# Serum Level of KL-6 as a Marker of Interstitial Lung Disease in Patients with Juvenile Systemic Sclerosis

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***ABSTRACT.*** ***Objective.*** Serum KL-6 has been found to be elevated in diseases characterized by diffuse interstitial lung involvement. The purpose of this study was to evaluate serum KL-6 as a marker of interstitial lung disease (ILD) in patients with juvenile systemic sclerosis (JSS).

***Methods.*** Serum concentrations of KL-6 were measured with an immunoassay in 39 serum samples from 12 children with diffuse cutaneous form of JSS (6 patients with and 6 patients without ILD) and from 20 healthy controls comparable for age. In patients sampled serially, the relationship of KL-6 concentrations with the severity of ILD and its response to treatment were evaluated.

***Results.*** Serum concentrations of KL-6 were significantly higher in patients with ILD (1687 ± 979 IU/ml) than in patients without (345 ± 95 IU/ml, $p < 0.01$) and healthy controls (311 ± 114 IU/ml, $p < 0.001$). Serum KL-6 concentrations of patients without ILD were not statistically different from those of healthy controls. We found a significant correlation of serum KL-6 concentrations with vital capacity and with diffusing capacity for carbon monoxide (DLCO). Analysis of individual patients showed that serum concentrations of KL-6 were correlated with ILD severity and its response to treatment.

***Conclusion.*** Measurement of serum KL-6 concentration is a useful noninvasive marker of pulmonary fibrosis in children with JSS. Its advantages over conventional methods of ILD assessment, such as pulmonary function test and high-resolution computerized tomography, are that it is easy to quantify and to measure repeatedly and it does not need children's cooperation. (J Rheumatol 2004;31:795–800)

*Key Indexing Terms:*
KL-6 JUVENILE SYSTEMIC SCLEROSIS INTERSTITIAL LUNG DISEASE

Juvenile systemic sclerosis (JSS) is a chronic multisystem connective tissue disease characterized by sclerodermatous skin changes and widespread abnormalities in the visceral organs, notably the gastrointestinal tract, lung, heart, and kidney[1]. Pulmonary involvement is a common feature of JSS and is among the leading factors influencing patients' prognosis[2]. Interstitial lung disease (ILD), together with pulmonary hypertension, has emerged in the recent years as one of the most common disease-related cause of death in patients with JSS[3]. Pulmonary function tests and high-resolution computerized tomography (HRCT) are the more sensitive methods for detecting and monitoring ILD in patients with JSS[4-7]. However, the former investigation, particularly the assessment of diffusion capacity for carbon monoxide (DLCO), is difficult to perform reliably in younger children and the latter involves considerable radiation exposure. Therefore, the availability of a noninvasive additional measure could be of great help in following the course of ILD in patients with JSS.

KL-6 is a high molecular mucin-like glycoprotein strongly expressed on type II pneumocytes in alveoli and epithelial cells of bronchioles in the lung. KL-6 has been reported to have various pathophysiologic roles such as inhibiting cell-to-cell adhesion of epithelial cells[8], decreasing the susceptibility of malignant cells to cytotoxic T cells[9], and chemotactic effect for fibroblasts[10]. Several studies have recently reported that serum levels of KL-6 are elevated in patients with ILD of different origins, including idiopathic pulmonary fibrosis, radiation pneumonitis, hypersensitivity pneumonitis, and drug-induced pneumonitis[11-13]. Elevated KL-6 levels were found in patients with diffuse and localized systemic scleroderma with

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pulmonary fibrosis, but not in those without pulmonary fibrosis[14]. Taken together, these studies suggest that KL-6 represents a marker of pulmonary fibrosis.

We investigated the role of serum KL-6 as a marker of ILD in children with JSS.

## MATERIALS AND METHODS

*Patients.* Serum samples were obtained from 12 children with JSS (3 followed at the Department for children and adolescents of Faculty Hospital in Kosice and 9 followed at the Pediatric Department of the IRCCS Policlinico San Matteo of Pavia, Italy). All patients had the diffuse cutaneous form of JSS. Six of the 12 patients were found to have ILD, defined as the presence of bibasilar interstitial fibrotic changes on chest radiography and/or a ground glass appearance, representing inflammation (alveolitis), on HRCT. Basic clinical characteristics of the patients are shown in Table 1. All patients were treated using standard antiinflammatory and immunosuppressive medications according to their clinical features and course. Due to the progressive course of ILD in spite of corticosteroid and immunosuppressive therapy in 3 patients, all followed in Pavia, Italy, an autologous stem cell transplantation was performed, as described[15,16]. A total of 39 samples were taken in different stages of the disease (1-5 samples from each patient). Of these 39 samples, 12 were obtained from patients without ILD and 27 from patients with ILD. Pulmonary function tests were performed as reported[17,18]. Briefly, measurement of lung volume was carried out using a water-sealed spirometer and a helium analyzer (Jaeger, Wuerzburg, Germany), with the vital capacity (VC) being registered as the best of 2 assessments. DLCO was determined using the single-breath method (Diffusion-test, Jaeger). The results of pulmonary function tests were expressed as % of predicted results based on reference standards obtained in normal children and adolescents. Reliable DLCO measurements were available for 7 patients. Testing could not be performed reliably in 3 patients (2, 3, and 6) because of their young age and in 2 patients (11 and 12) it was not performed at all.

Sera from 20 healthy children, comparable for age and hospitalized for bone marrow donation or for minor surgical procedures, were used as controls. Permission for drawing of extra blood during routine venipuncture was obtained from parents of all children.

*KL-6 measurement.* Serum KL-6 concentrations were measured retrospectively in sera that had been stored at -70°C using commercial enzyme-linked immunosorbent assay (EISAI, Tokyo, Japan). The assay was performed according to the instructions provided by the manufacturer. Briefly, 1:200 diluted sera were added to anti-KL-6 monoclonal antibody coated wells; a horseradish peroxidase-labeled anti-KL-6 mouse monoclonal antibody was used for detection, and revealed by a substrate solution containing 2,2'-azino-bis3-ethylbenzothiazoline-6-sulfonic acid. The detection limit of the assay was 200 U/ml.

*Statistical analysis.* Data were analyzed using the statistical analysis software package Statistica 5.0 (Statsoft Inc.). Descriptive statistics were calculated and reported in terms of means ± SD. The Mann-Whitney U test for unpaired samples was used to evaluate differences between groups. Correlations were analyzed using the Spearman rank correlation test. A p value < 0.05 was deemed statistically significant.

## RESULTS

When only the first sample obtained for each patient at the time of the diagnosis of ILD was considered, serum KL-6 levels were found to be significantly higher in patients with ILD (1687 ± 979 IU/ml) than in those without ILD (345 ± 95 IU/ml; $p < 0.01$) or in controls (311 ± 114 IU/ml; $p < 0.001$). Serum KL-6 concentrations in JSS patients without ILD were comparable with those of healthy controls (Figure 1A). When all samples were considered and a cut-off value of KL-6 levels at 653 IU/ml (mean + 3SD of controls) was set, elevated levels of KL-6 were found in 1 of 12 samples obtained from patients without ILD (8.3%), and in 24 of 27 samples obtained from patients with ILD at time of sampling (88.9%) (Figure 1B).

To investigate whether serum KL-6 levels reflected the severity of ILD, we evaluated their correlation with VC. As shown in Figure 2A, we found a significant correlation ($r = -0.777$; $p < 0.001$, $n = 28$) of serum KL-6 concentrations with the VC. Moreover, when patients with VC > 85% were excluded, KL-6 concentrations were still correlated with VC ($R = -0.528$; $p = 0.017$; $n = 20$). While VC can be influenced by factors other than ILD (i.e., muscle strength), DLCO reflects ILD more strictly. However, DLCO is difficult to

*Table 1.* Clinical characteristics of the children with diffuse systemic scleroderma.

| Patient | Gender | Age at Onset, yrs | ILD | Age at Diagnosis of ILD, yrs | Other Organ Involvement | Availability of Lung Function Tests | |
|---|---|---|---|---|---|---|---|
| | | | | | | VC | DLCO |
| 1 | M | 7.2 | Yes | 8.6 | Arthritis, Myositis | Yes | Yes |
| 2 | M | 5.3 | Yes | 9.8 | RP, GI, Arthritis | Yes | No |
| 3 | F | 5.2 | Yes | 5.6 | GI tract, RP | Yes | No |
| 4 | F | 6.8 | No | NA | RP | Yes | Yes |
| 5 | M | 14.5 | No | NA | RP, GI | Yes | Yes |
| 6 | M | 3.1 | No | NA | RP | No | No |
| 7 | F | 9.5 | Yes | 12.5 | RP, GI | Yes | Yes |
| 8 | F | 5.0 | Yes | 5.9 | RP, GI, Arthritis Myositis | Yes | Yes |
| 9 | F | 11.6 | No | NA | Arthritis, RP | Yes | Yes |
| 10 | F | 6.4 | Yes | 10.6 | RP, Myositis | Yes | Yes |
| 11 | F | 12.7 | No | NA | Arthritis | Yes | No |
| 12 | F | 15.8 | No | NA | | Yes | No |

RP: Raynaud's phenomenon, ILD: interstitial lung disease; GI: gastrointestinal tract; VC: vital capacity; DLCO: diffusing capacity for carbon monoxide; NA: not applicable.

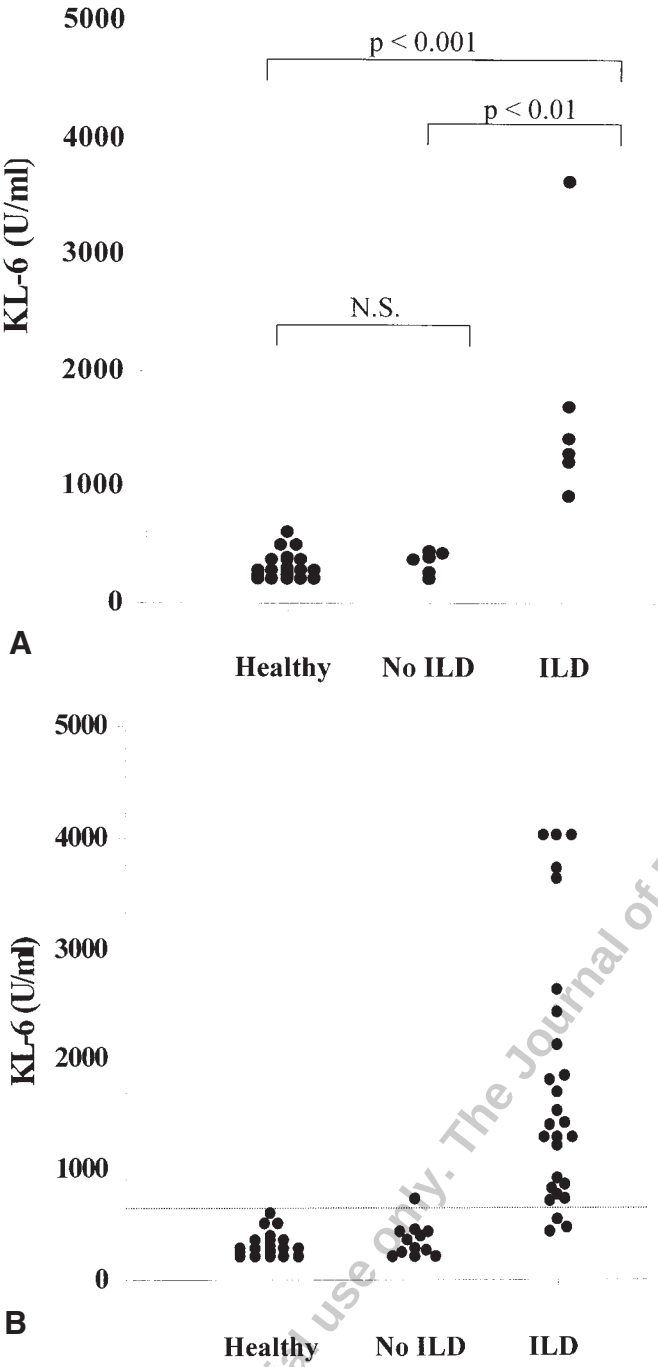


*Figure 1.* Serum KL-6 levels in healthy controls, and in patients with diffuse juvenile systemic scleroderma (JSS) divided according the presence or absence of interstitial lung disease (ILD). Panel A shows KL-6 levels from one sample from each patient. In patients with ILD, the first sample obtained at the time of the diagnosis of ILD is shown. Panel B shows KL-6 levels from all samples studied. The dotted line represents the arbitrary cut-off value for KL-6 levels corresponding to the mean + 3SD of controls.

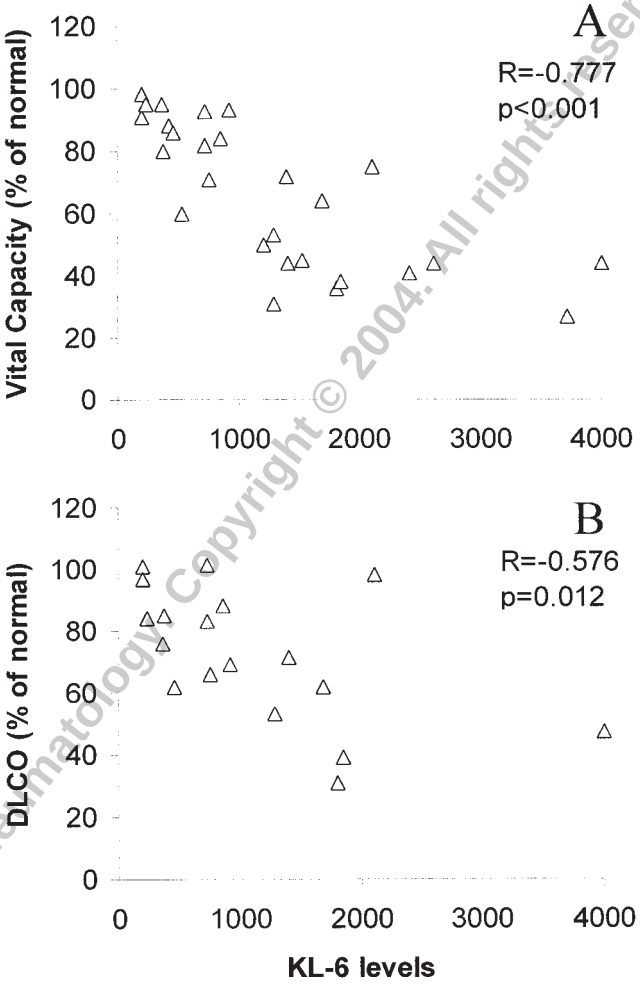


*Figure 2.* Correlation of serum KL-6 levels (U/ml) with vital capacity (A) and with DLCO (B) as measures of the severity of ILD in patients with diffuse JSS. The Spearman's R coefficient and the significance level p are shown.

perform reliably in young children. In our patients at least one reliable measurement of DLCO was available in 7 out of the 12 patients studied. In this smaller number of available observations a significant correlation of KL-6 levels with DLCO was found (R = –0.576; p = 0.012; n = 18) (Figure 2B). These results show that KL-6 concentrations are related to the severity of ILD.

The relationship of KL-6 concentrations with the severity of ILD and its response to treatment was also evaluated in patients sampled sequentially. In patient 1, a marked increase in serum KL-6 concentrations was observed when a lung HRCT scan showed diffuse active alveolitis (ground-glass changes) and initial decrease in VC. After immunosuppressive therapy, including daily prednisone and oral cyclophosphamide followed by D-penicillamine, a marked increase in VC and a marked amelioration in ILD at HRCT were associated with a progressive decrease in serum KL-6 concentrations (Figure 3A). In patient 2, a progressive decrease of VC and progression of ILD, as shown by 2 sequential HRCT scans, were associated with a progressive increase in serum KL-6 concentrations. Following autologous stem cell transplantation (ASCT), an HRCT scan

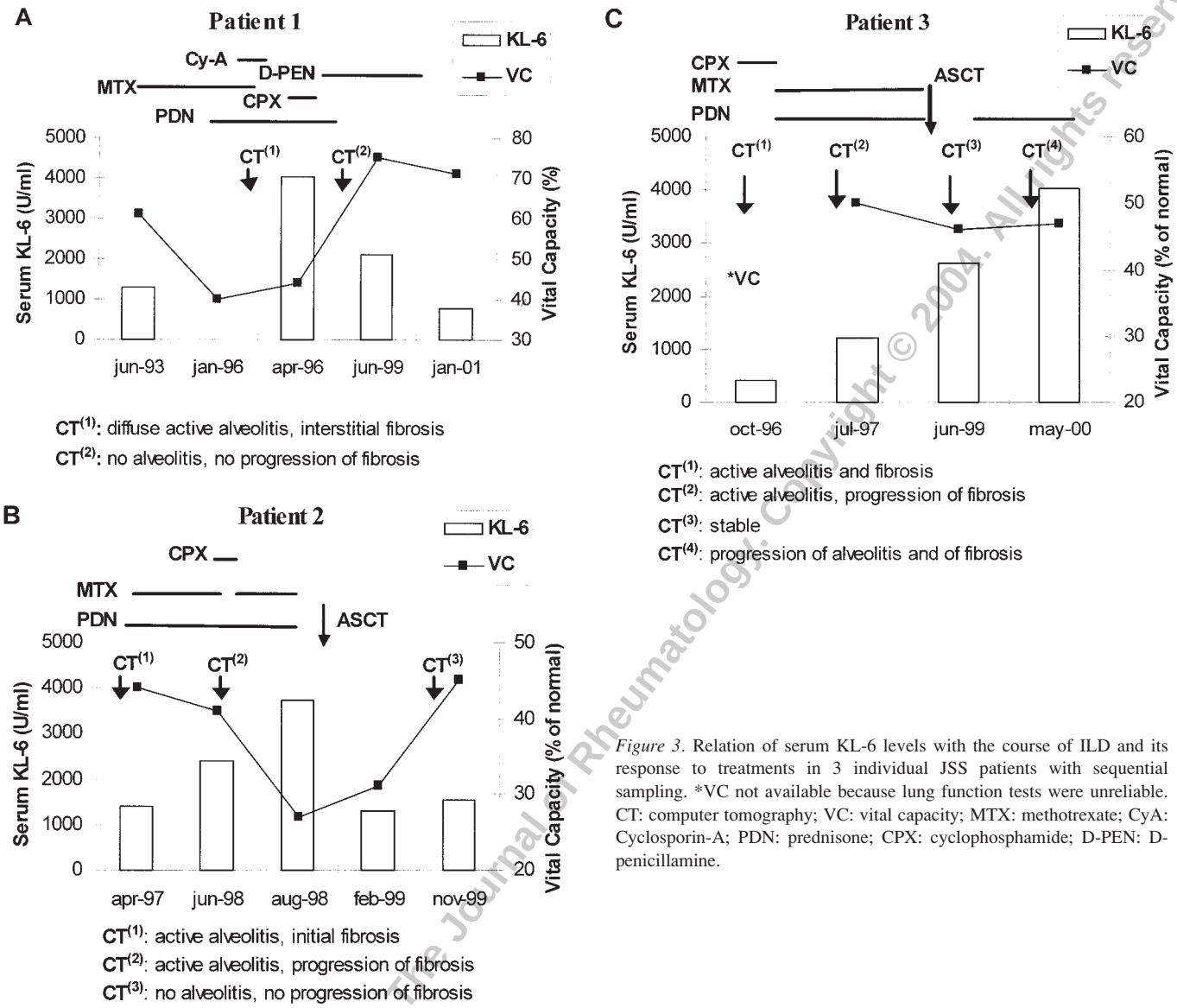


*Figure 3*. Relation of serum KL-6 levels with the course of ILD and its response to treatments in 3 individual JSS patients with sequential sampling. *VC not available because lung function tests were unreliable. CT: computer tomography; VC: vital capacity; MTX: methotrexate; CyA: Cyclosporin-A; PDN: prednisone; CPX: cyclophosphamide; D-PEN: D-penicillamine.

showed no progression of fibrosis and no signs of acute alveolitis, associated with an improvement of VC and a drop in serum KL-6 concentrations (Figure 3B). On the contrary, in patient 3, ASCT did not lead to a favorable response with a progression of lung involvement on HRCT, that was associated with a progressive increase in KL-6 concentrations (Figure 3C).

## DISCUSSION

Pulmonary function tests and radiographic investigations are considered the more sensitive approaches in the diagnosis and monitoring of ILD in patients with JSS[4-7]. Pulmonary function abnormalities most commonly reveal a restrictive ventilatory defect, indicated by a reduction in forced vital capacity and decreased lung compliance. Impairment in gas exchange, evidenced by a reduced DLCO, is also frequently detectable in patients with restrictive lung disease, but may occur as an isolated defect without significant alteration in ventilation or roentgenographic evidence of fibrosis. Chest radiograph reveals interstitial thickening in a reticular pattern of linear, nodular, and lineo-nodular densities most pronounced in the lower lung fields. The radiographic appearance in advanced stages is that of diffuse mottling or honeycombing, indicative of fibrosis with cystic lesions[19]. HRCT is a more sensitive method for detecting ILD and has been reported to be abnormal in 75% of JSS patients with normal chest radiographs[6,7]. This technique may identify a ground-glass appearance, which is believed to represent inflammation (i.e., alveolitis).

The monitoring of ILD progression in patients with JSS requires quantification of changes to allow comparison among followup assessments. However, the available diagnostic tools are not entirely satisfactory, particularly in

younger patients. Although pulmonary function tests are non-invasive, relatively cheap, and easy to repeat, they depend very much on the patient's ability to cooperate. In younger children, these tests, particularly DLCO, are difficult to perform reliably. Of the radiography imaging modalities, standard chest radiograph may not be sensitive enough and HRCT requires expensive equipment that might not be easily available and involves significant radiation exposure. Furthermore, cooperation of the patient to reach maximal breath for every scan is necessary for optimal results. Oyama, *et al* have proposed to grade the extent of interstitial pneumonitis on HRCT according to the extent of ground glass opacity in the following way: grade 1: < 1/3 lung fields; grade 2: 1/3-2/3; grade 3: > 2/3[20]. However, HRCT assessment and scoring of pulmonary fibrosis can be markedly affected by the subjective judgment of the radiologist.

In recent years, a great effort has been made to find a serological marker of pulmonary fibrosis that could overcome the above mentioned disadvantages. While erythrocyte sedimentation rate, C-reactive protein, lactic dehydrogenase, type III procollagen N-terminal propeptide, type IV collagen, von Willebrand factor peptide and propeptide, adhesion molecules, and interleukin-18 have been shown to be more or less non-specific[21,22], surfactant protein D[23] and KL-6[11-13,24] appear to be specific markers of pulmonary fibrosis.

Serum concentrations of KL-6 have been shown to be increased in interstitial pneumonitis — either idiopathic or hypersensitivity-related pneumonitis — sarcoidosis, radiation pneumonitis, drug induced pneumonia, and lung infections that may progress to cause lung fibrosis (*Pneumocystis carinii*, cytomegalovirus, *Legionella*, tuberculosis, etc.)[11-13,24,25]. Interestingly, KL-6 levels have been shown to remain constant in most patients with bacterial pneumonitis[26,27]. In a recent study, comparing the value of KL-6 levels with that of surfactant protein D levels as diagnostic markers for ILD, KL-6 levels were found to have the highest diagnostic accuracy, sensitivity, and specificity[27].

Specifically concerning connective tissue diseases, increased levels of KL-6 have been found to be associated to ILD in adult patients with rheumatoid arthritis[20], polymyositis[28], or systemic scleroderma[14,29]. The only study on KL-6 in children is that of Kobayashi, *et al*[30]. These authors found that the levels of KL-6 were significantly more elevated in 3 patients with juvenile dermatomyositis (JDM) who had ILD as compared to JDM patients without ILD. To the best of our knowledge, our study is the first to measure serum KL-6 concentrations in patients with JSS. Our results show that the measurement of serum KL-6 levels can help to distinguish patients with ILD from patients without ILD.

We found a significant relationship between serum KL-6 concentrations with VC and DLCO indicating a correlation with the severity of ILD. Furthermore, serial measurement of KL-6 concentrations over time showed that progression of ILD was accompanied by an increase of KL-6 levels and that effective treatment could stop the increase or even decrease KL-6 concentrations, whereas in case of therapeutic failure KL-6 levels continued to rise. This finding is in agreement with other studies in adult patients with ILD associated with connective tissue diseases showing a significant correlation of KL-6 levels with the activity and severity of ILD[29,31,32]. Moreover, KL-6 levels correlated strictly with the severity and progression of interstitial involvement in radiation-induced pneumonitis[33].

In conclusion, our study suggests that while HRCT remains the gold standard, KL-6 measurement provides a promising adjunctive and noninvasive tool for the diagnosis and the followup of ILD. Prospective studies in a larger number of patients are needed to evaluate the sensitivity and specificity of this test and, in particular, the value of sequential measurements of KL-6 concentrations, to select patients who may deserve a closer HRCT followup.

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