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Significance of serum Krebs von den Lungen-6 in systemic sclerosis

Noha Hosni Ibrahim[1*], Yasser Abd-Elaziz Abd-Elhamid[1], Refaat Mostafa El Tanawy[1], Rasha Abdel Hameed[1] and Hanaa Alaa Mahmoud Elbastawesy[1]

Abstract

Background Systemic sclerosis (SSc) is a well-known multi-system connective tissue disease, it has an unidentified aetiology that is characterised by abnormal immune system activation, vascular injury, which may progress to faulty neovascularization and inadequate vessel remodelling, and tissue scarring of the skin, lungs, and other internal viscera. Krebs von den Lungen-6 is a kind of transmembrane glycoprotein of type II alveolar epithelial cells and is specific for determining its damage. Regardless of the cause, serum Krebs von den Lungen-6 levels have been investigated in interstitial lung disease (ILD) of several etiologies and have been found to be a significant serum marker for ILD. The current research aims to look into the relationship between serum Krebs von den Lungen-6 levels and disease severity and clinical manifestations, specifically interstitial pulmonary fibrosis, in patients with SSc. In this study, 30 patients with systemic sclerosis and 30 control subjects—15 dermatomyositis patients and 15 healthy volunteers— were also incorporated to see if the change in serum Krebs von den Lungen-6 levels is specific for SSc as dermatomyositis is another connective tissue disorder with lung affection.

Results A statistically significant difference ($P < 0.001$) in the median value of Krebs von den Lungen-6 when compared to the control groups was observed, which was 447.95 (145.68–817.98) in the SSc patients group, 158.80 (130.00–730.70) in the dermatomyositis group, and 48.10 (39.50–103.90) in the healthy control group. A significantly higher median value of Krebs von den Lungen-6 in ground glass, honeycombing, and nodular HRCT was established, with *P*-value ($P < 0.001$). There was a highly statistically significant discrepancy in the median Krebs von den Lungen-6 value between patients with ILD (717.7) and patients without ILD (145.7) with *P*-value ($P < 0.001$). A statistically significant positive correlation was found between Krebs von den Lungen-6 (U/ml) and Disease duration (years), Medsger severity scale, Digital ulceration, modified Rodnan skin score (MRSS), and *P*-value ($P < 0.05$).

Conclusion Krebs von den Lungen-6 could be a scleroderma biomarker. It has been linked to the development and severity of interstitial lung disease in systemic sclerosis patients and may shed light on the pathophysiology of some fibrotic lung changes.

Keywords Systemic sclerosis, Interstitial lung disease, Krebs von den Lungen-6

Background

Among systemic rheumatic diseases, systemic sclerosis (SSc; scleroderma) possesses the highest case-specific mortality rate [1]. The evolution of progressive fibrosis brought on by the excess accumulation of extracellular matrix elements in a variety of organs and tissues is the most obvious feature of SSc. Additionally, SSc is characterised by vascular damage, inflammation, and the existence of specific autoantibodies [2]. The etiology of SSc

*Correspondence:
Noha Hosni Ibrahim
drnonon@yahoo.com
[1] Benha Faculty of Medicine, Al-Qalyubia Governorate, Banha, Egypt

is still mysterious. Several organs, counting the heart, lungs, kidneys, and digestive tract, may be affected. Interstitial lung disease (ILD) is a major reason for disease-related death in SSc patients [3].

Interstitial lung disease (ILD) is a diverse array of parenchymal pulmonary conditions with different degrees of fibrosis and inflammation. A staggering 80% of systemic sclerosis (SSc) patients have ILD, which is a significant cause of morbidity and mortality [4]. Age, male gender, and African American ancestry, diffuse cutaneous SSc, as well as positive anti-Scl70 autoantibodies, are risk elements for SSc-ILD, whereas anticentromere autoantibodies confer a lower risk [5]. Yet, until irreversible lung damage has occurred, an accurate diagnosis of SSc-ILD may not be made. Recognition of SSc-ILD in a timely and accurate manner to escort early treatment decisions is becoming more and more crucial in order to provide efficient treatments to stabilize and retard disease progression [6–8].

Krebs von den Lungen-6 (KL-6) represents a sialylated glycoprotein produced by type II pneumocytes (TIIP), which multiply after lung injury. It is a lung epithelial protein that has both antiapoptotic and profibrotic effects on lung fibroblasts. As a result, it has received extensive research as a pulmonary damage biomarker. An elevated KL-6 level was found to be a strong indicator of end-stage lung disease (ESLD) in a study that followed fifty patients with SSc and ILD progressively over time [9].

Serum biomarkers for SSc-related pulmonary involvement remain scarce, mainly those capable of detecting early lung interstitial fibrosis. As a result, finding high-risk ILD groups remains challenging.

Objectives

A case control study was carried out to figure out the significance of serum Krebs von den Lungen-6 as a diagnostic biomarker in systemic sclerosis associated with interstitial lung disease as well as its relationship with the disease severity & manifestation.

Methods

Target populations

This study enrolled 60 participants from the Rheumatology, Rehabilitation, and Physical Medicine inpatient and outpatient clinics at Benha university hospitals.

Participants in the work were split up into three groups:

Group (I) consisted of 30 patients with systemic sclerosis (SSc) who met the 2013 classification criteria for SSc designed by the American College of Rheumatology/European League Against Rheumatism [10]. Based on HRCT chest findings, the systemic sclerosis group was divided into ILD-associated patients and non-ILD-associated patients.

Control groups encompassed 15 age and gender-matched dermatomyositis patients diagnosed on the basis of the 2017 EULAR/ACR criteria for idiopathic inflammatory myopathies [11] (group II) as well as 15 age and sex-matched apparently healthy volunteers (group III).

Criteria for exclusion

1. Patients suffering from another connective tissue disease.
2. Patients suffering from tuberculosis, chronic obstructive pulmonary disease, or pulmonary infection.
3. Patients with other causes of pulmonary interstitial fibrosis such as pneumoconiosis and radioactive pneumonia.
4. Profound organ failure, for example, heart failure or renal failure.
5. Patients suffering from a malignant tumor.
6. Women who are pregnant or nursing.
7. Patient under the age of 18.

Ethical considerations

This research has been executed in agreement with the Declaration of Helsinki guidelines, with informed written consents acquired from all patients and controls before their participation in the study. The Research Ethics Committee at Benha Faculty of Medicine in Egypt approved this study.

Patient's clinical profile

All subjects had a clinical profile that included their demographic data, present and past medical histories, and pulmonary complains like coughing and dyspnea. Patients who exhibit symptoms similar to other connective tissue diseases were disqualified. Concurrent medications (like vasodilators and immunosuppressive agents) were accepted in SSc patients.

The medical parameters of the patients

Definite clinical parameters were observed in systemic sclerosis patients. Clinical palpation was used by MRSS-certified rheumatologists to weigh 17 body areas by means of the modified Rodnan skin score (mRSS), with a maximum score of 51 and each site being rated from 0 to 3 [12]. Using JAEGER CareFusion (234 GmbhLelbnizsr, Hochberg, Germany), spirometry was used to evaluate pulmonary function and carbon monoxide diffusing capacity (DLCO) in all patients. Every single patient with

scleroderma underwent a chest high-resolution computed tomography (HRCT).

Lung disease severity assessment

On the basis of the Medsger severity scale [13] that evaluates the degree of lung involvement on a scale of 0–4 as follows:

0, means normal.

1, mild (DLCO 70–80%, FVC 70–80%, basilar rales, radiographic fibrosis).

2, moderate (DLCO 50–69%, FVC 50–69%, and mild pulmonary hypertension).

3, severe (DLCO < 50%, FVC < 50%, moderate-severe pulmonary hypertension).

4, final stage (requires oxygen).

Measuring serum Krebs von den Lungen-6 (KL-6)

Following the manufacturer's instructions, a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) was used to quantify KL-6 serum levels, by adding KL-6 to a monoclonal antibody enzyme well that has been pre-coated with humen KL-6 monoclonal antibody, incubation; then, add Krebs von den Lungen-6 (KL-6) antibodies labelled with biotin and combined with Streptavidin-HRP. The colour eventually becomes yellow after adding chromogen solutions A, B. The colour chroma and the concentration of the humen substance Krebs von den Lungen-6 (KL-6) in the sample were found to be positively correlated.

Statistical analysis

Clinical data from medical charts was used to create statistical correlations. The statistical analysis was performed using IBM SPSS 25. Using conditional logistic regression, the odds ratio and 95% confidence interval for developing scleroderma were calculated.

The Student *T*, Mann–Whitney, and Kruskal–Wallis tests were utilized to compare variables. Correlation analysis was used to determine the degree to which two quantitative variables were related. The receiver operating characteristic (ROC) curve was created to assess KL-6's diagnostic potential in differentiating SSc patients with and without ILD.

Statistical significance

Based on the quantity of subjects and significant clinical effect sizes, a power analysis was carried out. Furthermore, the sample size was calculated using Stats Direct software. All statistical calculations used a two-tailed *P*-value.

Results

Subjects' demographic and clinical data

This study had 60 participants divided into three groups: Group (I), thirty individuals with systemic sclerosis; Groups (II) and (III), 15 patients with dermatomyositis, and 15 healthy volunteers were enrolled in the study as control groups. Tables 1 and 2 shows that the mean age and percentage of women were similar across all groups.

Table 1 Comparison of three groups based on demographic data

Demographic data	Patients group ($n = 30$)	Dermatomyositis group ($n = 15$)	Healthy control group ($n = 15$)	Test value	*P*-value
Age (years)					
Mean ± SD	51.13 ± 8.59	51.33 ± 7.99	51.00 ± 8.07	0.006	0.994
Range	35–68	35–63	36–62		
Sex					
Male	8 (26.7%)	5 (33.3%)	6 (40.0%)	0.847	0.655
Female	22 (73.3%)	10 (66.7%)	9 (60.0%)		
BMI (wt/ (ht)^2)					
Mean ± SD	23.60 ± 4.20	23.73 ± 3.51	23.93 ± 3.59	0.037	0.964
Range	17–30	18–30	18–30		
Disease duration (years)					
Mean ± SD	7.53 ± 3.60	6.47 ± 2.59	--	1.043	0.313
Range	2–20	3–12	--		

One way Analysis of Variance test was performed for mean ± SD

BMI body mass index, *SD* standard deviation

x^2, chi-square test for number (%) or Fisher's exact test, when appropriate

P-value > 0.05 is insignificant

Table 2 Disease characteristics of the studied SSc patient's group

Characteristic	No (30).	%
Esophgeal dysmotility		
Negative	6	20.00%
Positive	24	80.00%
Raynaud's phenomena		
Negative	2	6.70%
Positive	28	93.30%
Digital ulceration		
Negative	13	43.30%
Positive	17	56.70%
Digital gangerne		
Negative	25	83.30%
Positive	5	16.70%
PAH		
Mild	4	13.30%
Moderate	1	3.30%
No	25	83.30%
CRP		
Negative	10	33.3%
Positive	20	66.7%
Serological markers		
Anti-ANA (IU/ml)		
Negative	2	6.70%
Positive	28	93.30%
Anti-Centromere (IU/ml)		
Negative	22	73.3%
Positive	8	26.6%
Anti-SCL70 (IU/ml)		
Negative	18	60%
Positive	12	40%
HRCT chest changes		
Ground glass	9	30.00%
Honey combing	7	23.30%
Nodular	3	10.00%
Normal	11	36.70%
	Range	Mean ± SD
MRSS	4.00–22.00	14.5000 ± 4.95
ESR (mm/h)	20–70	41.9667 ± 13.75
Pulmonary function tests		
FVC (L)	38.00–130.00	78.5667 ± 23.54
TLC (L)	44.00–113.00	77.4333 ± 21.22
DLCO (L)	48.00–108.00	74.8000 ± 16.34

PAH pulmonary arterials hypertension, *CRP* C-reactive protein, *Anti-ANA* anti-nuclear antibody, *Anti-SCL70* anti-Scleroderma 70 antibody, *HRCT* high resolution computed tomography, *MRSS* modified Rodnan skin score, *FVC* forced vital capacity, *TLC* total lung capacity, *DLCO* diffusion lung carbon dioxide capacity

Serum Krebs von den Lungen-6 levels were significantly higher in systemic sclerosis patients than in control groups

When compared to the control group, the SSc group had significantly higher serum Krebs von den Lungen-6 levels ($P < 0.001$) (Table 3).

The median value of Krebs von den Lungen-6 showed a highly statistically significant difference, which was 447.95 (145.68–817.98) in the SSc patients group, 158.80 (130.00–730.70) in the dermatomyositis group, and 48.10 (39.50–103.90) in the healthy control group, with *P*-value ($P < 0.001$) (Table 4).

Figure 1 depicts a significantly higher median value of Krebs von den Lungen-6 in ground glass, honeycombing, and nodular compared to normal HRCT, with *P*-value ($P < 0.001$).

With *P*-value ($P < 0.001$), a statistically significant difference existed in the median Krebs von den Lungen-6 value between patients with ILD (717.7) and patients without ILD (145.7) (Table 5).

With *P*-value (P 0.05), there was a statistically significant positive relationship between Krebs von den Lungen-6 (U/ml) and Disease duration (years), Medsger severity scale, Digital ulceration, MRSS, ESR (mm/h), and CRP.

There was also a statistically significant negative correlation with *P*-value ($P < 0.001$) between Krebs von den Lungen-6 (U/ml) and FVC (L), TLC (L), and DLCO (L). The remaining correlations are insignificant, with *P*-values ($P > 0.05$) (Table 6).

Multivariate analysis revealed that the most significant predictors of ILD were age (years), BMI (wt/(ht)^2), MRSS, Anti-SCL70 (IU/ml), Krebs von den Lungen-6 (U/ml), FVC (L), TLC (L), DLCO (L), and Medsger severity scale, with *P*-value ($P < 0.05$), while the rest have insignificant predictors of ILD, with *P*-value ($P > 0.05$) (Table 7).

ROC curve analysis proved good discriminating power of the (Krebs von den Lungen-6 (U/ml)) between scleroderma patients with and without ILD where area under the ROC curve (AUC) = 0.921 with SE 0.0540 (95% confidence interval 0.762–0.988. Z statistic = 7.795, $P < 0.001$. Cutoff point > 171.2 with sensitivity = 89.5% and specificity = 90.9 (Fig. 2). Figure 3 shows two HRCTs chest of one SSc patient with advanced ILD and another with early ILD.

Discussion

Krebs von den Lungen-6 is a transmembrane glycoprotein found in type II alveolar epithelial cells that is responsible for determining cell damage [9]. Krebs von den Lungen-6 levels were significantly different between the control and patient groups in the current study, with the patient group having higher levels than the control

Table 3 Comparison of the patients group and the control group based on serum Krebs von den Lungen-6 levels (U/ml)

Krebs von den Lungen-6 (U/ml)	Patients group ($n = 30$)	Control group ($n = 30$)	Test value	*P*-value
Median (IQR)	447.95 (145.68–817.98)	106.45 (47.00–163.60)	−4.052	< 0.001**
Range	57.7–857.4	16.7–844		

Using *U*, Mann–Whitney test for non-parametric data "median (IQR)"; *IQR* inter quartile range

***P*-value < 0.001 is highly significant

Table 4 Comparison of three groups based on Krebs von den Lungen-6 (U/ml) levels

Krebs von den Lungen-6 (U/ml)	Patients group ($n = 30$)	Dermatomyositis group ($n = 15$)	Healthy control group ($n = 15$)	Test value	*P*-vlue
Median (IQR)	447.95A (145.68–817.98)	158.80B (130.00–730.70)	48.10C (39.50–103.90)	32.796	< 0.001**
Range	57.7–857.4	105.6–844	16.7–116.7		

Kruskal–Wallis was performed for median (IQR) interquartile range and multiple comparisons between groups through the Mann-Whitney test

Different capital letters indicate significant differences at ($P < 0.05$) among means in the same row

***P*-value < 0.001 is highly significant

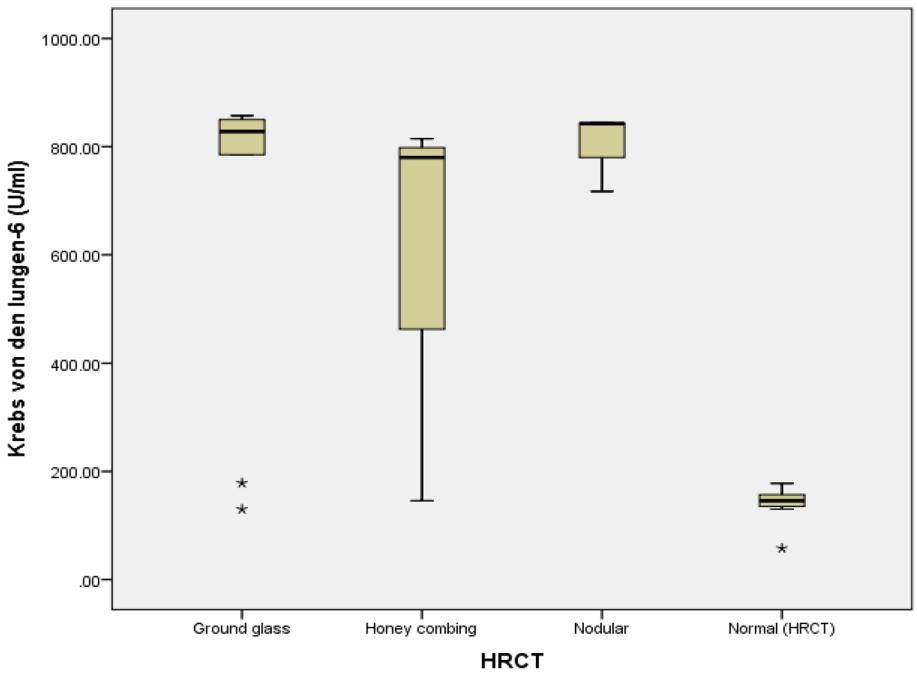


Fig. 1 The relationship between HRCT and Krebs von den Lungen-6 (U/ml) in the patient group. Serum Krebs von den Lungen-6 levels were found to be significantly related to HRCT changes

groups. There was a significant difference in the median value of Krebs von den Lungen-6 levels between the patients' group, dermatomyositis (subgroup), and healthy control group, with the scleroderma patients' group having the greatest value, followed by dermatomyositis, and the healthy control group having the lowest value, This is consistent with many previous studies [14–17]. This is, as far as we are aware, the first research to compare serum KL-6 levels in scleroderma and dermatomyositis, another connective tissue disease that shares many characteristics with systemic sclerosis, including pulmonary and skin affection.

The levels of Krebs von den Lungen-6 (U/ml) were found to have a statistically significant positive relationship with both digital ulceration and MRSS. This is in line with the results of Cao et al. [18] who discovered that

Table 5 Comparison of scleroderma patients with and without ILD based on Krebs von den Lungen-6 (U/ml) levels based on HRCT findings

ILD	Krebs von den Lungen-6 (U/ml)			*z*-test	*P*-value
	Median	IQR			
		25th	75th		
Without ILD (*n* = 11/36.7%)	145.70	131.20	157.10	15.933	< 0.001**
With ILD (*n* = 19/63.3%)	717.40	711.00	842.50		

ILD interstitial lung disease

Using *U*, Mann–Whitney test for non-parametric data "median (IQR)"

***P*-value < 0.001 is highly significant

Table 6 Correlations between Krebs von den Lungen-6 (U/ml) with different parameters in SSc patients group

Parameters	Krebs von den Lungen-6 (U/ml)	
	rs	*P*-value
Age (years)	0.121	0.203
Disease duration (years)	0.603	< 0.001**
BMI (wt/(ht)^2)	−0.023	0.903
Esophageal dysmotility	0.289	0.121
Raynaud's phenomena	0.046	0.808
Digital ulceration	0.478	0.008*
Digital gangerne	0.160	0.398
PAH	0.114	0.550
MRSS	0.451	0.012*
ESR (mm/h)	0.436	0.016*
CRP	0.400	0.028*
AntiANA (IU/ml)	−0.286	0.126
AntiSCL70 (IU/ml)	0.283	0.130
FVC (L)	−0.897	< 0.001**
TLC (L)	−0.794	< 0.001**
DLCO (L)	−0.857	< 0.001**
Medsger severity scale	0.936	< 0.001**

PAH pulmonary arterials hypertension, *MRSS* modified Rodnan skin score, *CRP* C-reactive protein, *Anti-ANA* anti- nuclear antibody, *Anti-SCL70* anti-Scleroderma 70 antibody, *FVC* forced vital capacity, *TLC* total lung capacity, *DLCO* diffusion lung carbon dioxide capacity

Using Spearman's rank correlation coefficient (rs); *P*-value > 0.05 NS; **P*-value < 0.05 S; ***P*-value < 0.001 HS

increased KL-6 levels were strongly related to the loss of finger pad, which was the clinical sequela of microvascular injury; however, they noticed an insignificant relationship between KL6 levels and skin scores. In their study, Bonella et al. [19] detected a significant link between MRSS and serum KL 6 levels, which is consistent with our findings.

This study shows a statistically significant higher median value of Krebs von den Lungen-6 in ground glass, honeycombing, and nodular opacities respectively compared to normal HRCT. Our findings were consistent with those of Audrey Benyamine et al. [14], who realised that KL-6 serum concentrations were significantly greater in SSc-ILD patients compared to controls as demonstrated on HRCT chest, and that they had a negative relationship with diffuse lung capacity of carbon monoxide, forced vital capacity together with total lung capacity.

In addition, Chen F et al. [15] found that KL-6 levels were considerably greater in ILD patients compared to those without, with a correlation to the progression of the ILD. Furthermore, KL-6 was predictive of the onset and progression of ILD [20–22].

There was also a statistically significant inverse relationship between Krebs von den Lungen-6 (U/ml) and DLCO, FVC as well as TLC. This corresponds to the findings of Bonella et al. [19] who found high serum KL6 levels in 33 patients diagnosed as pulmonary alveolar proteinosis. Additionally, Wang et al. [22] discovered an inverse linear relation between serum KL6 and PFTs such as FVC% ($r = 0.42$, $P < 0.001$) and FEV1% ($r = 0.49$, $P < 0.001$). This suggests that greater serum KL-6 levels in these patients are related to worsening pulmonary function.

According to Kuwana et al. [9], the most trustworthy and distinct predictor of FVC worsening and the progression of scleroderma lung disease was a high serum KL-6 level.

Interestingly, and in accordance with Bonella et al. [19], this study found an increase in KL-6 serum concentrations with increased severity of lung involvement as measured by Medsger's severity scale.

KL-6 is a high-molecular-weight transmembrane mucoprotein. It is secreted by proliferating or damaged type II alveolar epithelial cells, and its function is specific to type II alveolar epithelial cells. The increased serum KL-6 level will be caused primarily by an increase in KL-6 secretion or release by type II alveolar epithelial cells. As type II alveolar epithelial cells regenerate in fibrosis lung disease, KL-6 levels will significantly rise. The sensitivity marker for ILD, such as idiopathic pulmonary fibrosis, hypersensitive pneumonitis, and radiation pneumonitis, has been demonstrated to be serum KL-6 levels [23].

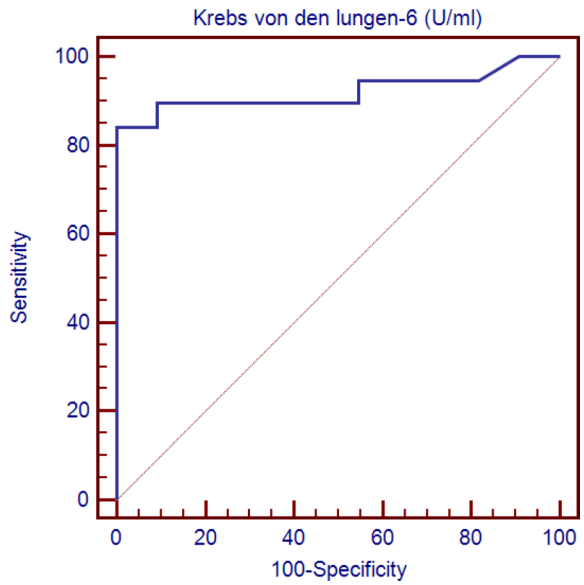
According to a meta-analysis, patients with progressive ILD have greater KL-6 levels than non-progressive patients. Nonetheless, severe ILD patients have higher KL-6 values than mild patients [24].

Furthermore, some research suggests that an elevated KL-6 level may be a sensitive indicator of ILD relapse [25].

Table 7 Multivariate logistic regression analysis for factors predictors for ILD in scleroderma patients

		Wald	Sig.	OR	95% C.I.	
					Lower	Upper
Age (years)	0.688	3.683	0.031*	1.732	1.235	4.423
Sex	0.247	1.362	0.162	1.682	1.105	2.748
BMI (wt/(ht)^2)	0.368	3.292	0.041*	2.896	1.341	7.696
Disease duration (years)	0.408	0.765	0.961	0.459	0.122	1.137
Esophgeal dysmotility	0.889	0.773	0.611	0.526	0.142	1.211
Raynaud's phenomena	0.289	1.594	0.190	1.968	1.293	3.215
Digital ulceration	0.192	1.293	0.340	1.366	0.974	2.207
Digital gangrene	0.266	1.587	0.294	1.842	1.213	2.893
PAH	1.040	0.904	0.715	0.615	0.166	1.417
MRSS	2.531	2.028	0.049*	1.848	1.452	2.945
ESR (mm/h)	0.349	0.654	0.821	0.392	0.104	0.972
CRP	0.225	1.513	0.398	1.598	1.140	2.582
ANA (IU/ml)	0.177	0.913	0.374	1.362	0.972	2.147
Anti-SCL70 (IU/ml)	0.366	2.547	0.043*	1.943	1.861	3.327
Krebs von den Lungen-6 (U/ml)	1.549	7.353	0.026*	2.822	1.486	5.461
FVC (L)	2.254	8.349	< 0.001**	3.014	1.985	6.068
TLC (L)	0.994	5.736	0.027*	2.712	2.056	6.446
DLCO (L)	0.889	4.710	0.029*	1.740	1.646	4.915
Medsger severity scale	1.272	5.838	0.027*	1.702	1.606	5.177

β regression coefficient, *SE* standard error, *CI* confidence interval, *OR* odds ratiol, *PAH* pulmonary arterial hypertension, *MRSS* modified Rodnan skin score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *ANA* antinuclear antibodies, *Anti-SCl70* anti-Sclerodema 70 antibody, *FVC* forced vital capacity, *TLC* total lung capacity, *DLCO* diffusion lung carbon dioxide capacity



Cut-off	Sen.	Spec	PPV	NPV	AUC (C.I.95%)	P-value
>171.2	89.5%	90.9%	94.4%	83.3%	0.921 (0.762-0.988)	<0.001**

Sen:sensitivity; Spec: specificity, PPV: positive predictive value; NPV:negative predictive value;AUC:area under the curve; CI:confidence interval.

Fig. 2 ROC curve (discrimination of scleroderma patients with and without ILD using the receiver operating characteristic curve)

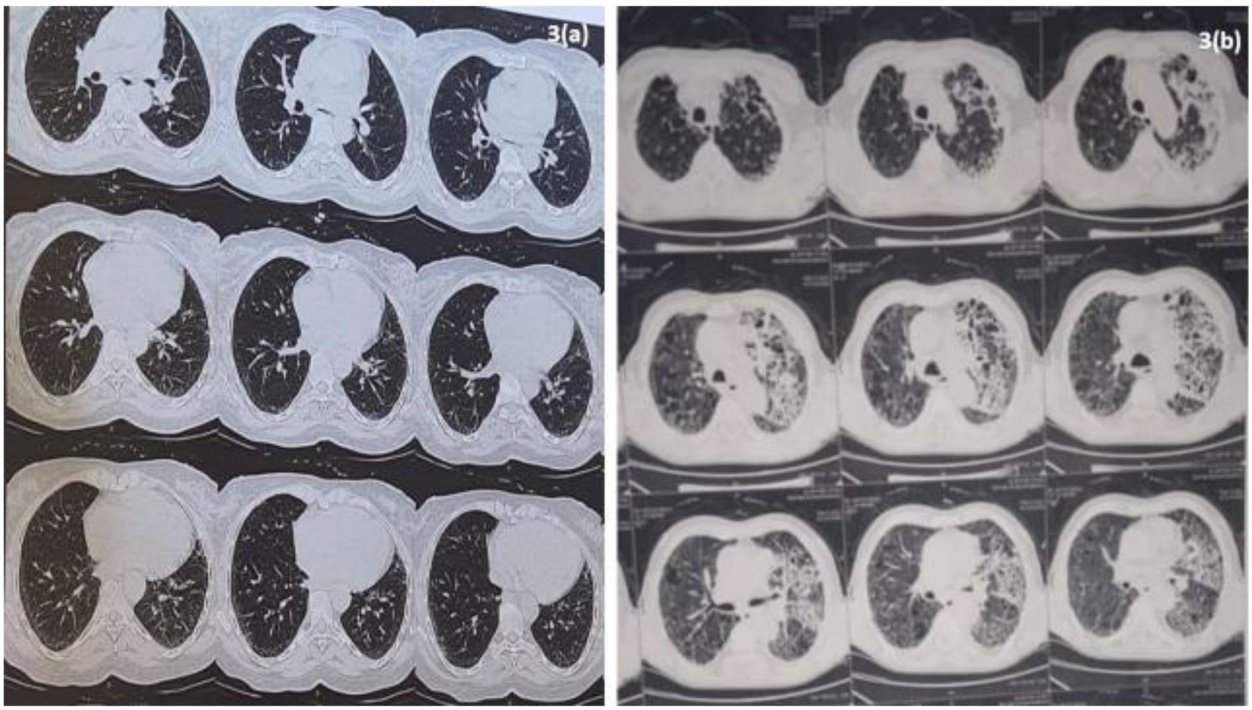


Fig. 3 **a** HRCT chest of SSc patient showing early ILD with fine reticular opacities (Krebs von den Lungen-6 was 722 U/ml). **b** HRCT chest of SSc patient with advanced ILD showing patchy ground glass associated with reticular changes (Krebs von den Lungen-6 was 812 U/ml)

The following are some of the current study's strengths: suitable participant selection, strict scleroderma diagnosis in accordance with the ACR/EULAR 2013 SSc criteria, the inclusion of two control groups for comparison, and the exclusion of patients who exhibit symptoms that are similar to those of other connective tissue disorders. Furthermore, this study could concentrate on microvascular injury and ILD, which are two of the most predominant pathologies associated with SSc and have been linked to noteworthy morbidity and mortality.

However, our research has some limitations, first is the relatively small sample size and single hospital participation, and second is the dermatomyositis cases could not be studied by HRCT chest for financial reasons. However, future studies on dermatomyositis patients are highly recommended. In addition, the drugs' relationship with KL-6 could not be judged due to the small sample size. The effect of treatment on SSc patients needs to be investigated in correlation with HRCT findings and PFT to determine whether Krebs von den Lungen-6 could be used as a prognostic marker and to see the effect of treatment on the expression of this marker.

Conclusion

Given that not all individuals with scleroderma exhibit this biomarker in a positive manner, KL-6 might function as a biological marker for scleroderma, enabling it to be an inclusion diagnosis rather than an exclusion diagnosis. It might also aid in focusing investigations on people who received negative results. In comparison to normal HRCT, ground glass, honeycombing, and nodular opacities changes had higher serum levels of Krebs von den Lungen-6, respectively; therefore, KL-6 may shed light on the pathophysiology of some fibrotic lung changes.

Abbreviations

ANA	Antinuclear antibodies
Anti-SCl70	Anti-scleroderma 70 antibody
AUC	Area under the curve
BMI	Body mass index
CI	Confidence interval
CRP	C-reactive protein
DLCO	Diffusion lung capacity of carbon monoxide
ESLD	End–stage lung isease
ESR	Erythrocyte sedimentation rate
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
KL-6	Krebs von den Lungen-6
MRSS	Modified Rodnan skin score
PAH	Pulmonary artery hypertension
TLC	Total lung capacity
TIIP	Type II pneumocytes
SSc	Systemic sclerosis

Authors' contributions

All authors have read and approved the manuscript. NHI: conceptualization, resources, data curation, formal analysis, validation, investigation, visualization,

and writing—original draft, review, and editing. YAAh: theorizing, resources, thorough analysis, research methods, investigation, and writing—the original draft, review, and editing—are all part of the research process, as is the final product. RMEl t: methodology and writing—the original draft, review, and editing of the finished version. RAH: data aggregation and curation; formal analysis; investigation; methodology; and writing—first draft, review, and editing. HAE: methodology and writing- resources; data aggregation and curation; formal analysis; investigation

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

Declarations

Ethics approval and consent to participate
The study was validated and approved by the ethical committee of the Benha Faculty of Medicine. Date 27-10-2020,No: MS21082020.
Written consents according to the Helsinki Declaration were taken from all participants prior to participation in the study that was approved by the ethical committee of the Faculty of Medicine, Benha University.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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