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ORIGINAL ARTICLE

Serum YKL-40 level is associated with severity of interstitial lung disease and poor prognosis in dermatomyositis with anti-MDA5 antibody

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Abstract

Objective We aimed to investigate the clinical value of checking serum chitinase-3-like-1 protein (YKL-40) levels in anti-MDA5 antibody-positive dermatomyositis (anti-MDA5$^+$DM) patients.

Methods One hundred and five consecutive anti-MDA5$^+$DM patients and 44 healthy controls were enrolled in this study. Baseline and follow-up serum YKL-40 were detected by ELISA. We evaluated the association of YKL-40 with rapidly progressive interstitial lung disease (RPILD), severity of interstitial lung disease (ILD), and ILD-related survival.

Results Forty-one out of 105 anti-MDA5$^+$DM patients had RPILD at the time of serum sample collection (39.0%). Serum YKL-40 levels were significantly higher in anti-MDA5$^+$DM patients with RPILD compared with those without ($p = 0.011$). One month after treatment, patients with aggravated ILD had increased YKL-40 levels, while those with stable/improved ILD had decreased YKL-40 levels. Higher serum levels of ferritin and YKL-40, as well as lower peripheral CD3$^+$T cell counts, were independently associated with poorer prognosis. Kaplan–Meier survival curve showed that the 6 months survival rate in patients with high serum YKL-40 level (> 80 ng/ml) was significantly lower than that in patients with low YKL-40 level (≤ 80 ng/ml) (67% vs 89%, $p < 0.01$).

Conclusion YKL-40 can be useful as an indicator for the occurrence of RPILD and correlates with severity of ILD and poor prognosis in anti-MDA5$^+$DM patients. Closely monitoring and intensive treatment are suggested in anti-MDA5$^+$DM patients showing high level of YKL-40, especially levels > 80 ng/ml.

Keywords Anti-melanoma differentiation-associated protein 5 antibody · Dermatomyositis · Rapidly progressive interstitial lung disease (RPILD) · YKL-40

Introduction

Dermatomyositis (DM) is an autoimmune inflammatory disease that affects skin, muscles, as well as internal organs. Interstitial lung disease (ILD), especially rapidly progressive interstitial lung disease (RPILD), is one of the most frequent extra-muscular manifestations that predict poor prognosis. Our previous study [1] and others [2, 3] have shown that

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anti-melanoma differentiation-associated protein 5 (anti-MDA5) antibody was associated with RPILD in patients with DM. However, in clinical practice, a considerable number of patients with anti-MDA5 antibody do not develop RPILD. They only have mild or even no pulmonary involvement. This phenotype indicates that there is clinical heterogeneity in anti-MDA5 antibody-positive dermatomyositis (anti-MDA5$^+$DM). Thus, there is a need to identify new biomarkers to predict disease outcome in anti-MDA5$^+$DM patients.

YKL-40, also known as chitinase-3-like-1 protein and human cartilage glycoprotein 39, is a member of the mammalian chitinase-like protein family. It is mainly secreted by macrophages, neutrophils, and certain types of local epithelial cells. Though the exact function is not completely clear, it has been reported to be involved in many pathophysiological processes such as inflammation, cell proliferation, and tissue remodeling [4–6]. Previous studies demonstrated elevated serum YKL-40 levels in various diseases, such as cardiovascular disease [7], diabetes [8], cancer [9], and idiopathic pulmonary fibrosis [10]. More recently, Hozumi et al. reported that serum YKL-40 levels are correlated with disease activity and associated with poor prognosis in PM/DM-ILD [11]. Since PM/DM is a highly heterogeneous group of diseases, and anti-MDA5$^+$DM is a unique subtype that is closely associated with ILD, especially RPILD, we aimed to investigate the clinical use of serum YKL-40 in anti-MDA5$^+$DM patients.

Materials and methods

Patients

The retrospective study included 574 consecutive patients admitted to China-Japan Friendship Hospital between 1 August 2003 and 31 December 2017. All the enrolled patients fulfilled Bohan and Peter criteria [12, 13] for classic DM or Sontheimer criteria [14] for clinically amyopathic dermatomyositis (CADM). During the same period, 44 sex- and age-matched subjects who visited China-Japan Friendship Hospital for a health check-up and had no evidence of illness were retrospectively selected as healthy controls. ILD was confirmed by high-resolution computed tomography (HRCT). RPILD was defined as rapidly progressive ILD within 3 months from the onset of respiratory symptoms, referring to the official statement of idiopathic pulmonary fibrosis of the American Thoracic Society and the European Respiratory Society [15, 16]. Clinical data were collected from medical records on admission. Serum samples were obtained meanwhile before treatment initiation. All the samples were stored at − 80 °C until further analysis. All the samples were obtained after the patients had provided written informed consent. This study was approved by the Research Review Committee and the Ethical Review Committee of the China-Japan Friendship Hospital (approval number 2016–117).

Detection of anti-MDA5 antibody

All the DM patients were detected for anti-MDA5 antibody using immunoblotting method (membrane strip with antigens; EUROLINE) according to the manufacturer's instructions.

Measurement of serum YKL-40 levels

Serum YKL-40 levels were determined using YKL-40 enzyme-linked immunosorbent assay (ELISA) kit (CircuLex Human YKL-40 ELISA Kit; MBL) according to the manufacturer's instructions. Briefly, patients' sera diluted 1:50 were added into 96-well polyvinyl plates pre-coated with anti-human YKL-40 antibody and incubated for 60 min. Horseradish peroxidase (HRP) conjugated detection antibody, substrate reagent, and stop solution were added in turn at appropriate intervals. Absorbance was measured using spectrophotometric microplate reader at dual wavelengths of 450/540 nm. All samples were examined in duplicate, and the antibody concentration was calculated with reference to a standard curve constructed using serial concentrations of a serum sample containing a high titer of the anti-YKL-40 antibody.

Statistical analysis

Values were expressed as mean ± SD, median (IQR), or number (%). Comparisons between different groups were performed using Student's t test, Mann–Whitney U test, Wilcoxon matched, paired-rank test, or chi-square test where appropriate. Receiver operating characteristic (ROC) curve was used to obtain optimum cut-off level. Comparisons of ROC curve were performed according to DeLong et al. [17]. Survival analysis was performed using Kaplan–Meier method. p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS (version22.0) and MedCalc software (version 18.5).

Results

Patients' characteristics

Anti-MDA5 antibody was detected in 105 out of 574 (18.3%) DM or CADM patients. The mean age of these 105 anti-MDA5$^+$DM patients was 47.5 years, and 65 (61.9%) were women. The median disease duration between the onset of myositis or dermatitis and hospitalization was 4 months (range 0.3–480 months). Only a few patients (9.5%, 10/105) had received a low or moderate dose of corticosteroids (less than

0.5 mg/kg/day) before admission; corticosteroid or immunosuppressive agents were not given to most patients on admission. These patients were further divided into RPILD ($n = 41$) group and non-RPILD group ($n = 64$). The comparison of demographic, clinical, and laboratory features between the two groups is listed in Table 1. Inevitably, some of the data were missing: creatine kinase (1.0%, 1/105), ferritin (19.0%, 20/105), Ro-52(1.9%, 2/105), $CD3^+$T cell (4.8%, 5/105), and pulmonary function (51.4%, 54/105). Compared with non-RPILD group, patients in RPILD group had older age, higher serum level of ferritin and C-reactive protein (CRP), lower peripheral $CD3^+$T cell number as well as poorer pulmonary function (predicted forced vital capacity [%FVC], and predicted diffusion capacity of the lung for carbon monoxide [$\%DL_{CO}$]). In consideration of the excessive missing data, we did not include pulmonary function parameters in further analysis.

Baseline serum level of YKL-40 in anti-$MDA5^+$DM patients

Serum level of YKL-40 was compared between anti-$MDA5^+$DM patients and healthy controls (Fig. 1a).There was no significant difference in age and sex between the two groups (age 45.6 ± 12.1 years, female 59.1% in healthy controls). Compared with healthy controls (14.94 [10.49, 22.22] ng/ml), the serum YKL-40 levels were significantly increased in anti-$MDA5^+$DM patients (48.75 [27.30, 89.23] ng/ml, $p < 0.0001$). Furthermore, anti-$MDA5^+$DM patients in RPILD group had significantly higher serum levels of YKL-40 than those in non-RPILD group (80.3 [28.7, 107.7] ng/ml versus 42.4 [26.6, 73.1] ng/ml, $p = 0.011$) (Fig. 1b).

Using ROC analysis, at a cut-off level of > 80 ng/ml, serum YKL-40 levels showed the best sensitivity (51.2%), specificity (82.8%), and accuracy (69.5%) to discriminate RPILD

Table 1 Comparison of clinical and laboratory data between RPILD and non-RPILD group

Characteristics	RPILD ($n = 41$)	Non-RPILD ($n = 64$)	p value
Age (years)	52.6 ± 10.5	44.3 ± 10.9	< 0.001*
Female, n (%)	25 (61.0%)	40 (62.5%)	0.875
Duration (months)	4 (2, 7)	4 (2, 9.8)	0.340
CADM, n (%)	12 (29.3%)	11 (17.2%)	0.144
ILD, n (%)	41 (100%)	57 (89.1%)	0.041*
Heliotrope, n (%)	31 (75.6%)	47 (73.4%)	0.804
Gottron sign, n (%)	33 (80.5%)	49 (76.6%)	0.635
Mechanic hands, n (%)	17 (41.5%)	36 (56.3%)	0.139
Skin ulcer, n (%)	12 (29.3%)	16 (25.0%)	0.629
Muscle weakness	25 (61.0%)	42 (65.6%)	0.629
CK (IU/l)	44.5 (28.0, 106.0)[a]	56.5 (28.0, 120.8)	0.726
Ferritin (ng/ml)	792.6 (517.5, 1694.5.3)[b]	304.5 (106.7, 827.1)[c]	< 0.001*
CRP (mg/dl)	0.6 (0.4, 1.3)	0.4 (0.2, 0.8)	0.004*
Ro-52, n (%)	21 (51.2%)	23 (37.1%)[d]	0.156
$CD3^+$T cell (cell/μl)	492.5 (331.0, 709.5)[e]	644.5 (505.0, 1001.5)[f]	0.002*
%FVC	70.6 ± 20.1[g]	86.3 ± 19.8[h]	0.004*
$\%DL_{CO}$	48.7 ± 11.1[i]	60.3 ± 15.8[j]	0.022*

p values were estimated using Student's t test, Mann–Whitney U test, or chi-square test where appropriate

CADM clinically amyopathic dermatomyositis, *ILD* interstitial lung disease, *CK* creatine kinase, *CRP* C-reactive protein, *FVC%* predicted forced vital capacity, *DLco%* predicted diffusion capacity of the lung for carbon monoxide

*$p < 0.05$

[a] Number of subjects, $n = 40$

[b] Number of subjects, $n = 33$

[c] Number of subjects, $n = 52$

[d] Number of subjects, $n = 62$

[e] Number of subjects, $n = 40$

[f] Number of subjects, $n = 60$

[g] Number of subjects, $n = 13$

[h] Number of subjects, $n = 40$

[i] Number of subjects, $n = 12$

[j] Number of subjects, $n = 38$

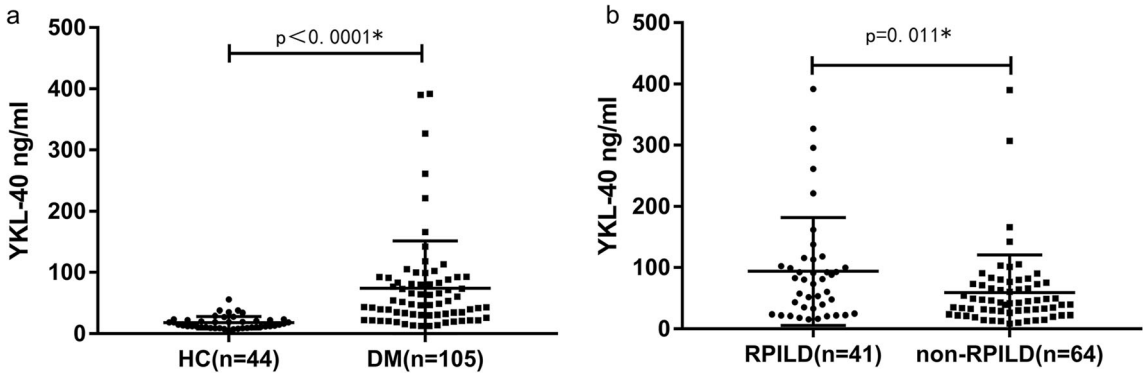

Fig. 1 Serum levels of YKL-40 in different groups. **a** YKL-40 levels significantly increased in anti-MDA5$^+$DM patients than those in in healthy control group. **b** YKL-40 levels in RPILD group were significantly higher than those in non-RPILD group. Comparison was performed using Mann–Whitney *U* test. HC healthy control, DM anti-MDA5 ab-positive dermatomyositis, RPILD rapidly progressive interstitial lung disease, non-RPILD patients without RPILD. *$p < 0.05$

from those without. The cut-off values and the discriminatory ability for CRP, ferritin, and CD3$^+$T cell are listed in Table 2. No significant difference was found in comparison of the discriminatory ability for RPILD between YKL-40 and other three parameters.

Correlations between baseline serum YKL-40 and other characteristics

Baseline serum YKL-40 levels weakly correlated with age ($r = 0.278$, $p = 0.004$), ESR ($r = 0.251$, $p = 0.011$) and CRP ($r = 0.332$, $p = 0.001$), and inversely correlated with CD3$^+$T cell counts ($r = -0.231$, $p = 0.021$). There was no significant correlation between levels of YKL-40 and ferritin (Fig. 2).

Serum YKL-40 level and disease activity in anti-MDA5$^+$DM patients

Twenty-one follow-up serum samples were obtained 1 month after treatment initiation. We further divided the patients into two groups: Patients with aggravated respiratory symptoms (such as worsening of dyspnea), and/or pulmonary function (decrease in FVC > 10% and/or DLco ≥ 15%), and/or chest HRCT (increase in existing or appearance of new infiltrates consistent with ILD) were defined as aggravated group. Otherwise, the patients were defined as stable/improved group. Changes in serum YKL-40 levels are presented in Fig. 3. In the stable/improved group ($n = 15$, nine with RPILD and six with ILD but not RPILD), YKL-40 levels significantly declined from 73.2 (25.8, 118.3) to 26.7 (13.0, 63.6) ng/ml 1 month after treatment initiation ($p = 0.007$). While in the aggravated group ($n = 6$, two with RPILD and four with ILD but not RPILD), YKL-40 levels increased from 25.4 (17.7, 40.4) to 43.6 (32.3, 76.1) ng/ml ($p = 0.031$).

Predictive value of YKL-40 for death in the early stage of anti-MDA5$^+$DM

We conducted the follow-up study from the admission of the first patient to 31 December 2017. The median follow-up time was 14.6 months (range 0.1–90.6). During the follow-up period, 20 patients died of ILD aggravation, 17 in the RPILD group, and 3 in the non-RPILD group. Since most of the deaths (17/20, 85%) occurred within 6 months (ranged 0.1 to 5 months) after enrollment, we further divided patients into death or survival group according to their 6 months survival. Table 3 shows comparison of treatments between the two groups. IVIG was more frequently used in the death group

Table 2 Cut-off values and the discriminatory ability of biomarkers by ROC analysis, which distinguishes RPILD form non-RPILD in MDA5$^+$DM patients

	YKL-40	CRP	Ferritin	CD3$^+$T cell
AUC (95%CI)	0.648 (0.535, 0.760)	0.667 (0.562, 0.772)	0.741 (0.638, 0.845)	0.688 (0.581, 0.794)
Cut-off value	80 ng/ml	0.4 mg/dl	410 ng/ml	390/μl
Sensitivity	51.2%	75.6%	87.9%	45.0%
Specificity	82.8%	53.1%	57.7%	88.3%
Diagnostic accuracy	69.5%	61%	68.2%	71%
Comparison of ROC	–	$z = 0.999$	$z = 1.332$	$z = 0.617$
(versus YKL-40)	–	$p = 0.318$	$p = 0.183$	$p = 0.537$

Comparisons of ROC curve were performed using MedCalc software, according to DeLong et al. (1988)

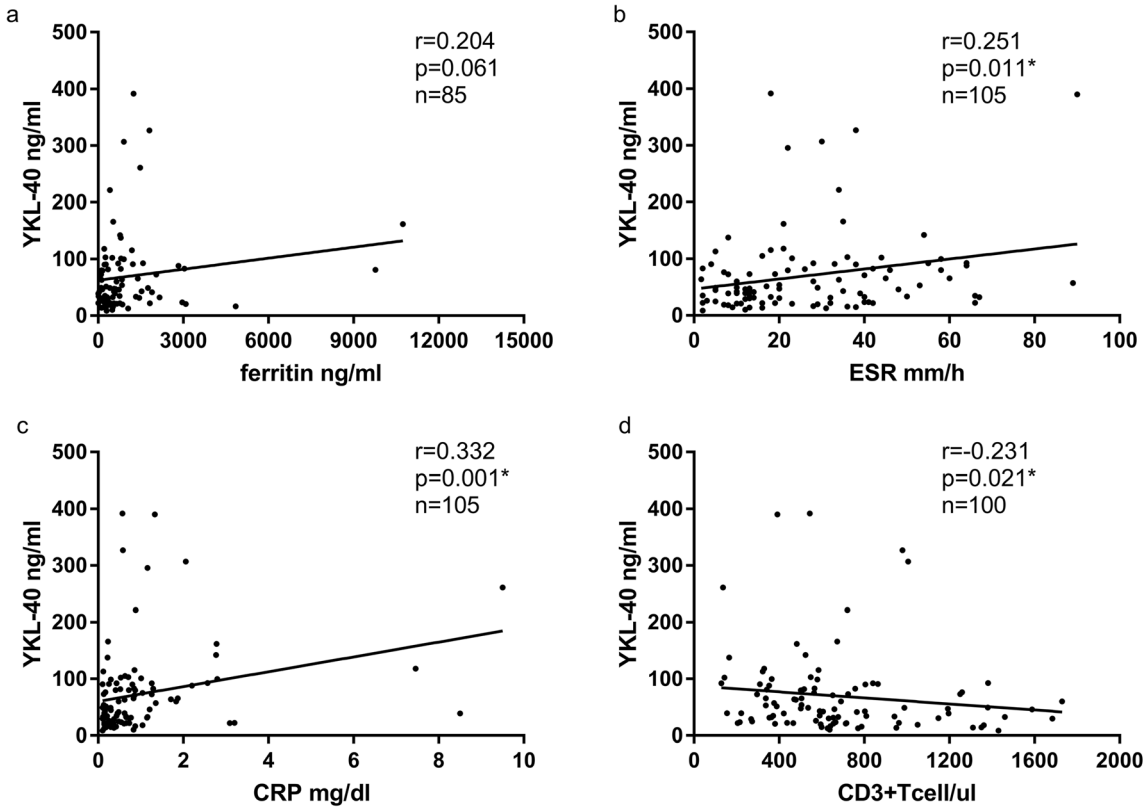

Fig. 2 Correlations between baseline serum YKL-40 and other characteristics. **a** Baseline YKL-40 levels did not correlate significantly with ferritin. **b** Baseline YKL-40 levels positively correlated with ESR. **c** Baseline YKL-40 levels positively correlated with CRP. **d** Baseline YKL-40 levels inversely correlated with $CD3^+$T cell counts. Dots represent single patients. Correlation was performed using Spearman's correlation coefficient

($p = 0.001$), whereas no significant differences were found in the use of other immunosuppressive agents. Considering the high heterogeneity, we did not include treatment regimens in further survival analysis.

The univariate Cox hazard analysis revealed that older age, higher serum level of ferritin, CRP, and YKL-40 were associated with shorter survival, while higher peripheral $CD3^+$T cell counts were associated with longer survival. When adjusted for age, sex, and CK level, higher serum level of ferritin and YKL-40 as well as lower peripheral $CD3^+$T cell counts were independently associated with a poorer prognosis (Table 4).

Using ROC analysis, at a cut-off level of > 80 ng/ml, serum YKL-40 levels showed the best sensitivity (58.8%), specificity (75.0%), and accuracy (83.8%) to predict death within 6 months from admission. The cut-off values and the predictive ability for ferritin and $CD3^+$T cell are listed in Table 5. No

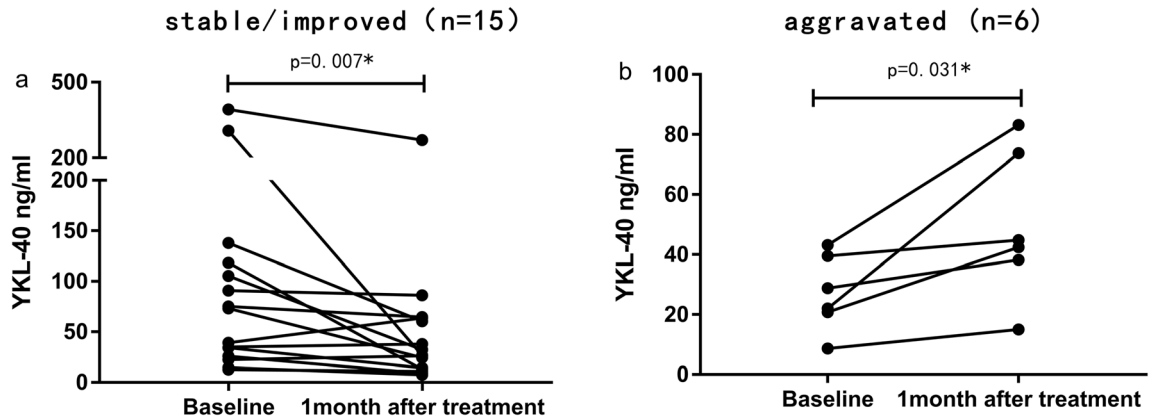

Fig. 3 Changes of serum YKL-40 levels 1 month after treatment initiation. **a** Serum YKL-40 levels significantly decreased in stable/improved group. **b** Serum YKL-40 levels significantly increased in aggravated group. Comparisons were performed using Wilcoxon matched, paired-rank test, $*p < 0.05$

Table 3 Comparison of treatment regimens between survival and death group within 6 months

Treatment	Survival ($n = 88$)	Death ($n = 17$)	p value
IVIG	20 (22.7%)	11 (74.7%)	0.001*
GC alone	26 (29.5%)	6 (35.3%)	0.637
GC+CSA/TAC	23 (26.1%)	6 (35.3%)	0.633
GC+CTX	24 (27.3%)	4 (23.5%)	0.984
GC+MMF	5 (5.7%)	0	0.589
GC+MTX	1 (1.1%)	1 (5.9%)	0.299
GC+CSA/TAC+another agent[a]	9 (10.2%)	0	0.365

Frequencies were compared using the Pearson's chi-square or Fisher's exact test where appropriate

IVIG intravenous immune globulin, *GC* glucocorticoid, *CSA* cyclosporine A, *TAC* tacrolimus, *CTX* cyclophosphamide, *MMF* mycophenolate mofetil, *MTX* methotrexate

*$p < 0.05$

[a] Include cyclophosphamide, rituximab, and methotrexate; the number of which is no more than 2 in either group

significant difference was found in comparison of the predictive ability for survival in the first 6 months between YKL-40 and other two parameters.

Kaplan–Meier survival curve showed that patients in RPILD group had significantly lower 6 months survival rate compared with those in non-RPILD group (55% vs 98%, $p < 0.0001$) (Fig. 4a). We further classified patients as low YKL-40 level group and high YKL-40 level group based on the cut-off level of 80 ng/ml. Kaplan–Meier survival curve showed that the 6 months survival rate in patients with high serum YKL-40 level (> 80 ng/ml) was significantly lower than that with low YKL-40 level (≤ 80 ng/ml) (67% vs 89%, $p < 0.01$) (Fig. 4b).

Discussion

Our study suggests that serum YKL-40 levels significantly elevated in anti-MDA5$^+$DM patients with RPILD than those without and is associated with ILD severity. Serum YKL-40 > 80 ng/ml predicts poor prognosis in an early stage of anti-MDA5$^+$DM. These findings indicate that YKL-40 may be involved in the pathophysiological process of ILD in anti-MDA5$^+$DM patients. To our knowledge, it is the first study to explore the significance of YKL-40 in anti-MDA5$^+$DM patients.

In the present study, elevated serum levels of YKL-40 were found in MDA5$^+$DM patients, especially in those with RPILD. Despite the fact that we failed to further clarify the source of YKL-40 in MDA5$^+$DM patients due to the lack of lung biopsy, former studies have demonstrated that YKL-40 is mainly secreted by local inflammatory cells at the site of inflammation. Furuhashi et al. [10] found that YKL-40 expression was enhanced in bronchiolar epithelial cells and alveolar macrophages adjacent to fibrotic lesions in idiopathic pulmonary fibrosis (IPF). In addition, an intense expression of YKL-40 protein was found in alveolar macrophages as well as bronchial epithelial cells in patients with severe asthma [18]. More recently, the study by Hozumi et al. [11] also demonstrated an enhanced expression of YKL-40 in intra-alveolar macrophages and alveolar epithelial cells in polymyositis (PM)/DM–ILD patients. These findings suggested that macrophages may be the major cellular source of YKL-40 in lung diseases.

Table 4 Cox proportional hazards model to predict the 6-month mortality of MDA5$^+$DM patients

Characteristics	HR (95%CI)	p value
Univariate analysis		
Age years (continuous)	1.068 (1.024, 1.115)	0.002*
Sex (male = 1)	1.080 (0.411, 2.837)	0.876
Diagnosis (DM = 1, CADM = 0)	1.337 (0.384, 4.653)	0.648
Heliotrope (positive = 1)	0.877 (0.309, 2.490)	0.805
Gottron sign (positive = 1)	0.656 (0.231, 1.861)	0.428
Mechanic hands (positive = 1)	0.715 (0.272, 1.880)	0.497
Skin ulcer (positive = 1)	0.813 (0.265, 2.494)	0.717
Muscle weakness (positive = 1)	1.413 (0.498, 4.012)	0.516
Ro-52 (positive = 1)	2.077 (0.790, 5.465)	0.138
CK IU/L (continuous)	1.001 (1.000, 1.001)con	< 0.001*
Ferritin ng/ml (continuous)	1.001 (1.000, 1.001)	< 0.001*
CRP mg/dl (continuous)	1.221 (1.000, 1.492)	0.051
CD3$^+$T cell cell/μl (continuous)	0.998 (0.996, 1.000)	0.017*
YKL-40 ng/ml (continuous)	1.004 (1.000, 1.008)	0.041*
Multivariate analysis[a]		
YKL-40 ng/ml (continuous)	1.006 (1.000, 1.011)	0.041*
CD3$^+$T cell cell/μl (continuous)	0.997 (0.994, 0.999)	0.018*
Ferritin ng/ml (continuous)	1.001 (1.000, 1.001)	< 0.001*

CADM clinically amyopathic dermatomyositis, *CK* creatine kinase, *CRP* C-reactive protein

*$p < 0.05$

[a] After adjustment for age, sex, and CK, backward and forward stepwise analyses were performed

Table 5 Cut-off values and the predictive ability of biomarkers by ROC analysis, which distinguishes between those survived the first 6 months or not

	YKL-40	Ferritin	$CD3^+T$ cell
AUC (95%CI)	0.658 (0.499, 0.817)	0.832 (0.714, 0.951)	0.740 (0.588, 0.891)
Cut-off value	80 ng/ml	1123	390
Sensitivity	58.8%	76.9%	62.5%
Specificity	75.0%	83.3%	82.1%
Diagnostic accuracy	83.8%	84.7%	84.0%
Comparison of ROC	–	$z = 1.375$	$z = 0.821$
(versus YKL-40)	–	$p = 0.169$	$p = 0.411$

Comparisons of ROC curve were performed using MedCalc software, according to DeLong et al. (1988)

A growing number of studies have revealed the pathogenic role of active macrophages in lung fibrosis, such as IPF [19, 20] and systemic sclerosis-related ILD [21, 22]. As far as DM-ILD is concerned, high levels of macrophage activation marker CD163 were found to be associated with ILD in PM/DM [23]. The study by Enomoto Y et al. [24] further revealed evident alveolar infiltration of CD163-positive macrophages in DM-related ILD. Limited reports indicated that diffuse alveolar damage (DAD) was the main pathological type in anti-$MDA5^+$DM with RPILD [25]. The typical features of DAD in the acute stage are the presence of hyaline membranes and infiltration of inflammatory cells (mainly macrophages, lymphocytes, and plasma cells) in the alveolar cavity. Our findings of high serum YKL-40 levels may further highlight the pathogenic role of macrophages in anti-$MDA5^+$DM-related RPILD.

From the clinical point of view, anti-$MDA5^+$DM is considered as an extremely unique subtype that presents with more skin ulceration, mild muscle involvement, peripheral lymphopenia, and RPILD [1–3, 26, 27]. Patients with this subtype experience an aggressive deterioration and high mortality, especially in the early stage of the disease. The 6-month mortality of RPILD in anti-$MDA5^+$DM reported by previous studies is around 50% [3, 28, 29]. This study showed that the mortality is 41.5% (17/41) in the RPILD group. Noteworthily, we found that all the deaths in the RPILD group occurred within 6 months after admission and the survivals seldom suffered from another exacerbation once they got through the first 6 months during the whole follow-up period. The same observation was also reported by Koga et al. [3]. This type of disease process is entirely different from patients with anti-synthetase syndrome-related ILD, which is characterized by a long-term recurrent clinical course [30].

Our previous studies showed that the prevalence of RPILD in DM during the entire observation period is 78.9% [1], while in this cross-sectional study, the point prevalence is 39.0%. The remaining cases of anti-$MDA5^+$DM have a relatively mild disease course, and consequently a favorable prognosis. The reason for this heterogeneity is unclear, but for clinicians, it is essential to identity risk factors for the occurrence of RPILD. Xu et al. reported skin ulcerations, elevated serum ferritin, and decreased counts of lymphocyte predict RPILD in CADM [31], which is mainly consistent with our findings, except that we did not find correlation between skin ulceration and RPILD. That may due to the different inclusion criteria in the two studies. What is more, we found that YKL-40 is associated with the severity of ILD and thus can be useful for evaluating therapeutic response.

There were several studies regarding prognostic factors of RPILD in DM patients, among which an elevation in anti-MDA5 antibody titer [2], high serum ferritin level, high alveolar-arterial oxygen gradient ($P[A\text{-}a]O_2$) [27], high serum levels of cytokines such as IL-6, IL-8, and IL-10 [32, 33], skin ulcerations, and low peripheral lymphocyte counts [31] have

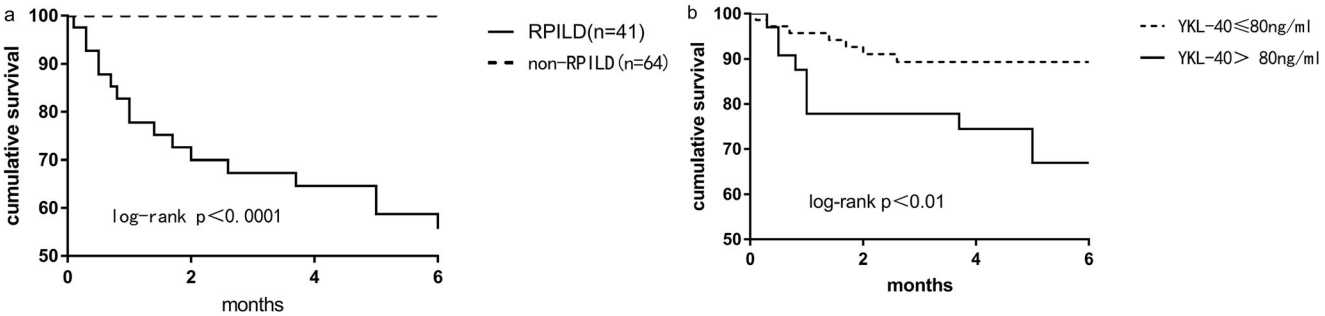

Fig. 4 Kaplan–Meier survival curve for anti-$MDA5^+$DM patients. **a** Patients in RPILD group had significantly lower 6 months survival rate compared with those in non-RPILD group. **b** Patients with high serum YKL-40 level (> 80 ng/ml) had significantly lower 6 months survival rate compared with those with low serum YKL-40 level (≤ 80 ng/ml). Comparisons were performed by log-rank test

been reported as poor prognostic factors. We also found high serum ferritin and YKL-40 level as well as low peripheral lymphocyte counts associated with lower 6 months survival rate in anti-MDA5$^+$DM patients, which validate and further enrich the conclusion of previous studies conducted in DM patients [1, 31, 33–35]. Considering the complexity of RPILD and the high heterogeneity of treatment agents, well-designed prospective studies are needed to explore factors affecting prognosis of RPILD in the future.

Compared with classical indicators such as ferritin, YKL-40 does not further improve discriminatory ability for RPILD and predictive ability for 6 months survival in anti-MDA5$^+$DM patients. However, the significance of this study is not limited to exploring the diagnostic value of YKL-40. We found that YKL-40 is associated with the occurrence of RPILD and correlates with severity of ILD in anti-MDA5$^+$DM patients, which provides a theoretical basis for further exploring its pathogenic role in ILD in these patients.

Due to several limitations in the current study, our results need to be interpreted with caution. First, the retrospective design and the inclusion of patients from a single center might cause potential selection bias. In addition, immunoprecipitation rather than immunoblotting method is considered the gold standard method to detect anti-MDA5 antibody. Therefore, the study participants may have included some false positive patients. Further study is needed to verify the sensitivity and specificity of immunoblotting method.

Taken together, we explored the significance of checking serum level of YKL-40 in a relatively large sample of anti-MDA5$^+$DM patients. The result implied that YKL-40 is a potential non-invasive biomarker for indicating the risk of RPILD, evaluating ILD severity and predicting disease outcome. Further study is needed to explore the pathophysiological mechanism of YKL-40 in anti-MDA5$^+$DM-related lung injury.

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Compliance with ethical standards

The authors declare that manuscript has been read and approved by all authors. We have obtained the approval from the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of the China-Japan Friendship Hospital. All the samples were obtained after the patients had provided written informed consent. This study was approved by the Research Review Committee and the Ethical Review Committee of the China-Japan Friendship Hospital (approval number 2016–117).

Disclosures None.

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