The relationship between serum level of matrix metalloproteinase-7 and interstitial lung disease in patients with systemic sclerosis

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Background
Interstitial lung disease (ILD) remains a leading cause of mortality in systemic sclerosis (SSc). Matrix metalloproteinases (MMPs) play an important role in inflammation, autoimmune diseases and aberrant fibrotic tissue remodeling.
Aim
The aim of this work was to evaluate the relation between serum level of MMP-7 and ILD in SSc patients.
Patients and methods
The study was conducted on 30 SSc patients. Pulmonary function tests and chest high-resolution computed tomography were assessed. Degree of fibrosis was assessed according to Warrick severity and extent scores. Serum level of MMP-7 was measured.
Results
The 30 patients had a mean age of 41.60±11.11 years and disease duration of 3.50 ±1.81 years; 23 with diffuse and seven with limited subtype. ILD was present in 20 patients. Serum MMP-7 was significantly higher in those with ILD (412.5±52.4 ng/ml) compared with those without (disease control group) (351.4±56.4 ng/ml) (P=0.007). In patients with ILD, MMP-7 was significantly higher in those with ground-glass opacities, honeycombing and reticular infiltration on high-resolution computed tomography; yet, it was comparable among the different grades of pulmonary restriction by pulmonary function test. There was a significant negative correlation between serum MMP-7 level and forced vital capacity and forced expiratory volume in one second (r=–0.46, $P<$ 0.05 and r=–0.65, $P<$ 0.0001, respectively). Correlations between MMP-7 and Warrick severity and extent were significant (P=0.002 and 0.007, respectively). MMP-7 at a cut-off value of 367.4 ng/ml was 85% sensitive and 80% specific for detection of ILD.
Conclusion
There is a strong association between serum MMP-7 and the presence, severity and extent of ILD in scleroderma patients. It might be a useful marker for ILD in SSc.

Keywords:
interstitial lung disease, matrix metalloproteinase-7, systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by the fibrosis of the skin and internal organs, vasculopathy and immune dysregulation [1]. In Egyptian SSc patients, pulmonary arterial hypertension (PAH) was reported as a serious complication of SSc that has a dramatic impact on the prognosis and survival and is a leading cause of death [2]. Moreover, pathological involvement of coronary arteries in asymptomatic SSc patients was not uncommon [3]. In a previous work on SSc, most of the patients had abnormal pulmonary function tests, and half the cases presented with interstitial lung disease (ILD), while PAH was recorded in around 20% [4] and, miscarriage in a pregnant SSc patient was reported due to PAH [5]. An increased risk of peripheral arterial disease in SSc has been documented [6]. Several biomarkers have been measured in Egyptian SSc patients, such as cartilage oligomeric matrix protein [7], cluster of differentiation 36 [8], toll-like receptor-9 [9], vascular endothelial growth factor [10], serum B-lymphocyte stimulator [11] and chemokines [12] with diagnostic and prognostic potentials.

The matrix metalloproteinases (MMPs) belong to the zinc-dependent endoproteases that participate in extracellular matrix remodeling, wound healing and

angiogenesis and have been implicated in the pathogenesis of ILD.

Several members of the MMP family are highly upregulated in ILD lungs, and protein expression (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9) has been found to be elevated in the bronchi-alveolar lavage fluid and in the blood of idiopathic pulmonary fibrosis (IPF) patients [13]. However, on the basis of the available data, MMP-1 and MMP-7 are the most significantly overexpressed proteins in the lungs of patients with IPF compared with healthy controls. Moreover, using a panel of 49 plasma proteins in a group of ILD patients, Rosas *et al.* [14] found increased concentrations of both MMP-1 and MMP-7, suggesting not only a determinant role in ILD pathogenesis but also potential utility as biomarkers in the differential diagnosis of this disease [15].

MMPs are known to play an important role in chronic inflammation, autoimmune diseases and aberrant fibrotic tissue remodeling [16,17]. However, MMP-7, a metalloproteinase that targets a broad range of extracellular matrix proteins, was originally seen to be highly overexpressed in ILD [16].

The aim of the study was to evaluate the relation between serum level of MMP-7 and ILD in patients with SSc.

Patients and methods

This randomized cross-sectional case–control study included 30 patients diagnosed as suffering from SSc fulfilling the 2013 ACR/EULAR classification criteria for scleroderma [18,19]. They were subgrouped according to the presence or absence of ILD into those with ILD (group I) and those without ILD (group II) as a disease control group. They were recruited from the Rheumatology Department and Outpatient Clinic at University Hospitals between January 2016 and January 2017. Patients with other systemic rheumatic diseases or those with ILD risk factors other than SSc were excluded from the study. The study was approved by the Local Research Ethical Committee of University and conforms to the provisions of the Declaration of Helsinki in 1995. All patients gave their informed consent before their inclusion and after explaining the nature of the study.

All patients were subjected to detailed history taking and thorough clinical examination and laboratory investigations including complete blood picture, erythrocyte sedimentation rate, and C-reactive protein. Serum level of MMP-7 (matrilysin) was estimated by enzyme-linked immunosorbent assay human kit (catalog no. E-EL-H1449, 96T; Technology Industry Park (Jingding Town XiangzhouDist Zhuhai, China); detection range: 0.16–10 ng/ml). The MMP-7's lowest detectable level is 0.16 ng/ml and is considered normal up to 10 ng/ml.

Pulmonary function tests were performed, including forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio; severity grading according to the FVC was mild (>75 to < 80%), moderate (50–75%) and severe (≤50%) [20]. Chest plain radiograph and high-resolution computed tomography (HRCT) were performed with an assessment of fibrosis score using the Warrick scoring system [21], which combines severity with the extent of disease with a maximum score of 15 for each [22]. Patients were subgrouped into those with and without ILD according to the chest HRCT. Transthoracic echocardiography was performed, and PAH was suspected if right ventricular systolic pressure was at least 35 mmHg [23].

Statistical analysis

Data were collected, tabulated and statistically analyzed using the statistical package for the social sciences (SPSS; software version 18, IBM Company, New York City, USA). Quantitative variables were described as mean, SD, median and range. Qualitative variables were described as number and percentage. The χ^2, Fisher exact and independent *t*-tests were used for comparison. The Spearman correlation coefficient was used and the receiver operating characteristics curve plotted. *P* value was considered significant if up to 0.05.

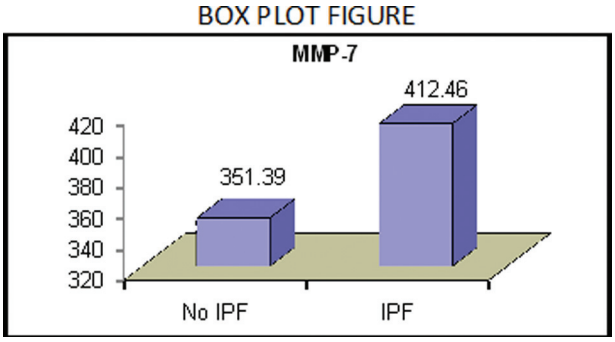
Results

The 30 SSc patients had a mean age of 41.60±11.11 years and a disease duration of 3.50±1.81 years; they were subgrouped into group I: patients with ILD (n=20) and group II: patients without ILD (n=10) as a disease control group. Group I patients comprised 18 (90%) female individuals and two (10%) male individuals with a mean age of 44.3±10.6 years and disease duration of 3.8±1.99 years; 16 (53.3%) had diffuse cutaneous SSc, and four (13.3%) had limited cutaneous SSc. Group II patients comprised nine (90%) female individuals and one (10%) male individual. Their mean age was 36.2±10.6 years, and disease duration was 2.9±1.3 years; seven (23%) had diffuse cutaneous SSc, and three (10%) had limited cutaneous SSc. The age, sex and disease duration were comparable between the two subgroups (P>0.05).

All studied patients (100%) had Raynaud's phenomenon, 96.7% had skin tightness, 83.3% had puffy fingers and 66.7% had sclerodactyly. An overall 26.7% had PAH, 83.3% had esophageal dysmotility, while 63.3% had gastroesophageal reflux disease. An overall 80% had arthralgia, 26.7% had arthritis and 20% had pericardial effusion. On comparing both groups with and without ILD, there was no significant difference with regard to laboratory data and the mean erythrocyte sedimentation rate (49.9±29.9 vs. 50.40±25.7 mm/h), and C-reactive protein (median 6; range: 6–18 mg/dl vs. median 6; range: 6–16 mg/dl) was also comparable ($P>0.05$).

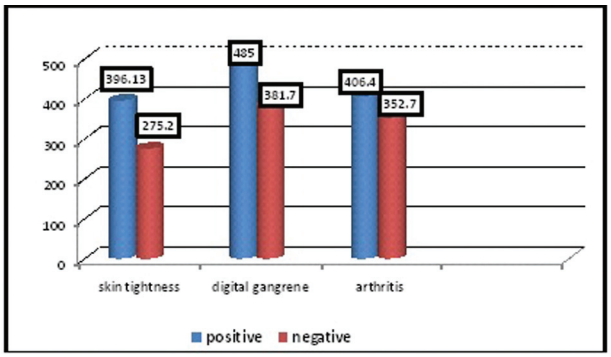
Serum MMP-7 was significantly higher in group I patients (412.5±52.4 ng/ml) compared with group II patients (351.4±56.4 ng/ml) ($P=0.007$; Fig. 1). In group I patients, the MMP-7 was significantly higher only in those with dyspnea ($P=0.008$), chest pain ($P<0.05$), skin tightness ($P<0.05$), arthritis ($P< 0.05$) and digital gangrene ($P=0.003$) compared with those without these clinical manifestations (Fig. 2). Comparisons of MMP-7 according to the presence and absence of HRCT findings are shown (Table 1).

Figure 1



Matrix metalloproteinase-7 (MMP-7) in systemic sclerosis patients with (group I) and without (group II) interstitial lung disease (ILD).

Figure 2



Comparison between the serum matrix metalloproteinase-7 (MMP-7) levels and skin tightness, digital gangrene and arthritis in patients of group I.

According to the Warrick (severity) score, one (3.3%) SSc patient had score I, five (16.6%) had score III, eight (26.7%) had score IV, one (3.3%) had score V, one (3.3%) had score VI, three (10%) had score VII, and one (3.3%) had score VIII. The Warrick (extent) score showed score II in two (6.6%) patients, score III in two (6.6%), score IV in eight (26.7%), score VIII in seven (23.3%) and score IX in one (3.3%). Comparison of the MMP-7 level according to the pulmonary restriction grade (FVC%) showed no significant difference (Table 2).

A significant association was found between MMP-7 serum level and pulmonary symptoms (dyspnea and chest pain) ($P=0.008$ and <0.05, respectively). There was a significant association between ILD with PAH and eosophageal dysmotility ($P<0.05$). There were no other significant associations.

There was a significant correlation between serum MMP-7 level with Warrick severity and extent scores and inversely with the FVC and FEV_1 (Table 3).

Table 1 Comparison of the serum matrix metalloproteinase-7 level according to the presence and absence of chest high-resolution computed tomography findings in group I patients with interstitial lung disease

HRCT findings	SSc patients with ILD ($n=20$)		
	MMP-7 (ng/ml)		
	Mean±SD	Range	*P*
Ground-glass opacities			
Negative	365.8±66.9	275.2–507.7	< **0.05**
Positive (13)	420.4±51.9	317.2–506.3	
Interstitial thickening/edema			
Negative	391.0±62.6	275.2–507.7	>0.05
Positive (5)	397.6±53.2	317.2–460.4	
Pleural thickening			
Negative	385.2±58.4	275.2–507.7	>0.05
Positive (3)	454.3±45.1	427.6–506.3	
Subpleural lines			
Negative	395.3±62.7	275.2–507.7	>0.05
Positive (3)	363.6±19.2	342.6–380.3	
Honeycombing			
Negative	358.1±61.9	275.2–506.3	< **0.05**
Positive (6)	438.1±55.9	342.6–507.7	
Reticular infiltration			
Negative	365.7±51.1	275.2–488.3	< **0.05**
Positive (8)	429.6±82.3	324.6–507.7	
Bronchiectasis			
Negative	390.3±58.5	275.2–507.7	>0.05
Positive (4)	403.9±80.6	324.6–505.6	
Air trapping			
Negative	391.1±62.2	275.2–507.7	>0.05
Positive (2)	406.6±29.7	385.6–427.6	

Bold values are significant at $P<0.05$. HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MMP-7, matrix metalloproteinase-7; SSc, systemic sclerosis.

Table 2 Comparison of the serum matrix metalloproteinase-7 level according to the pulmonary restriction grade forced vital capacity in group I patients with interstitial lung disease

Pulmonary restriction grade (FVC%)	MMP-7 (ng/ml) in SSc patients with ILD (n=20)		P
	Mean±SD	Range	
I (mild)	393.7±59.3	310.4–488.3	>0.05
II (moderate)	395.1±66.9	275.2–507.7	
III (severe)	396.4±75.5	343.6–506.3	

Bold values are significant at $P<0.05$. FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MMP-7, matrix metalloproteinase-7; SSc, systemic sclerosis.

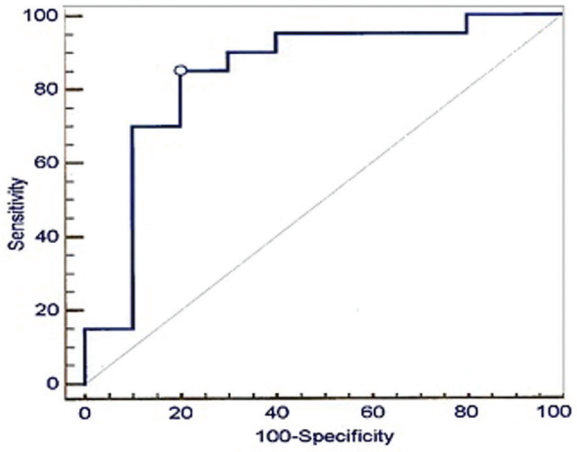
Table 3 Correlations between matrix metalloproteinase-7 with the forced vital capacity, forced expiratory volume in one second, Warrick severity and extent scores in systemic sclerosis patients

Parameters	MMP-7 (ng/ml) in SSc patients (n=30)	
	r	P
FVC%	–0.46	< **0.05**
FEV_1%	–0.65	< **0.0001**
Warrick severity score	0.55	**0.002**
Warrick extent score	0.48	**0.007**

Bold values are significant at $P<0.05$. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MMP-7, matrix metalloproteinase-7; SSc, systemic sclerosis.

The receiver operating characteristics curve showing that the best cut-off value of MMP-7 serum level as a predictor for ILD in SSc patients was more than 367.4 ng/ml, with a diagnostic sensitivity of 85%, specificity of 80%, positive predictive value of 89.5% and negative predictive value of 72.7% (Fig. 3).

Figure 3



Receiver operating characteristic curve (ROC) for matrix metalloproteinase-7 (MMP-7) as a predictor for interstitial lung disease (ILD) in systemic sclerosis patients.

Discussion

Cardiorespiratory manifestations, namely ILD and PAH, remain the leading causes of SSc-related deaths [24]. The functions of MMPs in the pathogenesis of SSc have not been fully elucidated. MMP-7 (matrilysin), a metalloproteinase that targets a broad range of extracellular matrix proteins, was seen to be highly overexpressed in IPF lungs [16]. In this study, 66.7% of SSc patients had ILD; this agreed with the results of Pasarikovski *et al.* [25] who reported that ILD was detected in 67% of 58 SSc patients. Moreover, Manetti *et al.* [26] and Moinzadeh *et al.* [16] recorded ILD in 47 and 45.5% of SSc patients, respectively.

The serum level of MMP-7 was significantly higher in SSc patients with ILD compared with those without. This is in harmony with the results of Moinzadeh *et al.* [16].

In patients with ILD, ground-glass abnormality was the most common, recorded in 65%, followed by reticular infiltration in 40%, honeycombing in 30%, interstitial thickening and oedema in 25%, bronchiectatic changes in 20%, pleural thickening and subpleural lines each in 15% and finally air trapping in 10%. These results agreed with that of Hafez *et al.* [27] who recorded ground-glass opacity in 83.3%, septal thickening in 56.7%, honeycombing in 43.3%, bronchiectasis in 23.3% and consolidations in 20% of a total of 30 patients. In contrast, De Oliveira Jezler *et al.* [28] reported that bronchiectasis was the most common CT finding recorded in 83.3% of their patients, honeycombing in 80%, ground-glass opacity in 66.7%, septal thickening in 20% and consolidations in 16.7%. Different disease duration, severity, early detection and better awareness may account for the difference.

In this study, there was no significant difference in age, sex or disease duration between those with and without ILD. Similarly, Pasarikovski *et al.* [25] reported that the presence of ILD had no relation to age, sex or disease duration.

As regards clinical manifestations, there was a significant association between ILD with PAH and eosophageal dysmotility, which was in agreement with the results of Hafez *et al.* [27] and Pasarikovski *et al.*

[25]. A significant association was found between MMP-7 serum level and pulmonary symptoms (dyspnea and chest pain), which was in agreement with the findings of Moinzadeh *et al.* [16].

In this study, there was a significant association between higher serum level of MMP-7 and ground-glass opacities, honeycombing abnormalities and reticular infiltration detected by HRCT chest, reflecting the link of MMP-7 with the fibrotic process, whether early or late. Moreover, MMP-7 showed a significant correlation with the Warrick severity and extent scores, and inversely with the FVC and FEV_1, denoting the key role of MMP-7 in disease progression. This agreed with the results of Bauer *et al.* [29] and Sokai *et al.* [30]. These findings throw light on the potential relation of MMP-7 not only to the presence of ILD but also to the type of pathology, severity and extent of the disease. Putman *et al.* [31] stated that serum MMP-7 levels showed not only a negative correlation with FVC and diffusing capacity but also an independent association with IPF mortality. MMP-7, the smallest member of the MMP family, has a profibrotic profile with diverse biological functions, ranging from innate immunity to inflammation, apoptosis, and fibroproliferation [32,33]. It is also able to process numerous bioactive substrates and activate proteases, including itself. The release of preformed transforming growth factor-β from extracellular matrix is the main regulation process related to transforming growth factor-β bioactivity, one of the presumptive mediators in IPF pathogenesis. In an animal model, MMP-7 knockout mice treated with bleomycin did not develop lung fibrosis [34]. In addition, MMP-7 has been found on the surface of epithelial cells and alveolar macrophages in IPF lung tissue, but not in healthy lung tissue [35,36]. Interestingly, enhanced levels of serum MMP-7 were also found in patients with asymptomatic IPF (although at lower levels than in symptomatic patients), pointing to its possible value as a marker for both early disease and progression [33].

This study showed that the best cutoff value for MMP-7 as a predictor for ILD in SSc patients was more than 367.4 ng/ml, with a diagnostic sensitivity of 85%, specificity of 80%, positive predictive value of 89.5% and negative predictive value of 72.7%. Morais *et al.* [15] found that the sensitivity and specificity for MMP-7 at a cutoff of 3.91 ng/ml was 72.3 and 66.3%, respectively; the positive predictive value was 52.3% and negative predictive value 82.4%. Their work was not conducted on SSc patients, which may account for the different values.

Unfortunately, some of the study's limitations included the small sample size and the lack of inclusion of the Rodnan skin score or autoantibody measurement for better comparative and correlative studies.

Conclusion

ILD is common in SSc. There is a strong association between serum MMP-7 and the presence, pathology, severity and extent of ILD in scleroderma patients. Serum MMP-7 might be a useful biomarker for ILD in SSc.

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Nil

Conflicts of interest

There are no conflicts of interest.

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