^{18}F-FDG PET Predicts Patient Survival in Patients with Systemic Sclerosis Associated Interstitial Lung Disease (SSc-ILD)

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Key Results = 75 words (max 75 words):

- Mortality in our cohort of patients with Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) was associated with high pulmonary ^{18}F-FDG uptake in affected lung (SUV_{max}, p=0.027), high background uptake in normal appearing lung (SUV_{min}, p=0.002) and high target-to-background ratio (TBR, p=0.016).
- Multi-variate Cox-regression analysis revealed that SUV_{min} (p=0.017) and ILD-GAP index (p=0.024) were the only independent predictors of overall survival which when combined (modified-ILD-GAP index) further refined the ability to predict mortality (p<0.001, log-rank test).

Summary Statement = 29 words (max 30 words):

Original data demonstrates that high pulmonary ^{18}F-FDG uptake is associated with poor survival

in SSc-ILD and may therefore be a much-needed sensitive biomarker to help risk stratify these patients.

Running Heading

^{18}F-FDG uptake in SSc-ILD

Word count= **3071** (2998 excluding conclusion, max 3000 words)

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Abstract = 300 words (max 300 words)

Rationale: There is a lack of effective prognostic biomarkers in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD).

Objective: To investigate the potential of ^{18}F-FDG-PET/CT to predict mortality in SSc-ILD.

Methods: 45 patients with SSc-ILD (12-male, 33-female, mean-age 58.9±9.9yrs) were prospectively recruited for ^{18}F-FDG-PET/CT. All patients underwent full clinical assessment including multidisciplinary team review, HRCT evaluation and standard pulmonary function tests (PFTs). The overall maximum pulmonary uptake of ^{18}F-FDG (SUV_{max}), minimum pulmonary uptake or background-lung-activity in unaffected lung (SUV_{min}) and target-to-background (SUV_{max}/SUV_{min}) ratio (TBR) were quantified using routine region-of-interest analysis.

Kaplan-Meir analysis was used to identify associations with mortality. Associations between PET metrics and PFTs and the established ILD-GAP (gender, age and physiology) scoring system to predict mortality were also performed. Stepwise forward Wald-Cox analysis assessed the independence of the significant PET measurement(s) from the ILD-GAP index. Synergies between pulmonary ^{18}F-FDG-PET measurements and ILD-GAP index for risk stratification in SSc-ILD patients were investigated.

Results: During a mean follow-up of 53.8 months there were 15 deaths. The mean SUV_{max}±SD was 3.2±1.1 , SUV_{min} was 0.5±0.3 and TBR was 6.8±2.6. Mortality was associated with high pulmonary SUV_{max} (p=0.027), high SUV_{min} (p=0.002), high TBR (p=0.016) and low forced vital capacity (FVC, p=0.021), low carbon monoxide diffusion coefficient (K_{CO}, p=0.021), and transfer factor (TL_{CO}, p=0.012) and high ILD-GAP score (p=0.010) and ILD-GAP index (p=0.005). Multi-variate Cox-regression analysis revealed that pulmonary SUV_{min} (p=0.017) and ILD-GAP

index (*p*=0.024) were the only independent predictors of overall survival. Combining ^{18}F-FDG-PET uptake with ILD-GAP score data (modified ILD-GAP index) refined the ability to predict mortality (*p*<0.001).

Conclusion: High pulmonary uptake of ^{18}F-FDG predicts increased risk of mortality in patients with SSc-ILD. High background uptake in normal appearing lung (SUV_{min}) may have an additional independent prognostic benefit in addition to the ILD-GAP index to further risk stratify these patients.

INTRODUCTION

Systemic sclerosis (SSc) is a rare chronic autoimmune rheumatic disease characterised by skin thickening and organ fibrosis (often involving the lung) (1). The aetiology is unknown but genetic and environmental factors are implicated and SSc is more frequent in women. The pathogenesis of SSc involves immune dysregulation, endothelial dysfunction and excess extracellular matrix deposition by fibroblasts leading to fibrosis.

SSc is a heterogeneous disease with wide variability amongst patients (2). Pulmonary complications, namely interstitial lung disease (ILD) and pulmonary vascular disease, have now surpassed renal disease as the main cause of death (3). Characteristic autoantibodies are associated with SSc-ILD. The severity ranges from mild, limited interstitial involvement to rapidly progressive fibrotic disease leading to respiratory failure and death (4). Among predictors of more progressive lung disease are a shorter time interval between onset of skin disease and pulmonary fibrosis, male gender, black race and concomitant cardiac disease.

Diagnosis for SSc-ILD requires cross-sectional imaging as a surrogate for histological analysis, except when biopsy is (rarely) available. SSc-ILD is recognised on high resolution CT (HRCT) as sitting on a spectrum ranging from inflammatory non-specific interstitial pneumonitis (NSIP), through fibrotic (f)-NSIP, to the more fibrotic usual interstitial pneumonitis (UIP) (5). In general, outcomes and response to treatment are correlated with the extent of lung involvement with a UIP pattern tending to be less responsive to treatment and demonstrating worse outcomes.

Clinical decisions for individual patients may be challenging with treatment approaches based on symptom monitoring, pulmonary function tests (PFTs) and HRCT. However, none of these give a dynamic view of disease activity nor the risk of progression. Functional measurements may be confounded by the multisystem nature of the disease (6). For instance, exercise testing performance can be impacted by cardiovascular, cutaneous, and musculoskeletal manifestations of SSc, with pulmonary function tests (PFTs), particularly lung carbon monoxide diffusing capacity (TL_{CO}) measurements, affected by patient compliance and pulmonary arterial hypertension (7). Furthermore, PFTs are often insensitive to early lung disease (8). With the advent of new immunosuppressive regimes and anti-fibrotic agents there is a necessity to identify novel prognostic biomarkers to predict outcome and treatment response or failure in patients with SSc-ILD.

Positron emission tomography (PET) offers the ability to non-invasively investigate cellular metabolism *in vivo*. The use of 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}F-FDG) PET is becoming increasingly established as a potential prognostic biomarker in idiopathic pulmonary fibrosis (IPF) (9–11), with evidence that ^{18}F-FDG PET may aid patient stratification (12–14). Furthermore, there have been small predominantly retrospective studies to elucidate ^{18}F-FDG PET metrics in SSc-ILD (15–19) with a single prospective study of 23 patients which attempted to define a link between the PET signal and serum biomarkers (20).

In this study, we investigate the use of established ^{18}F-FDG PET imaging and analysis techniques to risk stratify, with respect to mortality, a reasonably sized cohort of patients with SSc-ILD compared to the established ILD-GAP (gender, age and physiology) prognostic score (21).

METHODS

Patients

This prospective, institutional review-board approved study consecutively consented and recruited 45 patients with SSc-ILD from April 2010 to June 2018 (12-male, 33-female, mean age ± SD 58.9±9.9yrs). Subjects were recruited from the National Scleroderma Centre, Royal Free Hospital, and underwent ^{18}F-FDG PET/CT at our institution. All patients underwent full clinical assessment including multidisciplinary team review, HRCT evaluation and baseline PFTs (including forced vital capacity, FVC, forced expiratory volume in 1 second, FEV_1, and lung carbon monoxide transfer factor and coefficient, TL_{CO}/K_{CO}). Patients with infection and/or neoplasia were excluded on clinical and radiological grounds. The diagnosis of SSc-ILD was made on clinico-radiological grounds following multidisciplinary team (MDT) review. The recruitment process and subsequent observational phases are detailed in Figure 1.

---Figure 1---

Patient Follow-up

The patient follow-up period was defined from date of scan to death (all causes) or until August 2021 (8 years). Patient survival was confirmed using patient charts, electronic database, primary health care physician records, or telephone interview.

PET/CT Acquisition

PET/CT imaging was performed following MDT diagnosis. All images were acquired on the same PET/CT instrument (VCT PET/64-detector CT instrument, GE Healthcare, Waukesha, WI,

USA). Two imaging sequences of the thorax were performed whilst the patient remained supine on the table throughout. A CT was performed for attenuation correction and co-registration of the PET dataset. Maintaining the patient position, a whole-body ^{18}F-FDG PET emission scan (8 min per bed position) was performed 1 hr after injecting 200 MBq of ^{18}F-FDG and covered an area identical to the CT.

Image analysis

Observers

PET images were analyzed by a PET Radiologist and a Senior PET Technologist with > 10 years' experience in quantifying pulmonary ^{18}F-FDG PET uptake in SSc-ILD under the supervision of a senior dual-trained Radiologist/Nuclear Medicine Physician of >10 years' experience. CT images were checked by a Thoracic Radiologist in combination with the patient's previous dedicated HRCT images (acquired elsewhere).

Image display and processing

All images were loaded onto a propriety workstation. All datasets underwent image processing as previously described (9,14). Using a region of interest, the area of most intense pulmonary ^{18}F-FDG uptake was identified and the highest image value (SUV_{max}) measured (see Figure 2).

---Figure 2---

In addition, the uptake in normal appearing pulmonary parenchyma with the lowest SUV was

identified (SUV_{min}). In all cases this region was confirmed by the Thoracic Radiologist to conform to morphologically normal lung parenchyma on the co-registered CT (both on the lower resolution breath-hold CT component during the PET/CT and the previously acquired HRCT). SUV_{min} was therefore recorded as a measure of the background lung uptake and in turn used to calculate the target to background ratio (TBR= SUV_{max}/SUV_{min}) (9,14).

The CT images of the PET/CT and previously acquired HRCT images were reviewed by a Thoracic Radiologist with specialist knowledge of ILD (>10 years' experience), without detailed knowledge of the PET images as previously described (9,14). The pattern and distribution of abnormalities on the full HRCT dataset were classified into typical appearances, i.e. UIP, NSIP or other.

ILD-GAP Calculation

ILD-GAP calculation is based on four variables; gender (G), age (A), and 2 lung physiology (P) measurements (FVC and TL_{CO}) (21). The resulting ILD-GAP model comprised continuous predictors (ILD-GAP score) and a simple point-scoring system (ILD-GAP index), which varies from 0, potentially indicating a good outcome, to 8, suggesting a worse outcome, and a simple point-scoring system (ILD-GAP index, stages I-IV).

Statistical Analysis

Statistical analyses were performed using SPSS for Windows version 19.0 (IBM, Armonk, NY, USA). Data were reported as mean ± standard deviation. In all analyses probability (*p*) values < 0.05 were considered significant.

Univariate Survival Analysis

Relationships of PET parameters (SUV_{max}, SUV_{min} and TBR), PFTs (FEV_1, FVC, TL_{CO} and K_{CO}) and ILD-GAP (score and index) with patient survival were assessed using univariate Kaplan-Meier (KM) survival analysis. In this exploratory work, for each of the parameters, the best/optimized value was used as a threshold (cut-off) to separate the survival plots (poor and good prognostic groups). Differences in the survival plots were further evaluated using the non-parametric log-rank test. KM curves for patients above and below each threshold were constructed to display the proportion of patients surviving at a given time.

Multivariate Cox Regression Analysis

Multivariate Cox regression analysis (step-wise Forward Wald) was used to determine which significant parameters were independent in predicting patient survival.

Modelling PET Data with ILD-GAP Analysis

The computed ILD-GAP scores were then modified based on the significant PET parameters to determine whether combining ILD-GAP scores with PET measurements improved the ability to predict survival (14). Briefly, for a modified ILD-GAP calculation (*mGAP*), we proposed adding a fourth significant PET variable (SUV_{max}, SUV_{min} or TBR) to the existing ILD-GAP score. For each patient, the best PET marker was binarized, based on the cut-off, as an adverse (coded as 1) or favorable (coded as 0) PET signal, similar to the coding employed in ILD-GAP calculation itself. This was added to the existing ILD-GAP score calculation where the

mGAP score ranged from 0 to 9 (as opposed to 0 to 8). For example, if a patient with an original ILD-GAP score=0 had an adverse PET marker (i.e. score of 1), the *mGAP score* would be 0+1=1. The *mGAP* index was then *mGAP* I=0-2, *mGAP* II=3-4, *mGAP* III=5-6 and *mGAP* IV=7-9.

RESULTS

From 2010 to 2018, 45 SSc-ILD patients were recruited in total. The mean follow-up period was 44.8±26.1 months, with 15 deaths (33.3%) during follow-up. The clinical profile including demographics, PFTs and HRCT results of the patient cohort are summarised in Table 1.

	All patients (n = 45)
Clinical Data	
Age (years)	58.9±8.9
Sex (female)	33 (73%)
Lung Function Tests	
FVC (% predicted)	72.0±19.7
FEV_1 (% predicted)	69.0±18.2
K_{CO} (min^{-1})	75.1±20.7‡
TL_{CO} (mmol min^{-1} kPa^{-1})	47.8±18.4‡
Auto-antibodies	
Scl-70	19
ACA	4
RNAP-III	2
snRNP	1
"Other"	8
No specific antibodies	10
CT pattern	
NSIP	42
UIP	3

TABLE 1. Patient characteristics at baseline with PFT and CT findings. Values expressed as mean ± standard deviation for continuous variables and frequencies with percentages (%) for qualitative variables. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) expressed as percentage predicted. Lung carbon monoxide transfer coefficient (K_{CO}) and transfer factor (TL_{CO}). Antibodies include: Anti-Centromere Antibody (ACA), Anti-Scleroderma-70 (Scl-70), Anti-RNA-polymerase III (RNAP-III), Anti-small nuclear ribonucleoprotein (snRNP). CT findings separated patients

to predominantly non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP) patterns. ‡ Note: n=35 as 10 patients were unable to complete gas transfer measurements.

Values for SUV_{max}, SUV_{min} (background lung activity) and TBR are summarised in Table 2. Significant associations between pulmonary uptake of ^{18}F-FDG (SUV_{max} , SUV_{min} and TBR) and survival, where patients below the best/optimised cut-offs had a poorer prognosis than patients below these values, are summarised in Table 2 with the KM survival curves displayed in Figure 3.

PET / PFT Markers	Mean (±SD)	Cut-off (best-value)	Poor (Median survival)	Good (Median survival)	p-value
SUV_{max}	3.2 (±1.2)	≥2.975	23 (60.1)	22 (--)	0.027*
SUV_{min}	0.5 (±0.3)	≥0.85	6 (18.9)	39 (--)	0.002*
TBR	6.8 (±2.6)	<6.61	20 (44.3)	25 (--)	0.016*
FVC (%)	72.0 (±19.7)	<72.5	25 (60.1)	20 (--)	0.021*
FEV_1	69.0 (±18.2)	<65.5	20 (60.1)	25 (--)	0.142
TL_{CO}	47.8 (±18.4)‡	<55.5	32 (116.3)	13 (--)	0.012*
K_{CO}	75.1 (±20.7)‡	<63.5	20 (43.2)	25 (116.3)	0.021*
ILD-GAP-score	1 (0 - 2) #	≥1	26 (43.2)	19 (--)	0.010*
ILD-GAP-index	II (I - III) #	≥II	19 (21.4)	26 (116.3)	0.005*

Table 2: Kaplan Meier Survival Analysis based on optimised cut-off values for PET (SUV_{max}, SUV_{min}, TBR), and PFT (FVC, FEV_1, K_{CO}, TL_{CO}) parameters and ILD-GAP score and index. Estimates of median survival where applicable in months (– indicates that median survival not calculated). * Indicates significance $p<0.05$. ‡ Note: 10 patients were unable to complete gas transfer measurement of TL_{CO}/K_{CO} and these were set as poor values (i.e. below median). Calculation of mean and SD were however from n=35 while n=45 for the other variables. # ILD-GAP score and indices are expressed as median with inter-quartile ranges given the discrete values.

---Figure 3---

Approximately 65% of patients with a SUVmax ≥2.975 at baseline survived at 2 years and ~48% at 5 years, whilst survival was approximately 91% and 86% respectively below the threshold. The 50% mortality above the threshold was 5 years, while below the threshold the value did not drop below 50% during the follow up period. Of the patients with TBR≥6.61, approximately 60% survived at 2 years and 50% at 5 years, whilst survival was approximately 92% and 80% respectively below the threshold. The 50% mortality above the threshold was 44 months, while below the threshold the value did not drop below 50% during the follow up period.

Median SUV_{min}, did not significantly inform outcomes, we therefore worked out a discriminatory level of SUV_{min} which was ≥0.85. Of the patients with SUV_{min}≥0.85 (6 patients in total), 33% survived at 2 years and ~17% at 5 years, whilst survival was approximately 85% and 74% respectively below the threshold (39 patients). The 50% mortality above the threshold of SUV_{min}≥0.85 was 19 months, while below the threshold the value did not drop below 50% during the follow up period.

Similarly, significant associations were also seen between FVC, TL_{CO}, K_{CO} and ILD-GAP score and index with survival with the 2-year and 5-year survival and median survival values listed in Table 3 and displayed in Figure 4.

PET / PFT Markers with cut-off values	Survival at 2 years above threshold	Survival at 5 years above threshold	Survival at 2 years below threshold	Survival at 5 years below threshold	50% mortality above threshold (months)	50% mortality below threshold (months)
SUVmax ≥ 2.975	65%	48%	91%	86%	60	--
SUVmin ≥ 0.85	33%	17%	85%	74%	19	--
TBR ≥ 6.61	62%	48%	92%	83%	44	--
FVC < 72.5%	90%	90%	60%	32%	60	--
TL_{CO} <55.5%	100%	100%	69%	53%	60	--
K_{CO} < 63.5	96%	80%	91%	86%	41	--
ILD-GAP score ≥ 1	62%	54%	100%	89%	40	--
ILD-GAP index ≥ II	54%	47%	96%	85%	19	--

Table 3: Estimated 2 year and 5 year survival percentages with 50% survival in months for each of the significant variables based on the optimised cut-off values for PET (SUV_{max}, SUV_{min}, TBR), and PFT (FVC, K_{CO}, TL_{CO}) parameters and ILD-GAP score and index. Estimates of median survival where applicable in months (– indicates that median survival not calculated).

---Figure 4---

Mutlivariate Cox Regression Analyses Assessing Independence of PET markers and ILD-GAP Index

The only PET parameter found to be independent of ILD-GAP analysis was SUV_{min}. By including SUV_{min} and ILD-GAP index in the Cox regression model, SUV_{min} (threshold>0.85, HR: 4.2, 95% CI: 1.3-13.4, *p*=0.017) and ILD-GAP Index (threshold>1.5, HR: 3.9, 95% CI: 1.2–12.8, *p*=0.024) were both independent predictors of survival.

Modelling of PET Derived SUV_{min} in Combined ILD-GAP Analysis

There was synergy in survival associations between SUV_{min} and ILD-GAP index with the modified ILD-GAP index (*mGAP*) using SUV_{min} showing an improved risk stratification over the original ILD-GAP analysis (see Figure 5). It is hypothesised that this combined system may be useful to further risk stratify patients in future.

---Figure 5---

DISCUSSION

We present the largest cohort to date of prospective ^{18}F-FDG PET data from patients with SSc-ILD. In this population we have shown that baseline objective measures of ^{18}F-FDG uptake on PET are related to patient survival. High pulmonary ^{18}F-FDG uptake as measured by SUV_{max}, SUV_{min} and TBR were associated with poor survival. However, it was the uptake of background "unaffected" lung (SUV_{min}) that has proven to have an additional independent prognostic benefit in addition to ILD-GAP index rather than the uptake in clearly abnormal lung (SUV_{max} and TBR). This is similar to previous findings where the uptake in normal appearing lung on CT was found to provide prognostic information in ILD (10,12). Whether this relates to the relatively small sample size is unclear and these findings will need to be confirmed in a larger independent patient cohort. The findings may however give important insights into pathomechanisms and the basis of the ^{18}F-FDG-PET signal.

FVC, TL_{CO}, K_{CO} and the combination of these measures with gender and age in the ILD-GAP score and index in our population were also predictors of survival. PFTs including spirometry and TL_{CO} are often difficult for patients to perform, especially in the context of SSc where limitation of respiratory movements can be a feature in advanced disease (of note, 10 patients in our cohort were unable to perform TL_{CO}/K_{CO} measurements). Moreover TL_{CO} has been shown to be a composite marker of several physiological processes and has been noted to reduce in the context of pulmonary arterial hypertension (PAH) in patients with SSc (22). High pulmonary uptake of ^{18}F-FDG has been seen in PAH (23,24). It is therefore unclear whether the high uptake in background lung in the sub-cohort of patients is related to co-existing PAH.

Although SUV_{max} and TBR were not independent of ILD-GAP index in our cohort, these measurements were also prognostic and might be useful in patients in whom PFTs (including gas transfer measurements) are not possible. The advantage of assessing glucose uptake using TBR, rather than using the more common SUV_{max}, is that the use of a background lung region allows standardisation of measurements. Previous findings from a study in patients with IPF demonstrated that TBR was found to have an association with survival (14) and the current EANM consensus recommendations include the use of TBR as a quantitative biomarker in the monitoring of ILD (25).

As in our study, previous works investigating predictors of mortality in SSc-ILD have involved low numbers of patients due to the relatively low incidence of the disease. Currently SSc-ILD patients with FVC>70% predicted are thought to have limited disease even with up to 30% lung involvement on HRCT (26,27). A recent analysis of data from the SENSCIS® study investigating the efficacy and safety of nintedanib noted that a decrease in FVC% predicted of ≥3% was associated with a shorter time to first hospitalisation or death in the 52 week follow up period (28). Whether this is detectable outside the context of a clinical trial given the variation in spirometry measurements is open for debate. Furthermore, often progression is defined as >10% drop in FVC or >15% drop in TL_{CO} (29).

Methods of combining FVC and TL_{CO} using a variety of scoring systems (including ILD-GAP as in this work) appear more sensitive but require patients to complete both tests and often need intervals of 12-24 months between measurements. Indeed, the GAP scores were originally developed to stratify cohorts of patients rather than to predict individual outcomes.

In an era of precision medicine, the FDG-ILD-GAP (*mGAP*) may improve the clinical assessment in ILD.

Given the heterogeneous outcome in SSc-ILD, predictors of mortality are important to inform shared decision-making, including referral for hematopoietic stem cell or lung transplantation. Here, we show that SSc-ILD patients with high ^{18}F-FDG uptake (SUV_{max} and TBR) have approximately double the risk of death compared to those with low measurements. Furthermore, we provide early evidence that those patients with high uptake in normal appearing lung (SUV_{min}) have the highest mortality risk.

At present patients considered to have limited or stable disease may not be considered for treatment escalation to first-line mycophenolate mofetil or cyclophosphamide (30). Second-line treatment with immune modulators such as tocilizumab or ritixumab is usually reserved for those that fail to respond based on current PFT and HRCT surveillance, possibly requiring 6-12 months to become appreciable. Finally, antifibrotic drugs are often reserved for progressive fibrotic disease given the associated toxicities. Our data shows that a high pulmonary ^{18}F-FDG uptake may identify patients that have poor survival independent of PFT measurements. The use of ^{18}F-FDG PET in this context raises the possibility of selecting patients for escalated immune modulation in a wider subpopulation, or potentially using pulmonary uptake of ^{18}F-FDG on PET as a response biomarker for drug development.

There has been much interest in clinical models of risk prediction that consider clinical parameters and more recently imaging, to build a risk score. These have been aimed mainly at IPF although the original GAP model has been modified for use across all ILDs including SSc-

ILD and has been shown to perform well (21,31,32). These are mainly useful when stratifying cohorts of patients for clinical trials rather than for assessing individuals. Alternatively, serum biomarkers may be able to prospectively predict patients at most risk of disease progression. Future studies combining clinical models, serum biomarkers, and functional imaging may further refine the theranostic approach in SSc-ILD.

HRCT continues to be the main diagnostic imaging investigation in SSc-ILD. A number of investigations have provided associations between survival data and scoring/grading systems of HRCT findings (33). However, there is limited data showing the benefit of using this imaging technique in clinical trials to date. In contrast, our imaging approach utilises metabolic functional data and the exquisite sensitivity of PET.

Although HRCT is essential for diagnosis, the ^{18}F-FDG PET signal has been shown to arise from structurally normal lung parenchyma on HRCT in IPF (10,12) and in small cohorts of patients with SSc-ILD (13,15,17,19), although this has been more variable with 2 larger recent studies reporting no increased ^{18}F-FDG uptake in normal appearing lung (18,20). None of these prior smaller ^{18}F-FDG PET/CT studies have been able to find a link between uptake values and mortality, although most found associations with PFTs. Whether this is related to study size, differing acquisition and analysis methodologies, or the patient populations (several studies having patients with established pulmonary disease for several years) is unclear. We report the largest cohort to our knowledge of SSC-ILD patients with baseline ^{18}F-FDG PET data.

The precise cellular mechanisms underlying the observed FDG-PET signal in SSc-ILD are as yet unknown, although we have early data in fibrotic ILD suggesting that FDG-PET may report

neo-angiogenesis (34). In addition, the novel tracer ^{68}Ga-FAPI-04 which binds to fibroblast activation protein has been proposed as a biomarker in connective tissue disease associated ILD (35). It is unclear how ^{68}Ga-FAPI-04 and ^{18}F-FDG uptake correlate.

Study limitations include the fact that, to increase recruitment, the PET study was not always performed at diagnosis. Our data however imply prognosis may be determined at various stages of disease. There are many technical factors that need to be appreciated in this type of imaging such as respiratory gating, more complex air-fraction correction, and compartmental modelling approaches. The techniques used here acknowledge the challenges of such imaging with the methods recognised as robust (25). The authors have been able to make significant survival observations using these routine PET measurements.

CONCLUSION

We have shown that high pulmonary uptake of ^{18}F-FDG is associated with mortality in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD). Furthermore, we present early evidence that uptake in background normal appearing lung (SUV_{min}) may have an additional independent prognostic benefit in addition to ILD-GAP index. These PET findings could therefore potentially indicate that ^{18}F-FDG PET may be a much clinically needed sensitive biomarker to help risk stratify patients with SSc-ILD.

Author Disclosure

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REFERENCES

1. Pope JE, Denton CP, Johnson SR, Fernandez-Codina A, Hudson M, Nevskaya T. State-of-the-art evidence in the treatment of systemic sclerosis. Nat Rev Rheumatol. 2023;19(4):212–26.

2. Volkmann ER, Andréasson K, Smith V. Systemic sclerosis. Lancet. 2023;401(10373):304–18.

3. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis. 2007;66(7):940–4.

4. Benan M, Hande I, Gul O. The natural course of progressive systemic sclerosis patients with interstitial lung involvement. Clin Rheumatol. 2007;26(3):349–54.

5. Konopka KE, Myers JL. Interstitial lung disease pathology in systemic sclerosis. Ther Adv Musculoskelet Dis. 2021;13:1759720X211032437.

6. Lafyatis R, Valenzi E. Assessment of disease outcome measures in systemic sclerosis. Nat Rev Rheumatol. 2022;18(9):527–41.

7. Hoffmann-Vold AM, Aaløkken TM, Lund MB, Garen T, Midtvedt Ø, Brunborg C, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. Arthritis Rheumatol. 2015;67(8):2205–12.

8. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TDL, Maurer B, Jordan S, et al. Brief Report: Pulmonary Function Tests: High Rate of False-Negative Results in the Early Detection and Screening of Scleroderma-Related Interstitial Lung Disease. Arthritis Rheumatol. 2015;67(12):3256–61.

9. Groves AM, Win T, Screaton NJ, Berovic M, Endozo R, Booth H. Idiopathic pulmonary fibrosis and diffuse Parenchymal lung disease: implications from initial experience with 18F-FDG-PET/CT. J Nucl Med. 2009;50(4):538-45.

10. Win T, Thomas BA, Lambrou T, Hutton BF, Screaton NJ, Porter JC. Areas of normal pulmonary parenchyma on HRCT exhibit increased FDG PET signal in IPF patients. Eur J Nucl Med Mol Imaging. 2014;41:337-42.

11. Chen DL, Schiebler ML, Goo JM, Beek EJR van. PET imaging approaches for inflammatory lung diseases: Current concepts and future directions. Eur J Radiol. 2017;86:371–6.

12. Nobashi T, Kubo T, Nakamoto Y, Handa T, Koyasu S, Ishimori T, et al. 18F-FDG Uptake in Less Affected Lung Field Provides Prognostic Stratification in Patients with Interstitial Lung Disease. J Nucl Med. 2016;57(12):1899–904.

13. Justet A, Laurent-Bellue A, Thabut G, Dieudonné A, Debray MP, Borie R, et al. [18F]FDG PET/CT predicts progression-free survival in patients with idiopathic pulmonary fibrosis. Respiratory Research. 2017;18(1):74.

14. Win T, Screaton NJ, Porter JC, Ganeshan B, Maher TM, Fraioli F, et al. Pulmonary 18F-FDG uptake helps refine current risk stratification in idiopathic pulmonary fibrosis (IPF). Eur J Nucl Med Mol Imaging. 2018;45(5):806–15.

15. Uehara T, Takeno M, Hama M, Yoshimi R, Suda A, Ihata A, et al. Deep-inspiration breath-hold 18F-FDG-PET/CT is useful for assessment of connective tissue disease associated interstitial pneumonia. Mod Rheumatol. 2016;26(1):121–7.

16. Jacquelin V, Mekinian A, Brillet PY, Nunes H, Fain O, Valeyre D, et al. FDG-PET/CT in the prediction of pulmonary function improvement in nonspecific interstitial pneumonia. A Pilot Study. Eur J Radiol. 2016;85(12):2200–5.

17. Bellando-Randone S, Tartarelli L, Cavigli E, Tofani L, Bruni C, Lepri G, et al. 18F-fluorodeoxyglucose positron-emission tomography/CT and lung involvement in systemic sclerosis. Ann Rheum Dis. 2019;78(4):577–8.

18. Peelen DM, Zwezerijnen BGJC, Nossent EJ, Meijboom LJ, Hoekstra OS, Van der Laken CJ, et al. The quantitative assessment of interstitial lung disease with positron emission tomography scanning in systemic sclerosis patients. Rheumatology (Oxford). 2020;59(6):1407–15.

19. Ledoult E, Morelle M, Soussan M, Mékinian A, Béhal H, Sobanski V, et al. 18F-FDG positron emission tomography scanning in systemic sclerosis-associated interstitial lung disease: a pilot study. Arthritis Res Ther. 2021;23(1):76.

20. Bastos AL, Ferreira GA, Mamede M, Mancuzo EV, Teixeira MM, Santos FPST, et al. PET/CT and inflammatory mediators in systemic sclerosis-associated interstitial lung disease. J Bras Pneumol. 2022;48(4):e20210329.

21. Ryerson CJ, Vittinghoff E, Ley B, Lee JS, Mooney JJ, Jones KD, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest. 2014;145(4):723–8.

22. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J. 2007;37(7):485–94.

23. Marsboom G, Wietholt C, Haney CR, Toth PT, Ryan JJ, Morrow E, et al. Lung ^{18}F-fluorodeoxyglucose positron emission tomography for diagnosis and monitoring of pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012;185(6):670–9.

24. Zhao L, Ashek A, Wang L, Fang W, Dabral S, Dubois O, et al. Heterogeneity in lung (18)FDG uptake in pulmonary arterial hypertension: potential of dynamic (18)FDG positron emission tomography with kinetic analysis as a bridging biomarker for pulmonary vascular remodeling targeted treatments. Circulation. 2013;128(11):1214–24.

25. Chen DL, Ballout S, Chen L, Cheriyan J, Choudhury G, Denis-Bacelar AM, et al. Consensus Recommendations on the Use of 18F-FDG PET/CT in Lung Disease. J Nucl Med. 2020;61(12):1701–7.

26. Pokeerbux MR, Giovannelli J, Dauchet L, Mouthon L, Agard C, Lega JC, et al. Survival and prognosis factors in systemic sclerosis: data of a French multicenter cohort, systematic review, and meta-analysis of the literature. Arthritis Res Ther. 2019;21(1):86.

27. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial Lung Disease in Systemic Sclerosis. Am J Respir Crit Care Med. 2008;177(11):1248–54.

28. Kreuter M, Hoffmann-Vold AM, Matucci-Cerinic M, Saketkoo LA, Highland KB, Wilson H, et al. Impact of lung function and baseline clinical characteristics on patient-reported outcome measures in systemic sclerosis-associated interstitial lung disease. Rheumatology (Oxford). 2022;62(SI):SI43-SI53.

29. Tashkin DP, Volkmann ER, Tseng CH, Kim HJ, Goldin J, Clements P, et al. Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis. Ann Rheum Dis. 2016;75(2):374–81.

30. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39.

31. King TE, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164(7):1171–81.

32. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(4):459–66.

33. Khanna D, Nagaraja V, Tseng CH, Abtin F, Suh R, Kim G, et al. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. Arthritis Res Ther. 2015;17:372.

34. Porter, JC, Ganeshan B, Win T, Fraioli F, Khan, S, Rodriguez-Justo, M, et al. [18F]FDG PET signal correlates with markers of neo-angiogenesis in patients with fibrotic interstitial lung disease who underwent lung biopsy: Implication for the use of PET/CT in diffuse lung diseases [Internet]. 2022 [cited 2023 Jul 4]. Available from: https://www.researchsquare.com

35. Bergmann C, Distler JHW, Treutlein C, Tascilar K, Müller AT, Atzinger A, et al. 68Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. Lancet Rheumatol. 2021;3(3):e185–94.

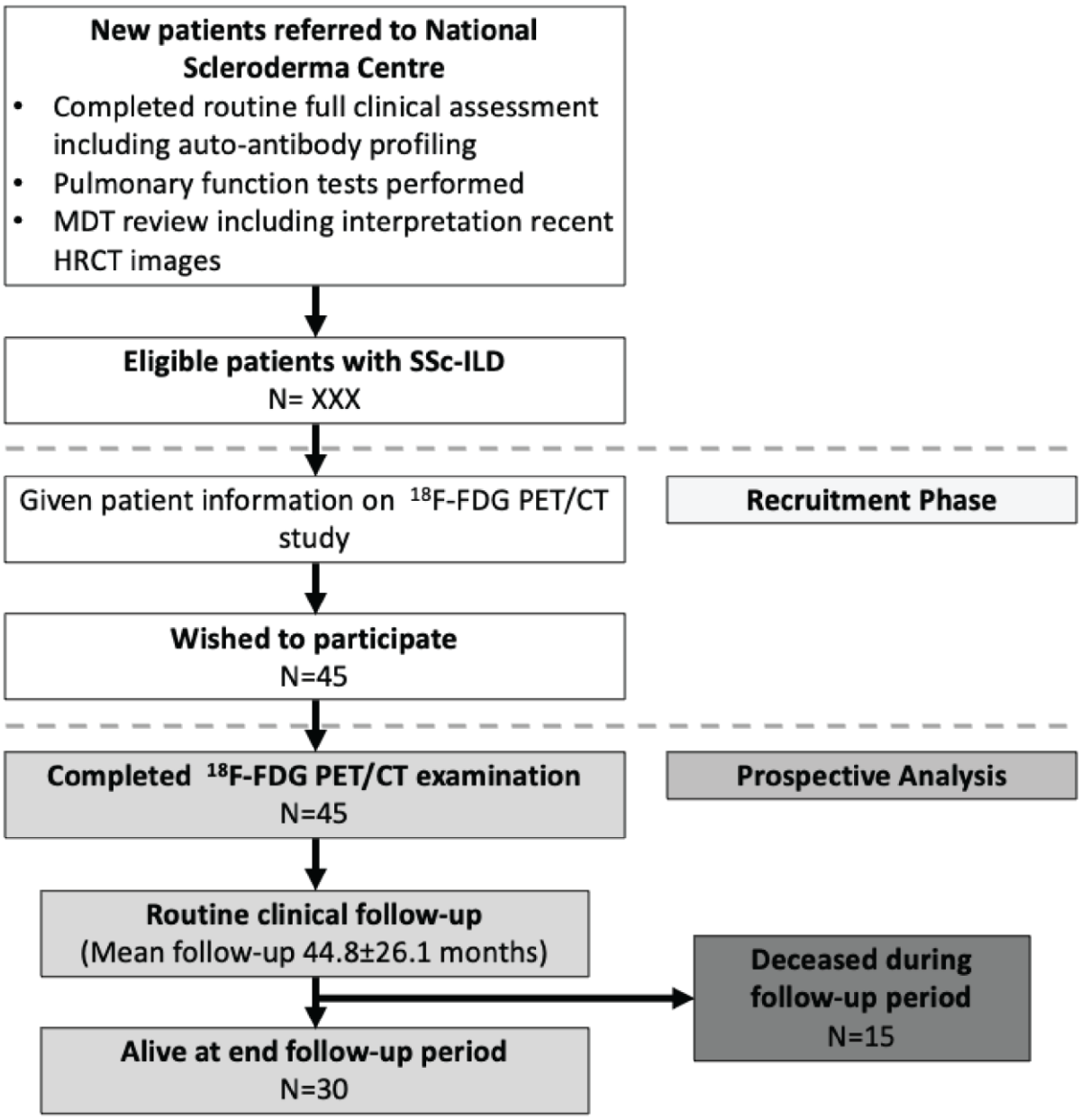

Figure 1. Flow diagram detailing the recruitment and analysis phases for patients included in this prospective observational study. Note that all patients who wished to participate completed the ^{18}F-FDG PET/CT examination.

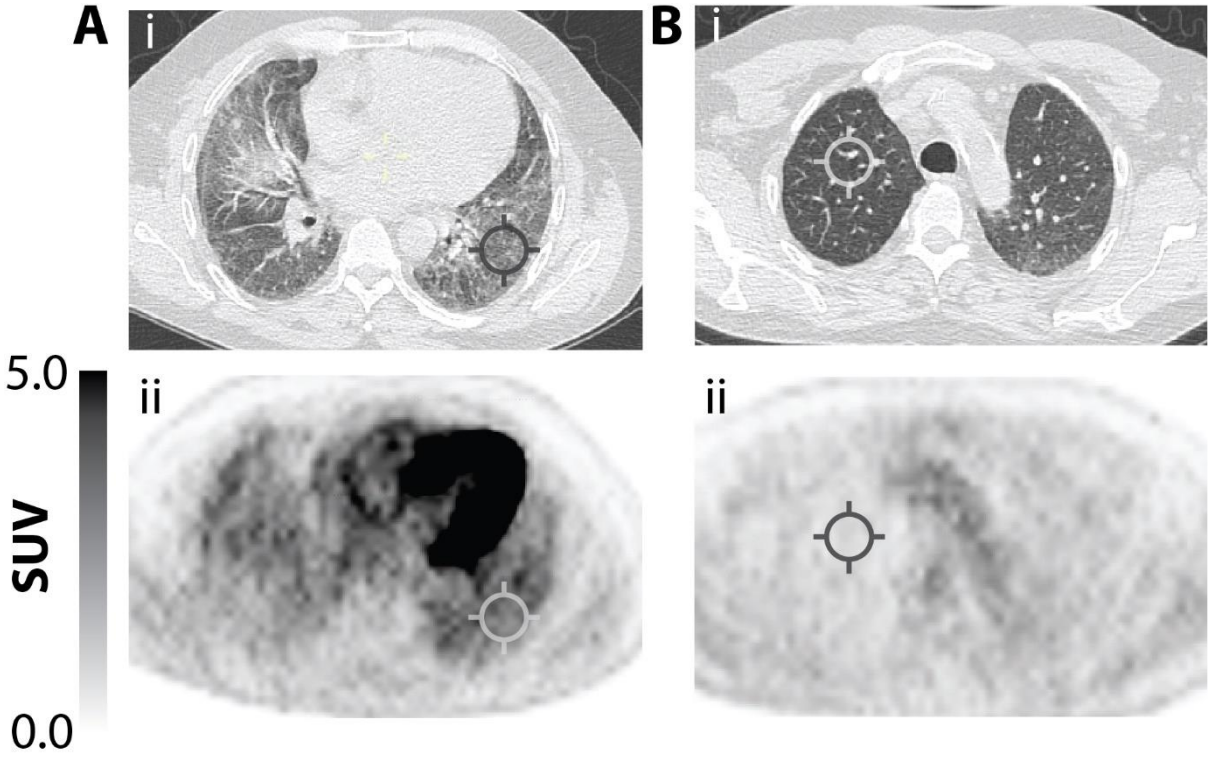

Figure 2. Co-registered i) CT and ii) ^{18}F-FDG PET of a patient with non-specific interstitial pneumonia (NSIP), showing A) region of interest placement measuring maximal pulmonary ^{18}F-FDG uptake (SUV_{max}) and B) background uptake in unaffected lung (SUV_{min}).

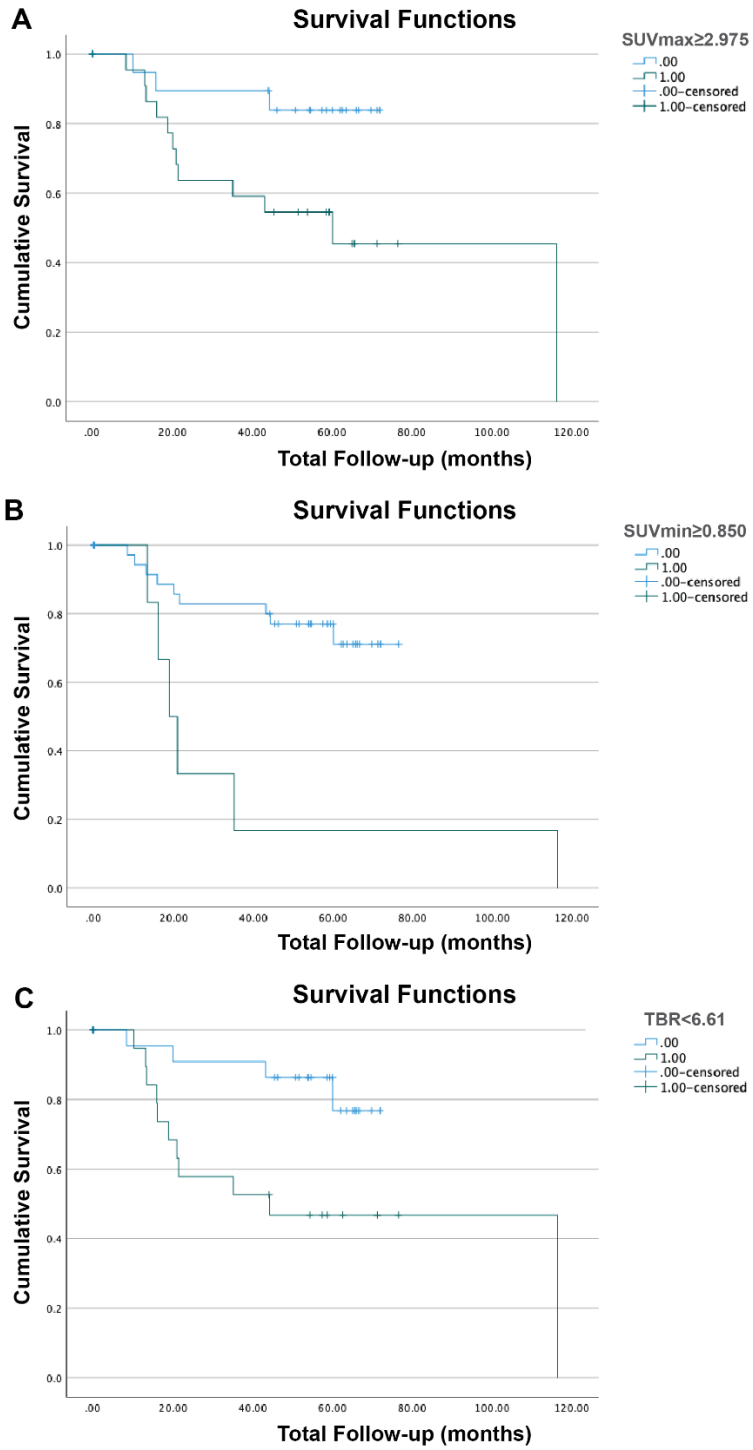

Figure 3. Kaplan-Meier survival analysis curves demonstrating relationship between A) SUV_{max} (cut-off value of 2.975), B) SUV_{min} (cut-off value of 0.85) and C) TBR (cut-off value of 6.61) and survival in all SSc-ILD patients showing that ^{18}F-FDG PET is able to risk stratify patients.

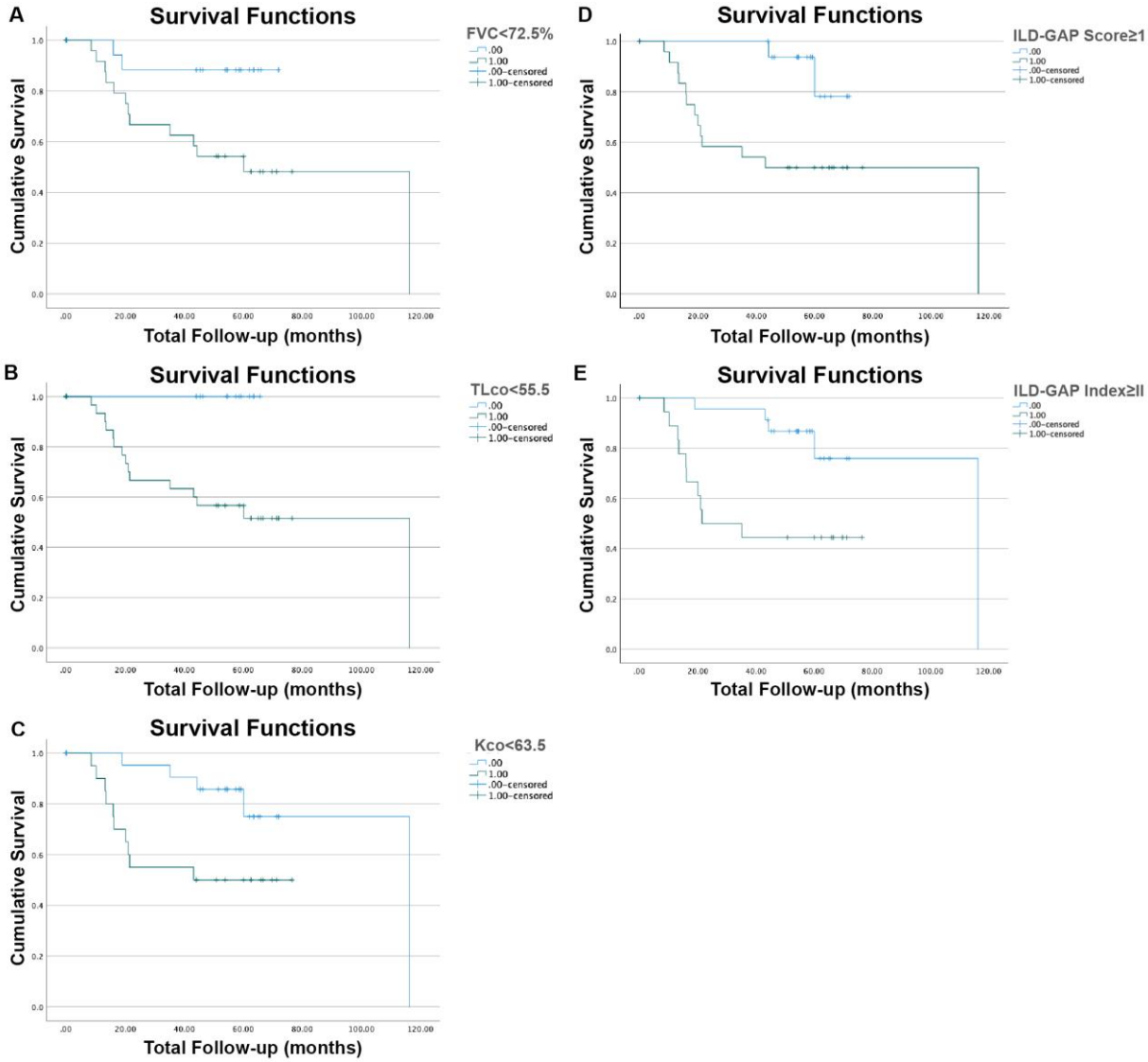

Figure 4. Kaplan-Meier survival curve analysis demonstrating relationship between A) FVC (cut-off value of 72.5%), B) TL_{CO} (cut-off value of 55%), C) K_{CO} (cut-off value of 63.5%), D) ILD-GAP score (cut-off value of 1) and E) ILD-GAP index (cut-off value of II) and survival in all SSc-ILD patients. Units of TL_{CO} are mmol min^{-1} kPa^{-1} and K_{CO} are min^{-1}.

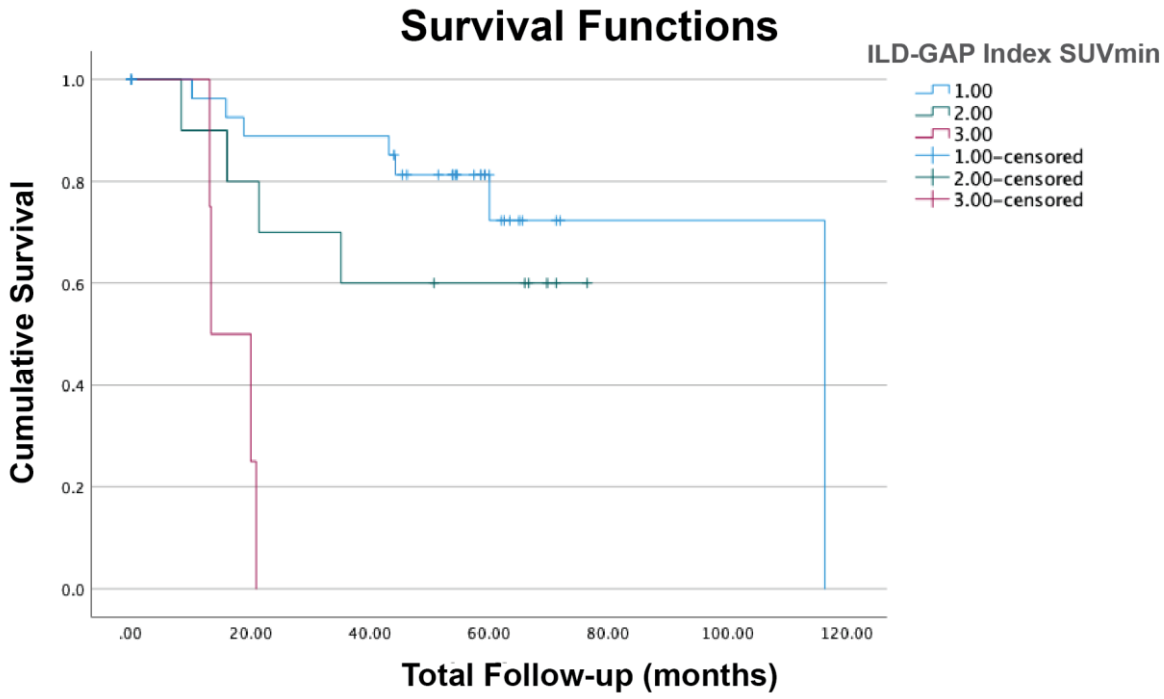

Figure 5. Kaplan-Meier survival curves from the modified ILD-GAP calculation (*mGAP*) combining SUV_{min}, showing that ^{18}F-FDG PET may be able to further enhance mortality prediction. *There was a significant difference in the survival curves based on the PET modified ILD-GAP index (p<0.001, log-rank test).