOPED category based on SOFIA-determined UIP probability are shown. PIOPED: Prospective Investigation of Pulmonary Embolism Diagnosis, UIP: usual interstital pneumonia

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
FVC				
UIP not included in the differential	41 (7.9)	26 (5.0)	17 (3.3)	18 (3.5)
Low probability of UIP	77 (14.8)	80 (15.4)	62 (11.9)	58 (11.2)
Intermediate/High probability of UIP	13 (2.5)	23 (4.4)	52 (10.0)	53 (10.2)
DLCO				
UIP not included in the differential	43 (8.3)	30 (5.8)	20 (3.8)	9 (1.7)
Low probability of UIP	75 (14.4)	79 (15.2)	71 (13.6)	54 (10.4)
Intermediate/High probability of UIP	8 (1.5)	26 (5.0)	39 (7.5)	67 (12.9)

Table 3. PIOPED categories according to FVC and DLCO quartile.

Data are presented as number (%). DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity, UIP: usual interstitial pneumonia

	HR (95% CI)	p-value
Age at baseline	1.04 (1.03-1.06)	<0.001
Gender	1.46 (1.31-1.88)	0.003
Ethnicity	0.65 (0.50-0.84)	0.001
Smoking history	1.42 (1.12-1.79)	0.004
Cutaneous involvement*	1.11 (0.94-1.48)	0.46
Autoantibodies[#]		
ATA	0.94 (0.73-1.21)	0.62
ACA	1.51 (0.99-2.31)	0.05
Baseline lung function		
DLCO% predicted	0.96 (0.95-0.97)	<0.001
FVC% predicted	0.99 (0.98-0.99)	<0.001
SOFIA		
UIP probability	4.46 (2.49-7.97)	<0.001
PIOPED categories	1.49 (1.25-1.77)	<0.001

Table 4. Univariable survival analysis.

15-year survival using Cox-regression analysis. *n=386, [#] n=472. ACA: anti-centromere antibodies, ATA: anti-topoisomerase antibodies, DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity, UIP: usual interstitial pneumonia

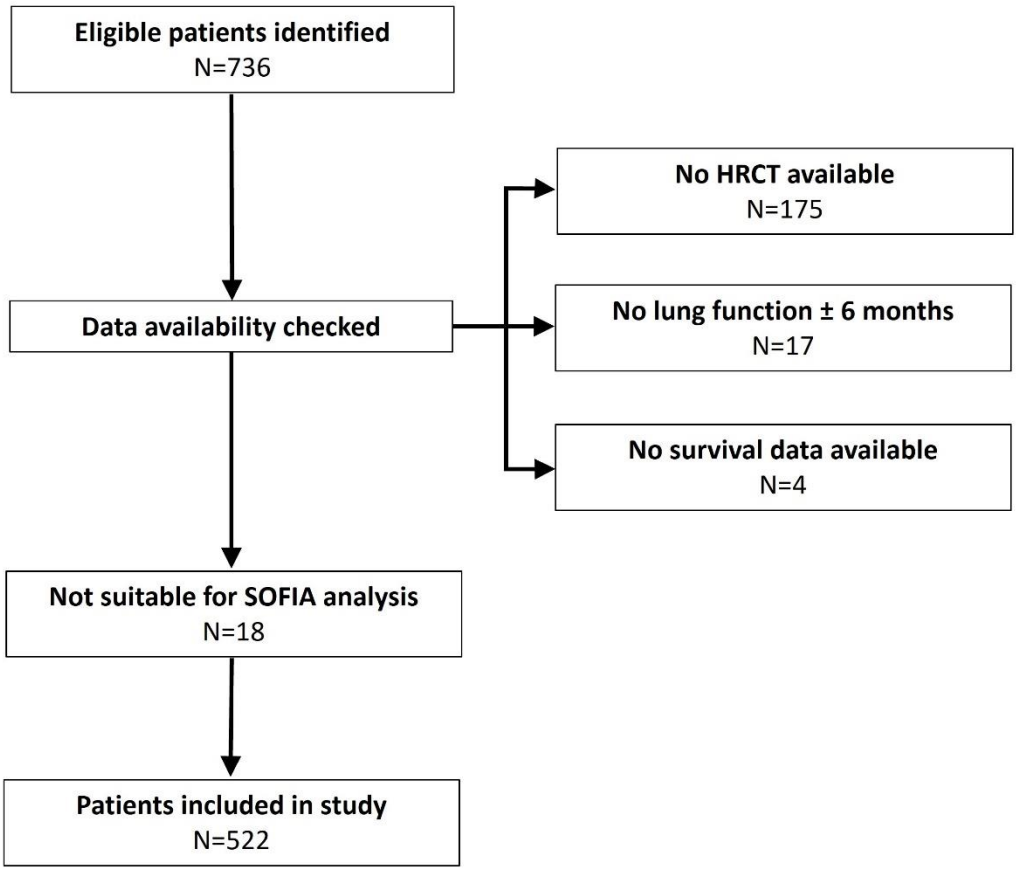

Figure 1. Flow diagram of patient selection

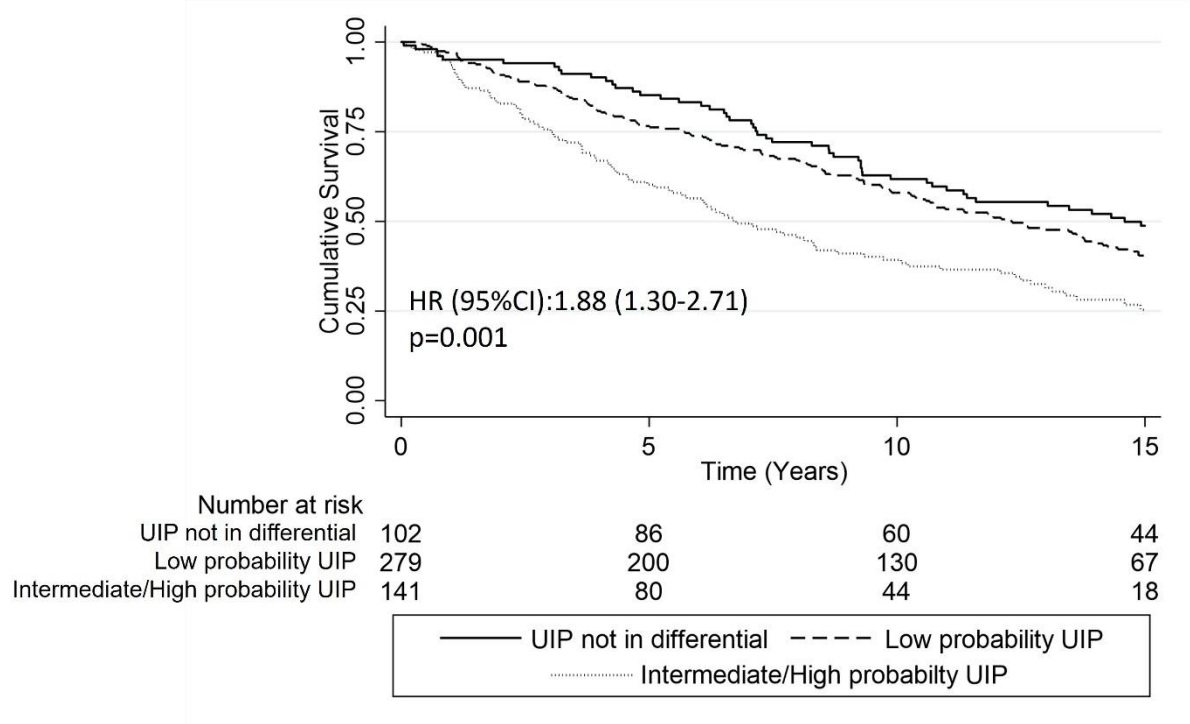

Figure 2. Survival according to PIOPED category. Kaplan-Meier survival analysis grouped by PIOPED category. HR and p-value shown are for multivariable analyses including age, gender, ethnicity, smoking history, and baseline FVC.

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Conflicts of interest

VK reports lecture fees from Novartis and Boehringer Ingelheim.

PMG reports research grant from Boehringer Ingelheim, personal fees from Boehringer Ingelheim, Roche, Teva, Cipla and Brainomix, conference attendance support from Boehringer Ingelheim, and Roche, and Stock in Brainomix.

FC reports lecture fees and conference attendance support from Boehringer Ingelheim.

AD reports personal fees from Boehringer Ingelheim, Roche, Brainomix, Astra Zeneca, and stock options in Brainomix.

CD reports consultancy fees from Janssen, GlaxoSmithKline, Bayer, Sanofi, Boehringer Ingelheim, Roche, CSL Behring, Corbus, Acceleron, Horizon, Arxx, Lilly, Novartis, Certa and research grants to institution from Abbvie, Servier, Horizon, and GlaxoSmithKline.

AUW reports consultancy and lecture fees from Roche, Boeringher Ingelheim and Veracyte, and is President of WASOG.

EAR reports advisory board and lecture fees from Boeringher Ingelheim and Roche, and lecture fees from Mundipharma.

All other authors declare no conflict of interest.

Ethics

This study was performed in accordance with the Declaration of Helsinki. The Ethics Committee of the Royal Brompton and Harefield Hospitals gave authorisation for the study (REC: 18/LO/1392, IRAS: 234527). Adult participant consent was not required for institutional approval as the research was based on retrospective review of previously collected non-identifiable information.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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