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Serial measurements of KL-6 for monitoring activity and recurrence of interstitial pneumonia with anti-aminoacyl-tRNA synthetase antibody

A retrospective cohort study

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Abstract

The aim of this study was to evaluate whether serial measurements of serum Krebs von den Lungen-6 (KL-6) could be used to monitor disease activity and to detect recurrence in patients with interstitial pneumonia (IP) with anti-aminoacyl-tRNA synthetase antibodies (ARS-IP).

This retrospective cohort study included 44 patients with ARS-IP. Thirty-six patients had serial data of blood tests and pulmonary function tests. Baseline and longitudinal analyses were performed to investigate whether lung function parameters were associated with serum biomarkers (KL-6, lactate dehydrogenase [LDH], and C-reactive protein [CRP]) using Pearson correlation coefficient. Additionally, the diagnostic accuracy of changes in these biomarkers for detecting ARS-IP recurrence was analyzed by receiver operating characteristic curve analysis.

Baseline levels of serum KL-6 were significantly associated with vital capacity (VC) and diffusion capacity for carbon monoxide (DLco) ($r=-0.40$, $P=.015$, and $r=-0.44$, $P=.010$, respectively). Longitudinal changes in KL-6 were inversely correlated with changes in VC and DLco ($r=-0.57$, $P<.001$ and $r=-0.42$, $P<.001$, respectively), whereas those in LDH and CRP were not. Moreover, longitudinal changes in serum KL-6 were significantly associated with recurrence of ARS-IP and could be used to detect ARS-IP recurrence; the area under the curve was 0.79 ($P=.002$).

The present study demonstrated that serial measurement of KL-6 is useful for monitoring disease activity and detecting recurrence of ARS-IP.

Abbreviations: ΔCRP = change levels of CRP, ΔKL-6 = change levels of KL-6, ΔLDH = change levels of LDH, ARS = aminoacyl-tRNA synthetase, ARS-IP = IP associated with anti-ARS antibody, ASS = anti-synthetase syndrome, AUC = area under the curve, CADM = clinically amyopathic dermatomyositis, CRP = C-reactive protein, CT = computed tomography, DLco = diffusing capacity for carbon monoxide, ELISA = enzyme-linked immunosorbent assay, IP = interstitial pneumonia, KL-6 = Krebs von den Lungen-6, LDH = lactate dehydrogenase, PM/DM = polymyositis/dermatomyositis, ROC = receiver operating characteristic, VC = vital capacity.

Keywords: anti-aminoacyl-tRNA synthetase antibody, interstitial lung disease, KL-6, monitoring marker

1. Introduction

Anti-aminoacyl-tRNA synthetase (ARS) antibody is associated with inflammatory myopathy, Raynaud's phenomenon, inflammatory arthritis, cutaneous lesion, and interstitial pneumonia (IP). These clinical features are referred to as anti-synthetase syndrome (ASS).[1,2] In particular, IP is a common clinical manifestation and major contributor to morbidity and mortality in patients with ASS.[3] IP associated with anti-ARS antibodies (ARS-IP) is relatively responsive to treatment using corticosteroids and/or immunosuppressive agents, but recurrence of the disease is a common and sometimes fatal event.[4–6] Therefore, blood biomarkers that reflect improvements and recurrences in ARS-IP would help clinicians optimize long-term treatment.

Krebs von den Lungen-6 (KL-6) is a type II pneumocyte-derived glycoprotein that is classified as human MUC1 mucin, and circulatory levels of KL-6 is elevated in patients with IP associated with connective tissue disease.[7,8] In patients with IP related to polymyositis/dermatomyositis (PM/DM), previous reports have shown that a change in serum KL-6 levels (ΔKL-6) is inversely correlated with a change in pulmonary function after initial treatment.[9–11] However, it is not clear whether serial

Editor: Fu-Tsai Chung.

This manuscript has not been published and is not under consideration for publication elsewhere.

Nobuoki Kohno holds a patent for KL-6. None of the remaining authors have any competing interests. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:49(e13542)

Received: 6 June 2018 / Accepted: 12 November 2018

http://dx.doi.org/10.1097/MD.0000000000013542

changes in KL-6 levels are correlated with changes in pulmonary function over a long period, and whether these changes can be used to monitor recurrence of the disease in patients with ARS-IP, including those with and without PM/DM.

The aim of this study was to investigate whether serial measurements of KL-6 can be used to monitor disease activity and detect recurrence in patients with ARS-IP. First, we investigated the baseline and longitudinal associations between pulmonary function and serum levels of KL-6, lactate dehydrogenase (LDH), and C-reactive protein (CRP) in patients with ARS-IP. Additionally, we analyzed the accuracy of these blood markers to detect ARS-IP recurrence.

2. Methods

2.1. Subjects

This retrospective cohort study consecutively recruited 44 patients with ARS-IP at Hiroshima University Hospital between October 2007 and August 2016.[1,2] IP was diagnosed on the basis of the presence of radiological abnormalities with respiratory symptoms.[12] In all patients, lung involvement was evaluated by computed tomography (CT). Infectious diseases were excluded on the basis of results of a sputum test and/or bronchoscopy. The presence of other connective tissue diseases and other known causes of IP was also evaluated using serological investigations and physical assessment. In the longitudinal analyses, we selected patients who had 2 or more measurements of pulmonary function and the serum biomarkers KL-6, LDH, and CRP. Spirometry measurements were performed within 2 weeks of blood collection. Ultimately, we enrolled 36 patients with ARS-IP (see Figure 1, Supplemental Content, Flow chart of subject selection, http://links.lww.com/MD/C685). Twenty patients were associated with PM/DM which were compatible with the Bohan and Peter criteria or clinically amyopathic dermatomyositis (CADM) criteria defined by Euwer and Sontheimer.[11,13,14] The other 16 patients with ARS-IP, who did not fulfill the criteria for other connective tissue diseases, were described as other ARS-IP. The accuracy of the biomarkers in detecting ARS-IP recurrence was evaluated in 23 patients, all of whom had undergone longitudinal assessment by CT, pulmonary function testing, and serum biomarker measurement (see Figure 1, Supplemental Content, Flow chart of subject selection, http://links.lww.com/MD/C685).

The median follow-up period was 28.1 months (range: 1.0–148.0 months). Throughout the observation period, no patients showed malignant disease, which can elevate serum levels of KL-6.[15] Of 36 patients treated with corticosteroids and/or immunosuppressants, 33 showed substantial improvement in symptoms and in the results of physical examinations. The remaining 3 patients had stable disease without immunosuppressive therapy during the observation period. This study was approved by the Ethics Committee of Hiroshima University Hospital (M326), and all participants provided written informed consent.

2.2. Evaluation of blood tests and pulmonary function

To detect the serum biomarkers, we used blood samples gathered in clinical visits. Anti-ARS antibodies were detected using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (MESACUP anti-ARS test; MBL, Nagoya, Japan) in Bio Medical Laboratories Inc. (Tokyo, Japan).[16] Serum levels of KL-6, LDH, and CRP were measured in the laboratory of Hiroshima University Hospital using an automatic biochemical analyzer. Pulmonary function variables were measured using spirometry in accordance with the American Thoracic Society recommendations.[17] Changes in serum biomarker levels and pulmonary function variables were calculated by subtracting the previous values from the follow-up values.

2.3. ARS-IP recurrence

ARS-IP recurrence was defined as deterioration of abnormal CT findings and vital capacity (VC) regardless of the amount. To evaluate the accuracy of KL-6 in the detection of ARS-IP recurrence, we analyzed 39 longitudinal changes in abnormal CT findings among the 23 patients after the induction of immunosuppressive therapy using corticosteroids and/or immunosuppressants (see Figure 1, Supplemental Content, Flow chart of subject selection, http://links.lww.com/MD/C685). The CT scans were investigated within 2 weeks of the blood collection, and the median interval between CT scans was 5.8 months. Two pulmonologists independently evaluated the CT images; they had no information about clinical symptoms, laboratory data, or pulmonary function. The pulmonologists compared each follow-up CT image with the previous image from the same patient. They then classified each patient as either improved or impaired. If conflicting results were found, a third pulmonologist additionally and independently evaluated the CT image, and the final decision was made by majority vote.

2.4. Statistical analysis

All values are expressed as mean ± standard deviation (SD). In the present study, n denote the number of patients, and N denoted the quantity of longitudinal data. The data from 2 groups were analyzed using a 2-tailed Student t test for parametric variables, Mann–Whitney U test for nonparametric variables. Fisher exact test was used for comparisons of proportions. Because the pulmonary function variables and serum biomarker levels were parametric variables as well as those serial changes, the associations were analyzed using Pearson correlation coefficient. Finally, receiver operating characteristic (ROC) curve analysis was conducted to determine the accuracy of serial biomarkers in detecting recurrence of the disease. All P values $<.05$ were considered significant. Data were analyzed using JMP statistical software version 11.2.1 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline analysis

The average of age of the subjects was 59.8 ± 11.2 years old, and 27 of the 36 patients were female. Patients with PM/DM had a significantly lower smoking history and higher levels of serum LDH than those classified as other ARS-IP (Table 1). Higher KL-6 levels were significantly associated with lower VC and diffusion capacity for carbon monoxide (DLco), while CRP was inversely associated with DLco only in the baseline analysis (Table 2).

3.2. Longitudinal correlations between changes in serum biomarkers and pulmonary function

We obtained 92 longitudinal data points among the 36 patients. ΔKL-6 was significantly and inversely correlated with changes in VC (ΔVC) and changes in DLco (ΔDLco) ($r = -0.57$ and

Table 1

Baseline characteristic.

Variables	ARS-IP Patients	Subgroups of ARS-IP	
		PM/DM related ARS-IP	Other ARS-IP
Subjects, *n*	36	20	16
Age, years	59.8 ± 11.2	57.6 ± 1.6	62.4 ± 8.9
Sex, male / female	9/27	3/17	6/10
BMI, kg/m^2	23.6 ± 3.45	23.7 ± 4.04	23.5 ± 2.64
Smoking history, pack-years	10.6 ± 20.5	4.48 ± 9.79	18.3 ± 27.2*
KL-6, U/mL	1183.6 ± 745.2	1421.1 ± 822.8	924.4 ± 527.5
LDH, U/L	265.6 ± 109.6	291.0 ± 122.3	230.7 ± 76.4**
CRP, mg/dL	1.31 ± 2.47	1.37 ± 2.54	1.17 ± 2.37
VC, % predicted	75.2 ± 17.2	71.8 ± 17.4	79.4 ± 16.5
DLco, % predicted	52.1 ± 17.3	50.9 ± 17.3	53.5 ± 17.9
Treatment, *n*			
Observation	3	3	0
Steroid only	10	3	7
Steroid/CNI	19	12	7
Steroid/AZA	1	0	1
Steroid/CNI/IVCY	2	1	1
Steroid/CNI/AZA	1	1	0
Longitudinal data, *N*	92	42	50

* $P<.05$ Mann–Whitney *U* test, compared to patients with PM/DM.
** $P<.05$ Student *t* test, compared to patients with PM/DM.
Values are mean ± standard deviation (SD) unless stated otherwise.
AZA = azatiopline, BMI = body mass index, CNI = calcineurin inhibitor, CRP = C-reactive protein, DLco = diffusing capacity for carbon monoxide, IP = interstitial pneumonia, IVCY = intravenous cyclophosphamide, KL-6 = Krebs von den Lungen-6, LDH = lactate dehydrogenase, PM/DM = polymyositis/dermatomyositis, VC = vital capacity.

r = −0.42, respectively) (Table 3). However, changes in serum LDH (ΔLDH) were significantly associated with ΔDLco only. No significant association was noted between changes in serum CRP (ΔCRP) and changes in pulmonary function parameters.

An additional subset analysis revealed that the associations between ΔKL-6 and changes in pulmonary function variables were significant in PM/DM related ARS-IP and other ARS-IP (Table 4). Although the number of data points was different for each patient (median 2, range 1–9), ΔKL-6 was significantly associated with both ΔVC and ΔDLco in patients with fewer than 4 longitudinal data points, as well as in those with 4 or more longitudinal data points (see Figure 2, Supplemental Content, which showed correlation between changes in KL-6 and pulmonary function based on the quantity of longitudinal data, http://links.lww.com/MD/C685).

3.3. Correlations between serial biomarker changes and ARS-IP recurrence

ARS-IP recurrence was investigated in 23 patients, among whom there were 39 changes in CT findings, lung function, and serum markers. Ten recurrences of ARS-IP were observed among 8 out of 23 patients after dose reduction of therapeutic agents. The ΔKL-6 was significantly higher during ARS-IP recurrence than in the stable phase (507.0 ± 756.5 U/mL and −390 ± 835.0 U/mL, $P=.005$) (Fig. 1A), while there was no significant difference in ΔLDH and ΔCRP (Figure not shown). ROC curve analysis revealed that the area under the curve (AUC) of ΔKL-6 for detecting recurrence of ARS-IP was 0.79 (Fig. 1B), which was higher than the AUCs of ΔLDH (0.63) and ΔCRP (0.61) (Figure not shown). The optimal cut-off levels of ΔKL-6 for identifying ARS-IP recurrence were -173 U/mL (Circle A; sensitivity 90.0%, specificity 62.1%), and ΔKL-6 of 303 U/mL was found as good cut-off levels with a higher specificity and PPV (Circle B; sensitivity 60.0%, specificity 86.3%) (Fig. 1B).

3.4. Case presentation

The clinical course of 2 representative cases is shown in Figure 2. Case 1 was a 39-year-old man classified as other ARS-IP (Fig. 2A). His serum levels of KL-6 and VC improved after starting combination therapy with 40 mg prednisolone and 150 mg cyclosporin. However, when the dosage of cyclosporine was decreased to 125 mg, increasing levels of serum KL-6 were observed, with decreased VC. Late in the observation period, the patient's serum levels of KL-6 decreased with improvement of

Table 2

Baseline correlations between serum levels of biomarkers and pulmonary function variables (n = 36).

Variables	KL-6		LDH		CRP	
	r	*P*	*r*	*P*	*r*	*P*
VC, %predicted	−0.40	.015*	−0.19	.267	−0.20	.260
DLco, %predicted	−0.44	.010*	−0.25	.165	−0.48	.006*

* $P<.05$.
** $P<.005$ Pearson correlation coefficient.
CRP = C-reactive protein, DLco = diffusing capacity for carbon monoxide, KL-6 = Krebs von den Lungen-6, LDH = lactate dehydrogenase, *n* = number of patients, VC = vital capacity.

Table 3

Longitudinal correlations between serum levels of biomarkers and pulmonary function variables (N = 92).

	ΔKL-6		ΔLDH		ΔCRP	
Variables	***r***	***P***	***r***	***P***	***r***	***P***
ΔVC, %predicted	−0.57	<.001**	−0.19	.069	−0.0553	.635
ΔDLco, %predicted	−0.42	<.001**	−0.26	.016*	−0.1243	.298

* $P<.05$.
** $P<.005$ Pearson correlation coefficient.
N = quantity of longitudinal changes, ΔCRP = change levels of C-reactive protein, ΔDLco = change levels of diffusing capacity for carbon monoxide, Δ KL-6 = change levels of Krebs von den Lungen-6, ΔLDH = change levels of lactate dehydrogenase, ΔVC = change levels of vital capacity.

Table 4

Correlations between ΔKL-6 and pulmonary functions in each subgroup of patients with ARS-IP.

	PM/DM related ARS-IP (N = 42)		Other ARS-IP (N = 50)	
Variables	***r***	***P***	***r***	***P***
Δ VC, %predicted	−0.50	<.001**	−0.62	<.001**
Δ DLco, %predicted	−0.42	.010*	−0.39	.005*

* $P<.05$.
** $P<.005$ Pearson correlation coefficient.
ARS-IP = interstitial pneumonia associated with anti-aminoacyl-tRNA synthetase antibody, DLco = diffusing capacity for carbon monoxide, *N* = quantity of longitudinal changes, ΔKL-6 = change levels of Krebs von den Lungen-6, PM/DM = polymyositis/dermatomyositis, VC = vital capacity.

chest CT findings after dose escalation of prednisolone and cyclosporin. Case 2 was an 80-year-old woman who was diagnosed with CADM (Fig. 2B). She was treated using prednisolone, tacrolimus, and cyclophosphamide. Initially, a marked improvement in VC was noted with decreased levels of serum KL-6. After the first dosage reduction of tacrolimus to 2.0 mg, her serum levels of KL-6 increased. However, the levels decreased with improvement of chest CT findings after dosage re-escalation of tacrolimus to 3.0 mg.

4. Discussion

The present study demonstrated that serial changes in KL-6 levels are correlated with changes in pulmonary function over a long

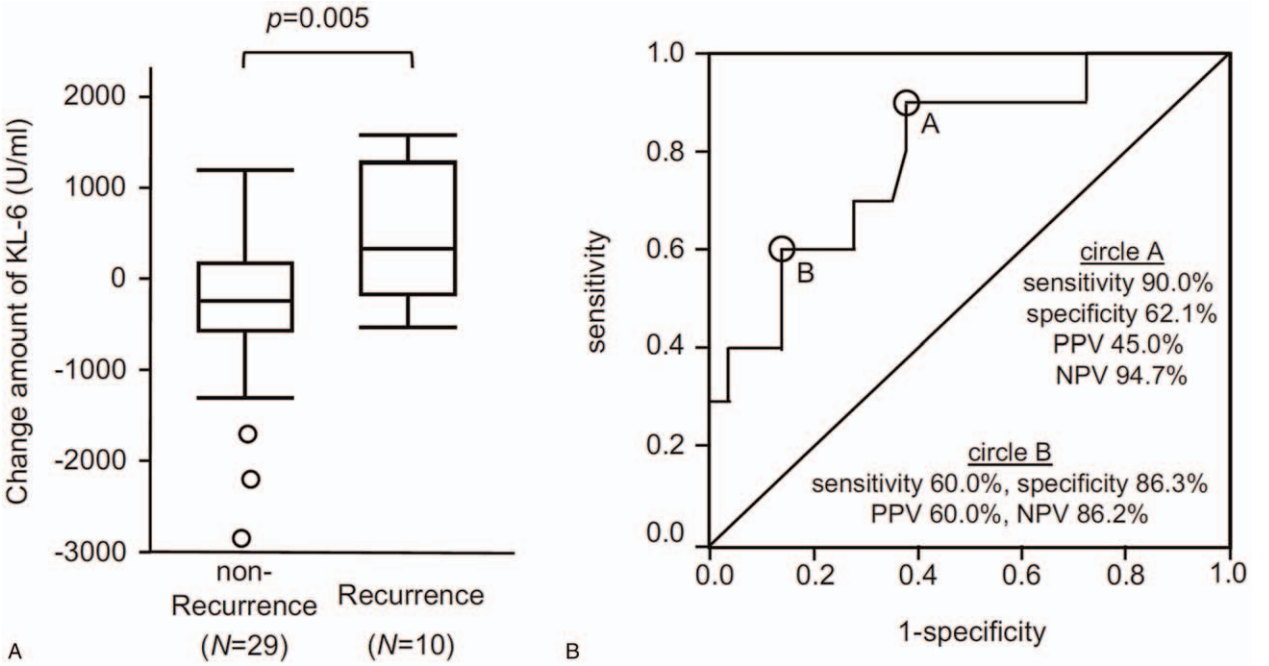

Figure 1. Associations between ΔKL-6 and recurrence of ARS-IP. (A) Changes in serum levels of Krebs von den Lungen-6 (ΔKL-6) were significantly higher in patients with interstitial pneumonia associated with anti-aminoacyl-tRNA synthetase antibody (ARS-IP) recurrence. (B) Receiver operating characteristic curve analysis revealed that ΔKL-6 gave the AUC; 0.79 (95% CI; 0.62–0.92, $P = .002$) for detecting ARS-IP recurrence. The cut-off levels are -173 U/mL (circle A) and 303 U/mL (circle B). ARS-IP = IP associated with anti-ARS antibody, AUC = area under the curve, KL-6 = Krebs von den Lungen-6, *N* = quantity of longitudinal changes, PPV = positive predictive value, NPV = negative predictive value.

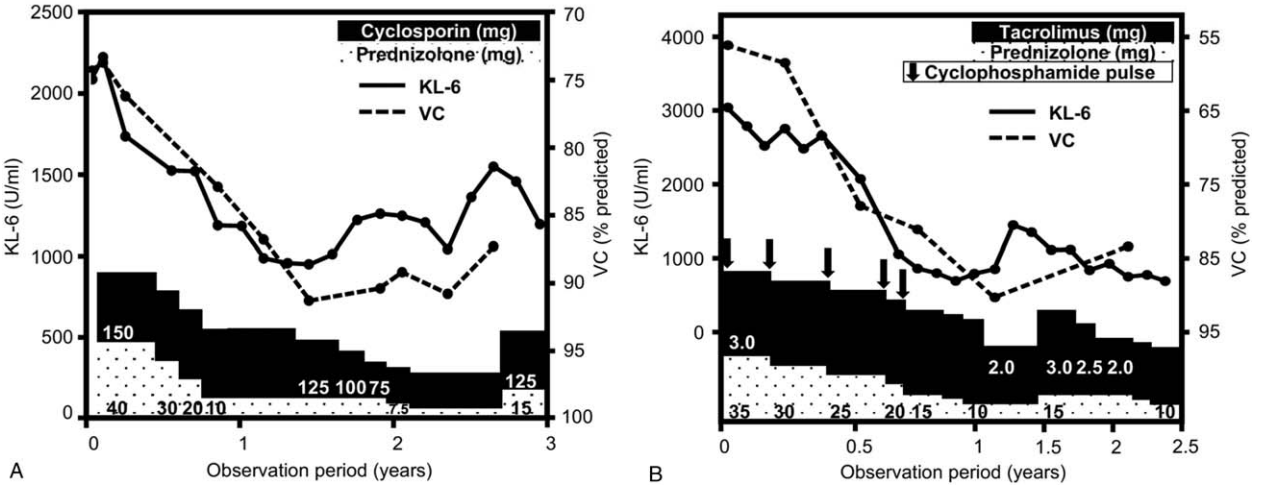

Figure 2. Serial changes of serum KL-6 and VC in 2 patients with interstitial pneumonia associated with anti-aminoacyl-tRNA synthetase antibody (A, B). The solid line indicates serum levels of KL-6. VC are inversely plotted and denoted by the dotted line. The therapeutic drug dosage is described in the horizontal bar. KL-6 = Krebs von den Lungen-6, VC = vital capacity.

follow-up period in patients with ARS-IP, and this correlation was observed regardless of PM/DM diagnosis. Moreover, re-elevation of serum KL-6 was significantly associated with ARS-IP recurrence during the disease course. These results indicate that serial measurement of serum KL-6 is useful for monitoring disease activity and detecting recurrence of ARS-IP. In general, corticosteroids and/or immunosuppressants are effective in treating ARS-IP, but prolonged high-doses can cause serious adverse events.[4,18] Therefore, treatment must be tapered to minimize drug-induced adverse events. However, as shown in our representative cases, the recurrence of the disease is common after dose reduction of immunosuppressive medications. Therefore, patients should be monitored closely for recurrence, but frequently repeated CT scans can be problematic because of radiation exposure, and pulmonary function tests are dependent on the maximum effort of patients, which may be occasionally difficult in patients with respiratory symptoms. Considering these disadvantages in CT scans and pulmonary function tests against blood tests, serial measurements of KL-6 could be an informative tool for evaluating disease activity of ARS-IP. Long-term treatment planning based on serial measurements of KL-6 potentially avoids life-threatening respiratory failure of ARS-IP via early detection of the recurrence.

The present study showed that longitudinal changes in serum KL-6, but not in LDH and CRP, were associated with pulmonary function and recurrence in patients with ARS-IP. We have previously reported that elevated serum KL-6 levels in patients with IP may be derived from regenerating type II pneumocytes in the lower respiratory tract.[8,19] Previous cross-sectional studies have shown that serum KL-6 levels are significantly higher in PM/DM patients with IP than in those without IP.[9,10] On the other hand, as in the present study, Tanizawa et al showed that serum levels of LDH were significantly higher in ARS-IP patients with myositis than in those without, although there was no significant difference in serum KL-6 levels between patients with myositis and those without.[20] These data suggested that serum KL-6 levels are more specifically associated with lung disease activity, and the present study confirmed this association during the disease course of ARS-IP.

There were some limitations to the present study. Firstly, the study could not include ARS-IP patients who were positive for OJ, Zo, or YRS antibodies—8 anti-ARS antibody subtypes have been reported: Jo-1, PL-7, PL-12, EJ, KS, OJ, Zo, and YRS,[21] but the ELISA system used in this study could not detect the OJ, Zo, and YRS antibodies.[16] Secondly, the follow-up schedules and the quantity of longitudinal data differed among patients, because the study design was retrospective. However, we showed that ΔKL-6 was significantly correlated with ΔVC and ΔDLco in patients with four or more longitudinal data points and in those with fewer than 4, indicating that the quantity of data from each patient had a negligible influence on our results. Lastly, the sample size was relatively small, and therefore, further prospective studies with larger sample sizes are needed to validate the utility of KL-6-based treatment planning for patients with ARS-IP.

In conclusion, the present study demonstrated that serial changes in KL-6 levels are correlated with changes in pulmonary function over a long period and can be used to monitor recurrence during the disease course of ARS-IP. These results indicate that serial evaluation of KL-6 can provide useful information to guide long-term treatment of ARS-IP.

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