Kinetic Changes in Serum KL-6 Levels Predict Disease Progression in Patients with Systemic Sclerosis-Associated Interstitial Lung Disease: A Retrospective Observational Study

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Abstract

Background: The clinical course of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) is highly variable. The Krebs von den Lungen-6 (KL-6) glycoprotein is a promising biomarker for reflectingepithelial injury. However, serum KL-6 and its association with the progression of SSc-ILD have been understudied.

Methods: We reviewed 77 consecutive patients with SSc-ILD seen from 2004 to 2016. A longitudinal study of forced vital capacity (FVC), serum KL-6 levels, and the changes in KL-6 levels from baseline (ΔKL-6) was conducted. The progression of ILD was defined as ≥10% relative decline in FVC predicted or 5%–10% decline in FVC predicted along with radiological progression on chest computed tomography. The risk factors for ILD progression were assessed by univariate and multivariate regression.

Results: The 77 study patients included 58 women (75%). The median age of the study patients was 56 years, and 59 (79%) patients had diffuse cutaneous SSc. During a 5-year follow-up period, 10 (13%) showed rapid progression of ILD within 2 years, 39 (51%) had overall progressionduring the 5 years, and 28 (36%) had stable disease. Most patients with progressive ILD showed elevationsin serum KL-6 levels over the initial 1-year follow-up period. The best cut-off value for ΔKL-6 that predicted progression of ILD was 193 U/mL (sensitivity 81.6%, specificity 92.9%). Multivariate analysis with adjustment revealed that diffuse cutaneous SSc(hazard ratio [HR] 3.1; 95% confidence interval [CI] 1.05-9.36]) and ΔKL-6 > 193 U/mL from baseline(HR, 4.7; 95% CI, 2.14-10.4)were independent predictors for progression of SSc-ILD.

Conclusion: Changes in the KL-6 level can be useful for predicting disease progression in patients withSSc-ILD.

Introduction

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a connective tissue disease that is characterized by vascular and immunological abnormalities and fibrosis of the lung. Pulmonary fibrosis is a significant cause of morbidity and a leading cause of mortality in patients with SSc-ILD. Currently, the pharmaceutical management of SSc-ILD includes cyclophosphamide, mycophenolate, nintedanib, or hematopoietic stem cell transplantation [1–3]. It is important to determine which patients are likely to progress, in order to select an appropriate therapy and timing of therapy for patients with SSc-ILD. However, no consensus exists regarding which assessment tools and predictors are most useful for monitoring disease progression.

The natural history and pattern of progression of SSc-ILD are highly variable. A recent longitudinal study of SSc-ILD patients identified several distinct subgroups with different rates of decline in FVC: some patients progress rapidly, and others progress slowly or exhibit stable disease [4–6]. Several studies have evaluated the clinical factors that might be associated with the progression of SSc-ILD. Goh et al suggested that a chest high-resolution computed tomography (HRCT) scan showing > 20% of the lungs affected by disease was associated with deterioration of ILD and death [7]. A decreased oxygen

saturation after a 6-min walk test and the presence of arthritis were also predictors of ILD progression [8]. A recent study showed that a decline in forced vital capacity (FVC) or diffusing capacity of the lung for carbon monoxide (DLco) over 2 years was a better predictor of mortality than baseline FVC or DLco [9]. Although these approaches are effective for evaluating patients with ILD in clinical practice, physiological tests are effort dependent, and HRCT increases the amount of radiation to which the patient is exposed. Thus, useful biomarkers associated with the progression of SSc-ILD are needed.

Krebs von den Lungen-6 (KL-6) is a high–molecular-weight mucin-like glycoprotein expressed on type II pneumocytes. It is used as a biomarker for detecting and assessing the activity of various types of ILD [10]. An elevated KL-6 serum level is associated with radiologic evidence of ILD in SSc-ILD patients, and its levels are inversely correlated with FVC and DLco [11]. Levels of KL-6 > 1273 U/mL are associated with end-stage lung disease [12]. Although KL-6 is a promising biomarker for detecting ILD in patients with SSc, the utility of KL-6 in monitoring disease progression in SSc-ILD has not been fully investigated. This retrospective study aimed to evaluate the trajectories of FVC values and serum KL-6 levels in patients with SSc-ILD and identify the utility of KL-6 in monitoring disease progression.

Methods

Study population

This study was approved by an ethics board at Kanazawa University Hospital (#3028), and written informed consent was waived because of its retrospective design. We examined consecutive patients with SSc-ILD who visited the Department of Respiratory Medicine at Kanazawa University Hospital from April 2004 to March 2016. SSc-ILD was diagnosed by rheumatologists or dermatologists according to the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria [13]. The presence of ILD was determined by pulmonologists and radiologists based on chest HRCT. Exclusion criteria included missing data from pulmonary function measurements and serum KL-6 levels at baseline and over 3 serial measurements, pulmonary resection, and lung complications other than SSc-ILD. The follow-up time was calculated from the date of the diagnosis of SSc-ILD to the date of last visit or death. Follow-up data were collected until July 2021.

Clinical assessments

We collected the following data from the study patients' clinical records: age, sex, smoking status, occupational history, immunosuppressant use before initial presentation, type of SSc, presence of anti-topoisomerase I, history of Raynaud phenomenon, history of gastroesophageal reflux, estimated right ventricular systolic pressure (RVSP), and arterial blood gases. Pulmonary function test results during follow-up were assessed by the criteria of the American Thoracic Society /European Respiratory Society [14]. The relative changes in predicted FVC were evaluated during follow-up. ILD patterns on chest HRCT were determined by pulmonologists and radiologists according to the official clinical practice guidelines [15]. Disease extent on HRCT scans was measured by a quantitative scoring system, as previously described [7]. ILD progression was defined as a relative decrease in FVC of ≥ 10% from baseline, or a

relative decrease in FVC of 5–10% from baseline along with radiological progression on chest HRCT [16, 17]. Patients who did not meet the criteria for progressive disease were considered to have stable disease. Serum KL-6 concentration (U/mL) was routinely measured by a chemiluminescent enzyme immunoassay according to the manufacturer's instructions (Fujirebio Inc., Japan). We collected longitudinal data on serum KL-6 levels during follow-up period and calculated the changes in KL-6 levels from baseline (ΔKL-6), and compared them with the FVC values. Univariate and multivariate analysis was conducted to identify useful predictors of disease progression. The effects of intravenous cyclophosphamide (IVCY) pulse therapy on FVC and KL-6 levels were also assessed.

Statistical analysis

Continuous values were represented as medians and range, and were compared by the Mann-Whitney U test. Categorical variables were compared by the chi-squared test. A useful predictive cut-off value for ΔKL-6 was determined by receiver operating characteristic (ROC) curve analysis. Cox proportional hazards modeling was used for univariate and multivariate analysis. Univariate models were used without adjustment, and multivariate models were adjusted for age, gender, smoking status, and immunosuppressant use during follow-up. The results are shown as hazard ratio (HR) with 95% confidence interval (CI). Statistical analysis was performed by IBM SPSS Statistics, version 20 and GraphPad Prism, version 6. A p-value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 127 consecutive patients with SSc-ILD who visited our hospital from April 2004 to March 2016 were screened for eligibility (Fig. 1). Of the 127 patients, 19 patients were excluded because of the unavailability of baseline test results on lung physiology and serum KL-6 levels. Of 108 patients with available baseline data, 31 patients were excluded for missing follow-up data (n = 24) or a history of thoracic surgery (n = 5) or malignancy (n = 2) during follow-up. Finally, a total of 77 of 127 (78%) patients with SSc-ILD who had results of more than 3 pulmonary function tests and serum KL-6 levels available during a 5-year follow-up period were included in this analysis.

Patient characteristics at baseline are shown in Table 1. The median age of the patients was 56 years, and 75.3% of the patients were female. Of 77 patients, 49 (64%) exhibited progressive SSc-ILD, and 28 (36%) had stable SSc-ILD during the 5-year follow-up period. The median number of pulmonary function tests was 8 (interquartile range, 6–12) for the patients with progressive SSc-ILD and 7 (6–8) for the patients with stable SSc-ILD. The median follow-up time was significantly longer for the patients with stable SSc-ILD compared to the patients with progressive SSc-ILD. The patients with progressive SSc-ILD had a more diffuse cutaneous SSc; anti-topoisomerase I positivity; and greater disease extent on HRCT, with extensive disease according to the Goh criteria; compared with the patients with stable disease. The differences between baseline FVC and DLco values of the patients with progressive and the patients with stable ILD were not statistically significant. The differences between baseline serum KL-6 levels of the

patients with progressive and the patients with stable ILD were not significant. Although more patients with progressive disease showed serum KL-6 levels > 1273 U/mL, overall, the majority of patients (n = 60/77, 77.9%) showed baseline KL-6 levels ≤ 1273 U/mL, including the patients with progressive disease (n = 34/49, 69.4%).

Table 1
Patient characteristics at baseline

Characteristics	Total # cases (n = 77)	Progressive ILD (n = 49)	Stable ILD (n = 28)	p value[a]
Age, years	56 (46–63)	53 (43–60)	59 (49–66)	0.076
Female, n (%)	58 (75.3)	37 (75.5)	21 (75.0)	1.000
Former or current smoker, n (%)	30 (39.0)	19 (38.8)	11 (39.3)	1.000
Occupational exposure, n (%)	14 (18.2)	9 (18.4)	5(17.9)	1.000
Immunosuppressant use				
At baseline	9 (11.7)	7 (14.3)	2 (7.1)	0.474
During follow-up	36 (47.4)	31 (63.3)	5 (18.5)	**< 0.001**
Diffuse cutaneous SSc, n (%)	59 (76.6)	45 (91.8)	14 (50.0)	**< 0.001**
Anti-topoisomerase I, n (%)	40 (51.9)	31 (63.3)	9 (32.1)	**0.010**
Raynaud phenomenon, n (%)	60 (77.9)	37 (75.5)	23 (82.1)	0.578
Gastroesophageal reflex, n (%)	37 (48.1)	23 (46.9)	14 (50.0)	0.817
Estimated RVSP, mmHg	30 (24–34)	30 (24–32)	30 (23–35)	0.841
Estimated RVSP ≥ 40 mmHg, n (%)	6 (9.4)	4 (9.3)	2 (9.5)	1.000
PaO_2, mmHg	91.3 (84.7–97.7)	91.3 (81.1–96.0)	88.0 (85.6–98.3)	0.956
Chest HRCT findings				
UIP-like pattern, n (%)	5 (6.5)	1 (2.0)	4 (14.3)	0.056
NSIP-like pattern, n (%)	69 (89.6)	46 (93.9)	23 (82.1)	0.131
Disease extent on HRCT, %	10.9 (6.2–22.6)	15.9 (7.3–24.8)	7.4 (4.9–13.5)	**0.015**
Pulmonary function tests				
FVC predicted, %	88.3 (81.9-100.8)	87.0 (81.4-102.6)	93.5 (87.7–108)	0.154

ILD interstitial lung disease, *SSc* systemic sclerosis, *RVSP* right ventricular systolic pressure, *HRCT* high-resolution computed tomography, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *FVC* forced vital capacity, *DLco* diffusing capacity of the lung for carbon monoxide, *KL-6* Krebs von den Lungen-6

[a]p values are for comparison between patients with progressive ILD and patients with stable ILD.

Characteristics	Total # cases (n = 77)	Progressive ILD (n = 49)	Stable ILD (n = 28)	p value[a]
DLco predicted, %	59.5 (44.7–69.0)	59.5 (43.1–69.0)	60.4 (47.6–70.9)	0.495
Serum biomarker				
KL-6, U/mL	778 (467–1292)	841 (455–1565)	693 (460–910)	0.105
KL-6 > 1273 U/mL, n (%)	17 (22.1)	15 (30.6)	2 (7.1)	**0.022**
Goh criteria				
Extensive disease, n (%)	26 (33.8)	22 (44.9)	4 (14.3)	**0.007**
Duration of follow-up, yr	9.4 (6.9–12.3)	9.4 (5.6–11.1)	10.3 (7.7–13.2)	**0.033**
End-stage lung disease	25 (32.5)	22 (44.9)	3 (10.7)	**0.002**
Death	15 (19.5)	13 (26.5)	2 (7.1)	0.070

ILD interstitial lung disease, *SSc* systemic sclerosis, *RVSP* right ventricular systolic pressure, *HRCT* high-resolution computed tomography, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *FVC* forced vital capacity, *DLco* diffusing capacity of the lung for carbon monoxide, *KL-6* Krebs von den Lungen-6

[a]p values are for comparison between patients with progressive ILD and patients with stable ILD.

Trajectories of FVC values and KL-6 levels

We examined the trajectories of FVC values and serum KL-6 levels to evaluate the association between the progression of SSc-ILD and serum KL-6 levels. The FVC predicted values of the patients with progressive SSc-ILD were lower at any time compared to those of the patients with stable SSc-ILD (Fig. 2A). The serum KL-6 levels and ΔKL-6 values were higher at any time in the patients with progressive SSc-ILD compared with the patients with stable SSc-ILD (Fig. 2B and 2C).

We identified the following 3 kinetic patterns of FVC predicted values over the clinical course of patients: group 1) rapid progression with decrease in FVC predicted values > 20% within 2 years, with plateauing or further progression (n = 10 [13.0%]); group 2) overall progression with decrease in FVC predicted values > 5–10% over 5 years (n = 39 [50.6%]); and group 3) 28 (36.4%) stable or improved FVC predicted overall (n = 28 [36.4%]) (Fig. 2D). Serum KL-6 levels of patients with group 1 were higher than the other groups at all timepoints up to 4 years of follow-up, whereas the patients with group 2 showed moderately increased serum KL-6 levels that were maintained over the 5-year follow-up period. The KL-6 levels in patients with group 3 were low and stable over the 5-year follow-up period (Fig. 2E). The ΔKL-6 values showed several distinct patterns, as follows: the ΔKL-6 FVC predicted values of patients with group 1 rapidly increased over 1 year of follow up, showed increased levels until 3 years of follow up, and then showed decreased

values thereafter; the ΔKL-6 values in patients with group 2 FVC predicted values were maintained at higher levels compared with the values of patients with group 3 over the 5-year follow-up period (Fig. 2F).

An increase in serum KL-6 values in the patients with progressive SSc-ILD occurred mostly over the initial 1-year follow-up period. Although the differences between the baseline KL-6 levels of progressive ILD and stable ILD were not significant (Supplemental Fig. 1A), the median value of ΔKL-6 levels in patients with progressive SSc-ILD was significantly higher than the median value of ΔKL-6 levels in patients with stable SSc-ILD (197 vs 50 U/mL at 3 months, 194.5 vs -13 U/mL at 6 months, and 151 vs -57 U/mL at 12 months, respectively) (Supplemental Fig. 1B-D).

Predicted cut-off value of serum KL-6

We conducted ROC curve analysis to determine the optimal ΔKL-6 cut-off value for prediction of disease progression within 5 years. ROC curve analysis showed an AUC of 0.89 (95% CI 0.815–0.961), with the best cut-off value for ΔKL-6 being 193 U/mL, with a sensitivity of 81.6% and specificity of 92.9% (Supplementary Fig. 2A). We also examined the ΔKL-6 values at 3 months for prediction of the progression of SSc-ILD. ROC curve analysis showed that the AUC was 0.86 (95% CI 0.769–0.949), and the best cut-off value for ΔKL-6 was 195 U/mL, with a sensitivity of 81.3% and specificity of 88.0% (Supplementary Fig. 2B). The cut-off value for progression obtained at 3 months was similar to that of the value for predicting progression within 5 years. We further examined the value of ΔKL-6 for the prediction of rapid progression (group 1 described in the previous section). ROC curve analysis showed that the AUC was 0.91 (95% CI: 0.848–0.979), and the best cut-off value for ΔKL-6 was 455 U/mL, with a sensitivity of 100% and specificity of 84.4% (Supplementary Fig. 2C).

Risk factors predictive of SSc-ILD progression

We performed Cox proportional hazards modeling to assess the predictive factors of SSc-ILD progression during the 5-year follow-up period (Table 2). A univariate model without adjustment found the following factors significant for predicting SSc-ILD progression: immunosuppressant use during follow-up, diffuse cutaneous SSc, anti-topoisomerase I positivity, extensive disease by the Goh criteria, KL-6 level > 1273 U/mL, and ΔKL-6 from baseline > 193 U/mL. After adjustment, the multivariate model found the following independent factors significant for predicting SSc-ILD progression: diffuse cutaneous SSc and ΔKL-6 from baseline > 193 U/mL.

Table 2
5-year risk of progression of SSc-ILD (Cox proportional hazards model)

	Univariate model				Multivariate model[a]			
	HR	95% CI		p value	HR	95% CI		p value
Age	0.988	0.967	1.01	0.282	—	—	—	—
Female sex	0.955	0.498	1.832	0.89	—	—	—	—
Smoker	0.999	0.562	1.775	0.997	—	—	—	—
Immunosuppressant use during follow-up	2.669	1.483	4.802	**0.001**	—	—	—	—
Diffuse cutaneous SSc	4.884	1.75	13.635	**0.002**	3.139	1.051	9.38	**0.04**
Anti-topoisomerase-I positive	2.007	1.119	3.599	**0.019**	1.222	0.622	2.403	0.561
Extensive disease	2.069	1.171	3.658	**0.012**	1.628	0.736	3.602	0.229
KL-6 > 1273 U/mL	2.065	1.115	3.824	**0.021**	0.731	0.282	1.894	0.519
ΔKL-6 > 193 U/mL from baseline	6.141	2.92	12.913	**< 0.001**	4.727	2.144	10.42	**< 0.001**

SSc systemic sclerosis, *ILD* interstitial lung disease, *KL-6* Krebs von den Lungen-6, *HR* hazard ratio, *CI* confidence interval

[a]Multivariate model is adjusted for age, female, and smoking status.

Effect of treatment on KL-6 levels

To assess the effect of immunosuppressive therapy on FVC and serum KL-6 levels, we examined 36 of 77 (46.8%) SSc-ILD patients who were treated with IVCY pulse therapy. The patients received 6 cycles of IVCY (750–1000 mg/m^2) during the clinical course. FVC and serum KL-6 levels were evaluated at 0, 6, 12, and 24 months after IVCY. The median FVC values at 0, 0.5, 1, and 2 years after IVCY were 2.26 L, 2.19 L, 2.21 L, and 2.12 L, respectively. The beneficial effects of IVCY persisted for 1 year but waned at 2 years, as had been previously described [18]. On the other hand, the median serum KL-6 levels at 0, 0.5, 1, and 2 years after IVCY were 1318 U/mL, 1406 U/mL, 1343 U/mL, and 1155 U/mL, respectively. The serum KL-6 levels tended to decrease or be stable after IVCY treatment, regardless of a decrease in the FVC at 2 years.

Discussion

Our study reported the association between serum KL-6 levels and disease progression in patients with SSc-ILD over a long follow-up period. The increase in serum KL-6 levels and decrease in FVC values occurred simultaneously. To the best of our knowledge, this is the first study to show the utility of kinetic changes in KL-6 levels for monitoring disease progression in patients with SSc-ILD.

Serum KL-6 levels reflect disease progression in patients with SSc-ILD. In our cohort of 77 patients, around 64% showed progression of SSc-ILD at any time over the 5-year follow-up period, and 36% did not show decrease in FVC. Of the patients who progressed, 13% showed rapid and continuous decreases in their FVC values. The progression patterns were consistent with those of previous studies [4, 6]. Longitudinal analysis of the FVC values and serum KL-6 levels showed that the increase in KL-6 levels appeared mostly at the time of the decrease in FVC values. Since the course of SSc-ILD is highly variable and heterogeneous, baseline serum KL-6 levels or a single measurement of the KL-6 level during follow-up are unable to predict changes in FVC [19]. Furthermore, a change in the KL-6 level from baseline was an independent significant predictor for decrease in FVC over a 5-year follow-up period. These findings are similar to those in patients with idiopathic pulmonary fibrosis: serial increases in serum KL-6 levels have been associated with poor survival [20].

The results of previous studies suggest that KL-6 levels > 1273 U/ml at baseline are associated with disease progression, or “end-stage lung disease” [12, 21]. However, the baseline KL-6 levels were not associated with disease progression in our study. This discrepancy may be accounted for by differences in the disease severity of patients at baseline. In the cohort study of Kuwana et al, the mean FVC predicted was 83.7%, and the DLco predicted was 55.6% [12]. In the retrospective/prospective cohort study of Stock et al, the median FVC predicted values were 80.1%/73.8% and the median DLco predicted values were 55.5%/39.9% [21]. The parameters of lung function in those cohorts were worse than the parameters in our cohort, which showed a median FVC predicted of 88.0% and DLco predicted of 57.5% at baseline in the patients with progressive disease. Moreover, the mean KL-6 levels of the patients from the retrospective/prospective cohort study of Stock et al were 2189 U/mL in patients with end-stage lung disease and 1679 U/mL in those with extensive disease, which is much higher compared to the levels seen our cohort, which included the median KL-6 level of 841 U/mL in our patients with progressive disease. Thus, our cohort consisted of patients with relatively mild to moderate disease with normal lung function and low KL-6 levels at baseline.

The results of our study indicate an association between KL-6 levels and disease progression in patients with SSc-ILD. Although the pathogenesis of SSc-ILD has not been fully investigated, repetitive epithelial and endothelial cell injury is believed to be a first step in pathological process. This leads to activation of the innate and adaptive immune system, differentiation of fibroblasts to a myofibroblast phenotype, with accumulation of extracellular matrix and development of pulmonary [22, 23]. KL-6 is expressed more prominently by proliferating, regenerating, or injured type II cells than by uninjured type II cells, and may leak into the circulation after damage to lung epithelium [24]. Thus, KL-6 is likely to reflect the initial worsening of lung function instead of predicting long-term survival.

The limitation of this study is that it is a retrospective and single-institution study of a small number of patients with relatively mild SSc-ILD. The timing of pulmonary function testing varied, which could have led to an underestimation of disease progression. However, the strength of this study is the detailed analysis of the association between longitudinal serum KL-6 levels and progression of SSc-ILD. KL-6 has

been available for routine clinical use in Japan. Additional multicenter prospective studies are needed to confirm the utility of serial changes in KL-6 for monitoring patients with SSc-ILD.

In conclusion, kinetic change in KL-6 levels is useful for the prediction of disease progression in patients with SSc-ILD. Serial monitoring of serum KL-6 levels in relation to baseline indices may provide additional prognostic information, even when results of repeated pulmonary function tests are unavailable. The results can also be helpful for deciding on the types and timing of treatments such as antifibrotic agents for patients with SSc-ILD.

Abbreviations

SSc, systemic sclerosis

ILD, interstitial lung disease

SSc-ILD, systemic sclerosis-associated interstitial lung disease

KL-6, Krebs von den Lungen-6

HRCT, high-resolution computed tomography

FVC, forced vital capacity

DLco, diffusing capacity of the lung for carbon monoxide

RVSP, right ventricular systolic pressure

ΔKL-6, serial changes in KL-6

IVCY, intravenous cyclophosphamide

ROC, receiver operating characteristic

HR, hazard ratio

CI, confidence interval

PaO_2, partial pressure of arterial oxygen

UIP, usual interstitial pneumonia

NSIP, non-specific interstitial pneumonia

Declarations

Ethics approval and consent to participate: This study was approved by an ethics board at Kanazawa University Hospital (#3028), and written informed consent was waived because of its retrospective observational design.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions: SW and KKase contributed to the conception and design of the work. SW, KKase, KS, NO, AM, YW, HT, YI, MY, and KKasaharacontributed to the data acquisition. SW, KKase, and YW contributed to the analysis and interpretation of the data. SW drafted the article. All authors revised it critically for important intellectual content. All authors approved the submitted version and agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Figures

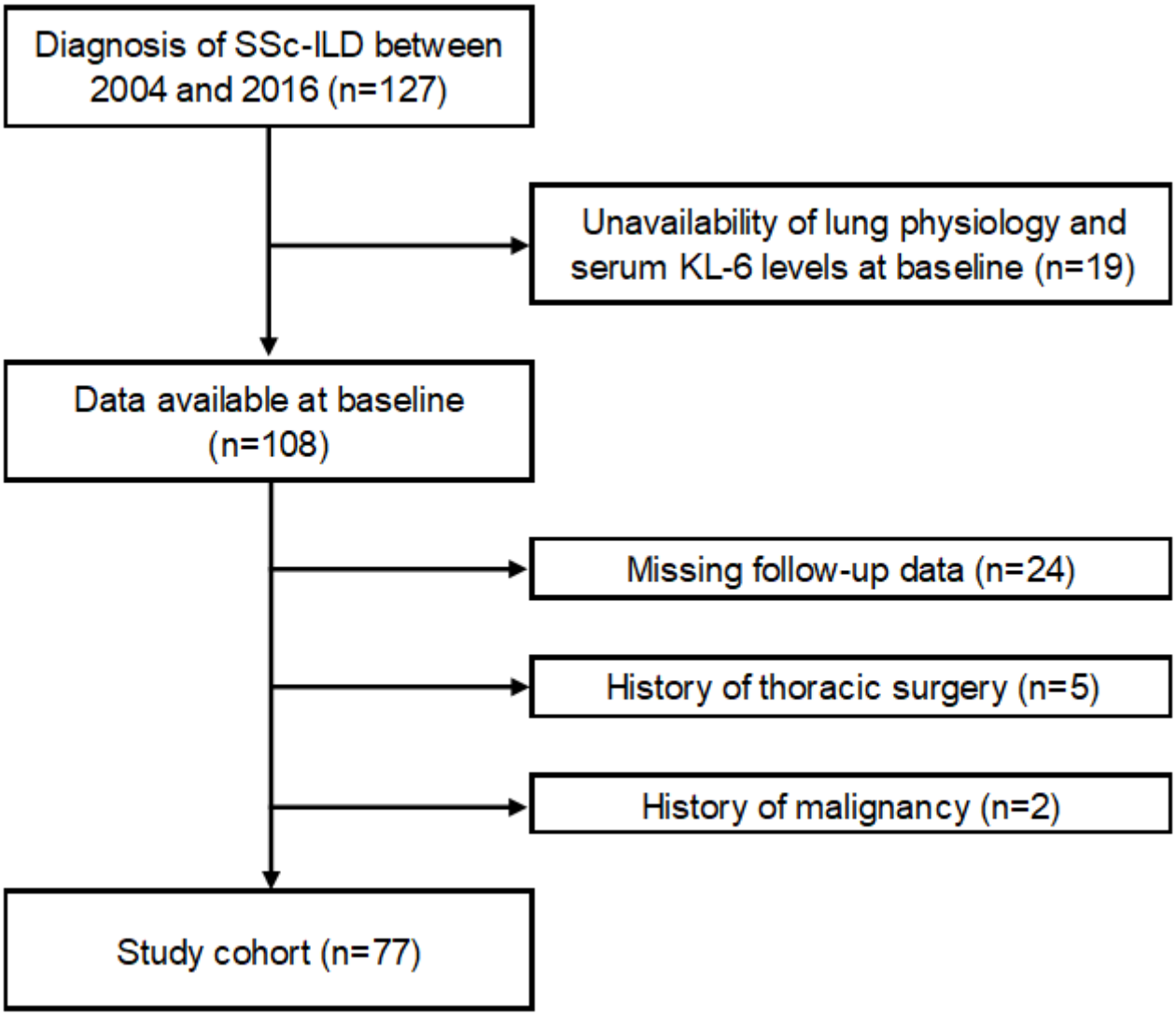

Figure 1

Flowchart of study enrollment. Abbreviations: SSc-ILD, systemic sclerosis-associated interstitial lung disease; KL-6, Krebs von den Lungen-6

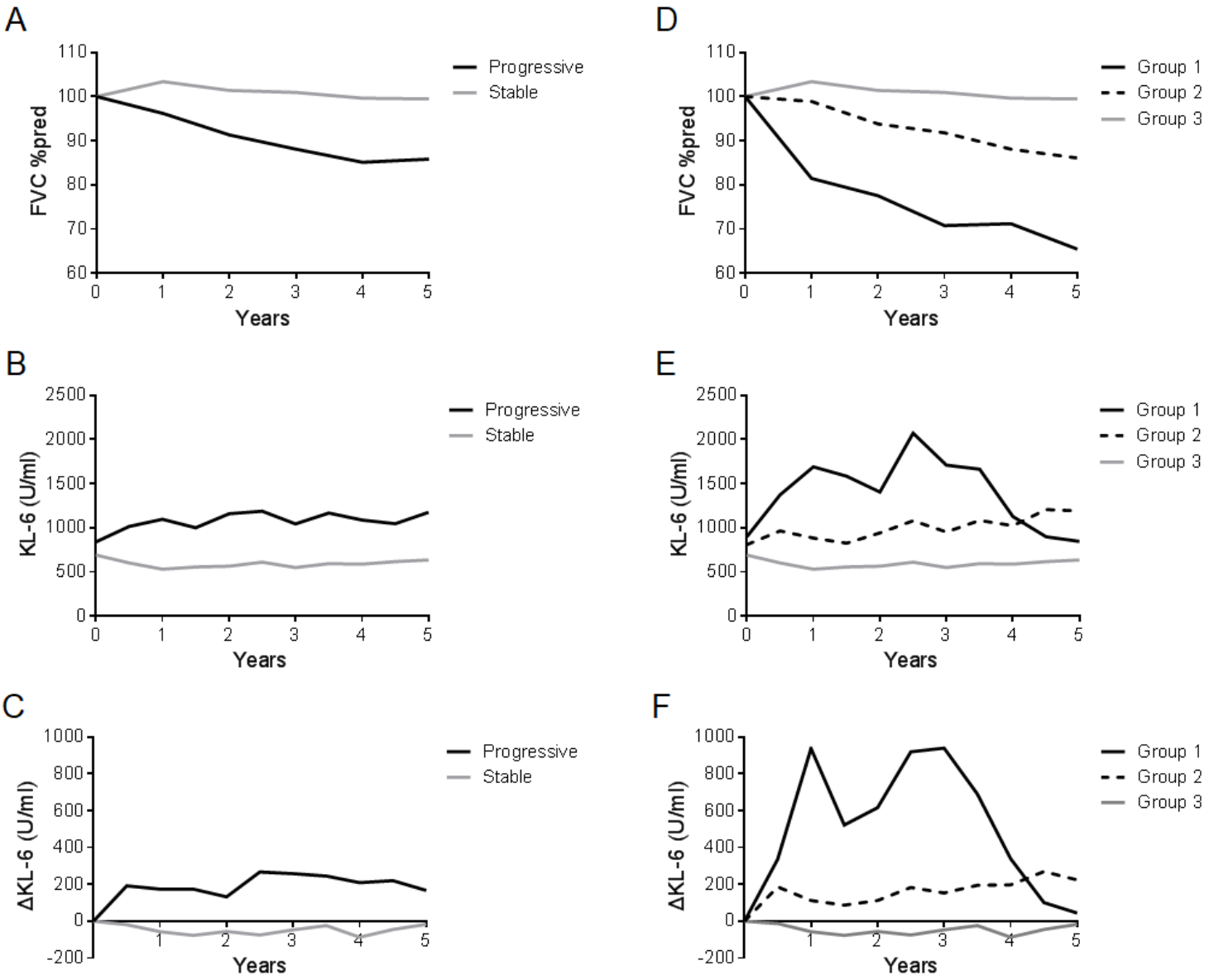

Figure 2

Trajectories of FVC, KL-6, and ΔKL-6 values from baseline. A FVCpredicted; B KL-6; C ΔKL-6from baseline in patients with progressive and stable ILD. D FVC predicted; E KL-6; F ΔKL-6from baseline among group 1 (rapidly progressive disease), group 2 (moderately progressive disease), and group 3 (stable disease). Abbreviations: FVC, forced vital capacity; KL-6, Krebs von den Lungen-6; ΔKL-6, serial changes in KL-6.

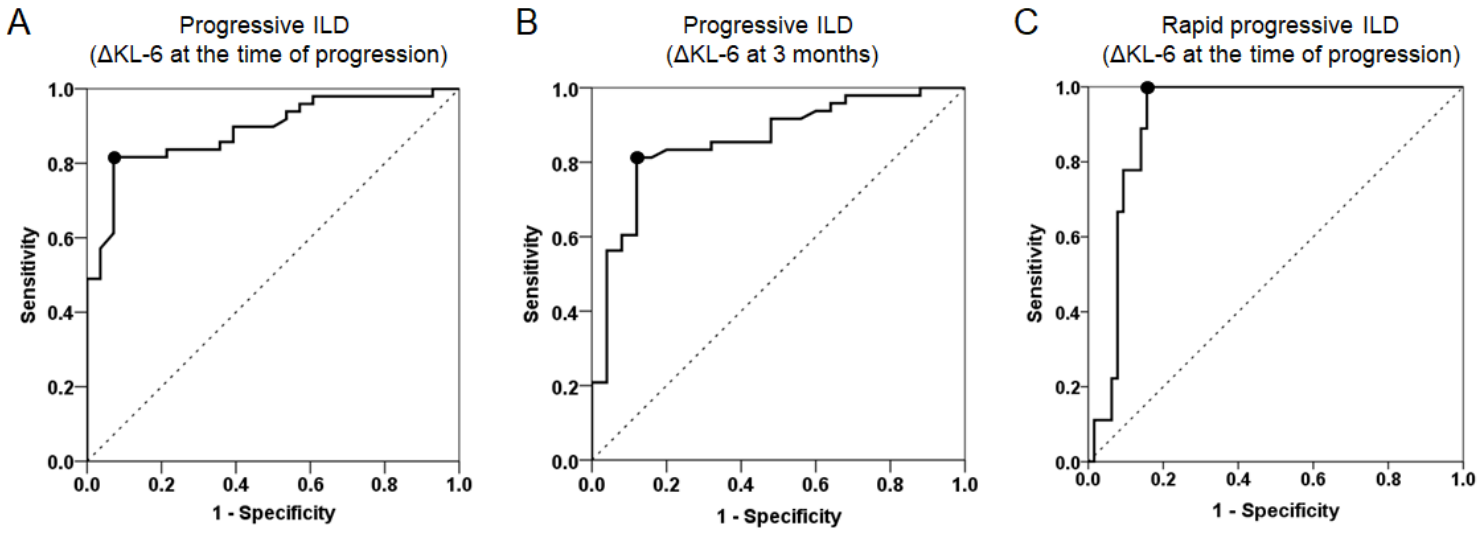

Figure 3

Receiver operating characteristic (ROC) curves for changes in KL-6 (ΔKL-6)values from baseline as predictors of ILD progression. A ΔKL-6 at the time of progression in predicting progressive ILD. B ΔKL-6 at 3 months from baseline in predicting progressive ILD.C ΔKL-6 at the time of progression in predicting rapidly progressive ILD. A dot indicating the cut-off value.Abbreviations: ROC, receiving operating characteristics; KL-6, Krebs von den Lungen-6; ΔKL-6, serial changes in KL-6; ILD, interstitial lung disease.

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