


## REVIEW ARTICLE

# Clinical value of YKL-40 in patients with polymyositis/dermatomyositis: A cross-sectional study and a systematic review

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## Abstract

**Introduction:** We performed a cross-sectional study to investigate the clinical usefulness of YKL-40 in patients with dermatomyositis (DM) and conducted a systematic review to summarize the clinical value of YKL-40 in patients with polymyositis (PM)/DM.

**Materials and methods:** A cross-sectional study and a systematic review were performed to study the clinical value of YKL-40 in patients with PM/DM. Serum YKL-40 level was detected using enzyme-linked immunosorbent assay, and its association with clinical and laboratory parameters was analyzed. In the systematic review, electronic databases of OVID Embase, OVID Medline, and web of science were searched to collect studies that reported clinical use of YKL-40 in patients with PM/DM.

**Results:** In the cross-sectional study, serum YKL-40 level was higher in patients with DM than in healthy controls (median [interquartile range]: 84.09 [52.72–176.4] ng/ml versus 27.37 [12.30–53.58] ng/ml,  $p < 0.0001$ ). Serum levels of YKL-40 were associated with the course of DM ( $r = -0.469$ ,  $p < 0.001$ ), CRP ( $r = 0.303$ ,  $p = 0.043$ ), CK ( $r = 0.263$ ,  $p = 0.037$ ), and global disease activity ( $r = 0.628$ ,  $p < 0.001$ ). The area under the ROC curve was 0.835 (95% confidence interval 0.751–0.920). In the systematic review, a total of four studies were included with moderate to high quality. Serum level of YKL-40 has the possibility for diagnosing PM/DM, identifying PM/DM patients with interstitial lung disease (ILD) or rapid progress ILD, and predicting death.

**Conclusion:** Serum YKL-40 level is a possible useful biomarker for PM/DM diagnosis and may be used to predict prognosis.

## KEYWORDS

biomarker, dermatomyositis, polymyositis, systematic review, YKL-40

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## 1 | INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) belong to the idiopathic inflammatory myopathy group of disorders. The hallmark of PM is the presence of weakness in the proximal muscles; for DM, the clinical characteristics are rashes, such as heliotrope rash and Gottron rash, as well as muscle weakness.<sup>1</sup> PM/DM are associated with malignant tumors, pulmonary fibrosis, and cardiac abnormalities, which are risk factors for poor prognosis, as low as 62%.<sup>2</sup> Thus, early diagnosis and optimal treatment are critical to improving prognosis. The serum levels of myositis-specific antibodies play a critical role in establishing the diagnosis, predicting the prognosis, and guiding the management.<sup>3-5</sup> However, the prevalence of currently available traditional or myositis-specific autoantibodies is low, as it ranges from rare prevalence to about 50% in patients;<sup>6-8</sup> furthermore, the currently available disease-specific autoantibodies only cover 70% of patients.<sup>7</sup> Therefore, novel serum biomarkers are still needed in clinical practice.

YKL-40, also named chitinase-3-like-1 protein, has a wide range of physiological functions, including participation in the regulation of cell growth and proliferation, promoting cell survival, driving the activation and differentiation of immune cells, promoting angiogenesis in cancer, and regulating inflammation. YKL-40 has also been associated with several diseases such as arthritis, diabetes, and liver fibrosis.<sup>9</sup> Several studies have investigated the clinical use of YKL-40 in patients with PM/DM.<sup>10-13</sup> Nevertheless, skin lesions are the hallmark feature of DM, and microvasculopathy plays a critical role in immune pathogenesis, which is different from the pathogenesis of PM.<sup>14</sup> In order to investigate the clinical usefulness of YKL-40 in patients with DM, especially for association of serum YKL-40 level with the severity and disease activity of skin lesions, a cross-sectional study was performed. Furthermore, a systematic review was conducted to summarize the clinical use of YKL-40 in PM/DM subgroup patients.

This study had two study aims. One was to conduct a cross-sectional study to assess the serum level and diagnostic value of YKL-40 in patients with DM. The other was to systematically review the clinical value of YKL-40 in patients with PM/DM. The systematic review was registered in PROSPERO (CRD42021270316) and performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.<sup>15</sup>

## 2 | MATERIALS AND METHODS

### 2.1 | Methods for cross-sectional study

#### 2.1.1 | Study population

Patients with a definite diagnosis of DM on the basis of the EULAR/ACR 2017 classification criteria, or patients with a definite diagnosis of DM accompanied with interstitial lung disease (ILD) identified by high resolution computed tomography (HRCT), who visited the West China Hospital between December 2019 and November 2020, were consecutively included. Patients' information was collected at enrollment by a researcher who was blinded to the state of the disease.

Disease activity of DM was assessed by the myositis intention to treat activity index (MITAX).<sup>16</sup> Scores  $\geq 4$  were considered moderate or severe, while scores  $\leq 3$  were considered mild. Pulmonary function was examined in DM-ILD patients. Patients were excluded if they had other lung diseases, other skin diseases, or other muscle diseases, or if they were pregnant or in a poor condition. Thirty healthy volunteers who visited hospital for annual healthy checking were enrolled into control group. The exclusion criteria of the control group included obesity, cardiovascular disease, tumor, metabolic syndrome, asthma, infection, and renal insufficiency. The enrolled healthy controls did not have any complaints when visiting hospital and their routine examinations, including liver function, kidney function, blood routine, and muscle enzymes test, were all within the normal range. This study was approved by the ethics committee of West China Hospital (NO. 246 in the year 2019) and written informed consent was obtained from all participants.

#### 2.1.2 | Serum level of YKL-40 and routine laboratory tests

Serum levels of YKL-40 were measured using the YKL-40 human ELISA kit (EHCHI3L1, Thermo Fisher) according to the manufacturer's instructions. The sera were diluted by 150 folds. The detection sensitivity of the kit was 6 pg/ml. The ELISA set was BioTek Eon140423C. The quality control measurements were applied during running of all routine laboratory tests. The intra-assay % coefficient of variation (CV%) and inter-assay CV% were less than 10% and less than 12%, respectively. The results of ELISA were calculated on ELISACalc software.

We collected blood samples from each participant at enrollment for routine laboratory tests, including serum Krebs von den Lungen (KL-6), C3, C4, C-reactive protein (CRP), IgG, IgM, IgA, IgE, CD4, CD8, creatine kinase (CK), lactate dehydrogenase (LDH), hydroxybutyrate dehydrogenase (HBDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), troponin T (TnT), creatine kinase M subunit (CKMB), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). Pulmonary function was examined in DM-ILD patients.

#### 2.1.3 | Statistical analysis

IBM SPSS Statistics version 22.0 and GraphPad Prism version 6.0 were used. Normal distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. As the data were not normally distributed, data were expressed as medians (interquartile range). Spearman correlation coefficient ( $r$ ) was used to analyze the correlations. Mann-Whitney test or Kruskal-Wallis test were used to compare continuous variables and Bonferroni correction was used for multiple pairwise comparisons. Serum level of YKL-40 was calculated based on the standard curve. Correlations between the serum level of YKL-40 and clinical characteristics, including the duration and course of the disease, disease activity, lung function, and laboratory tests

were analyzed. If a patient did not have the clinical characteristics for the correlation study, they were excluded. Receiver operating characteristic (ROC) curve analysis, sensitivity, specificity, accuracy and Youden index were used to determine the diagnostic accuracy and select optimal cutoff values of YKL-40 in patients with DM. *p*-values <0.05 was considered statistically significant.

## 2.2 | Methods for systematic review

### 2.2.1 | Eligibility criteria

A study was included if it met all the following requirements: (1) study participants were PM and/or DM patients; (2) controls without PM/DM; (3) serum level of YKL-40 was detected; (4) the study assessed the clinical use of YKL-40 in patients, such as diagnostic value, prognosis prediction, and association with clinical characteristics, including the duration and course of the disease, disease activity, lung function, and laboratory tests; (5) study design was a cross-sectional study or diagnostic accuracy study. A study was excluded if it was a duplicate, a commentary, a conference abstract, or without related outcomes.

## 2.3 | Study selection and assessment

Electronic databases of OVID Medline, OVID EMBASE, and Web of science were searched on July 26, 2021. Search terms were “polymyositis,” “dermatomyositis,” “myositis,” “chitinase-3-like-1 protein.” Reference lists of included studies were manually searched.

Studies selection and data extraction were performed independently by two reviews. Any disagreement on data extraction

was resolved via discussion or adjudication by a third reviewer if necessary. The agency for healthcare research and quality (ARHQ) assessment tool was used to assess the methodological quality of included studies.<sup>17</sup>

## 3 | RESULTS

### 3.1 | Results for cross-sectional study

#### 3.1.1 | Baseline characteristics

The characteristics of the enrolled participants are listed in Table 1. A total of 65 patients with DM and 30 healthy controls were included. Among DM patients, 33 had ILD and 32 did not have ILD. For treatment of DM, 98.46% of patients with ILD and 90.77% of patients without ILD used glucocorticoids and more than two immunosuppressors, such as hydroxychloroquine and tacrolimus. For treatment of ILD, the most commonly used agents were pirfenidone (18.46%) and flumucil (27.69%). The mean age of the patients with DM was 47.71 years, and 73.8% were women. Among the healthy controls, the mean age was 47.73 years and 86.7% were women. The number of patients with DM that has antibodies against ANA, MDA-5, and Ro-52 was 35 (53.85%), 27 (41.54%), and 22 (33.85%), respectively. The serum levels of YKL-40 in healthy controls and patients with DM were 27.37 (12.30–53.68) ng/mL and 84.09 (52.72–176.4) ng/mL, respectively.

#### 3.1.2 | Serum level of YKL-40

Serum was collected from all patients and serum level of YKL-40 was detected by ELISA. The serum level of YKL-40 in patients

TABLE 1 Characteristics of included participants

Characteristics	HC (n = 30)	DM (n = 65)
Age (years, mean ± SD)	47.73 ± 7.64	47.71 ± 10.88
Sex (F/M)	26/4	48/17
ILD (Y/N)		33/32
ANA (+), number (percentage)		35 (53.85)
MDA-5 (+), number (percentage)		27 (41.54)
Ro-52 (+), number (percentage)		22 (33.85)
Treatments for DM, number (percentage)		
Glucocorticoids		64 (98.46)
More than two immunosuppressors		59 (90.77)
Treatments for ILD, number (percentage)		
Pirfenidone		12 (18.46)
Fluimucil		18 (27.69)
Serum YKL-40 level (ng/mL, median and quartile)	27.37 (12.30–53.68)	84.09 (52.72–176.4)
CRP (mg/L, median and quartile)		3.11 (1.43, 5.77)
CK (U/L, median and quartile)		60 (39, 133)
LDH (U/L, median and quartile)		247 (215, 343)
HBDH (U/L, median and quartile)		194 (173, 285)

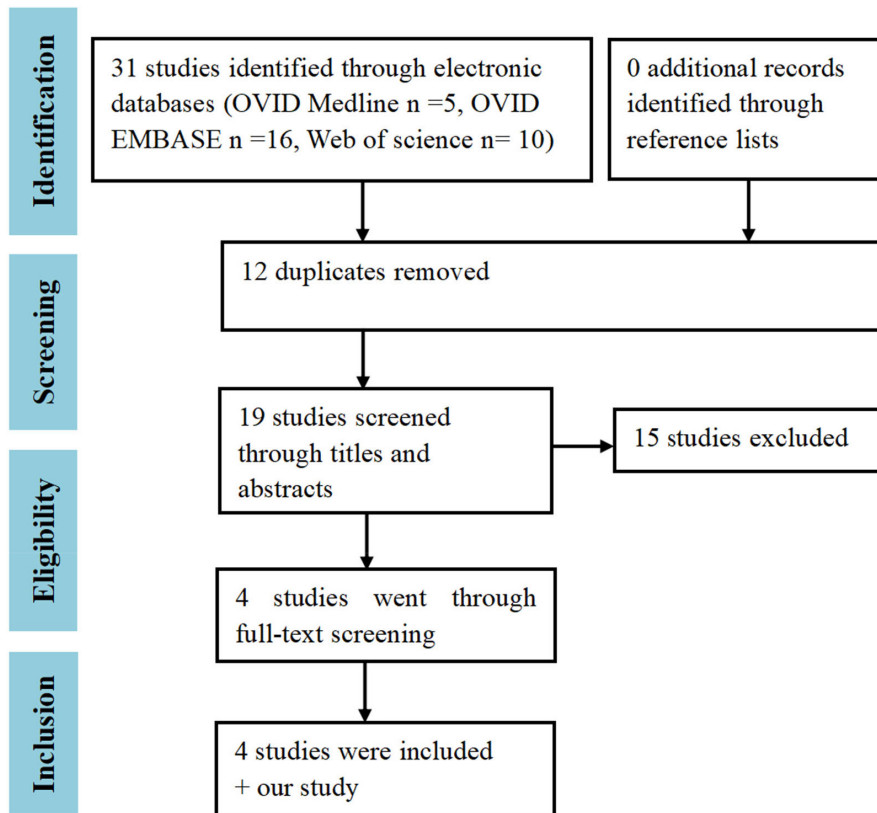


FIGURE 1 Study selection flow chart

with DM was 84.09 (52.72–176.4) ng/ml, and this was higher than that in healthy controls (27.37 [12.30–53.58] ng/ml,  $p < 0.0001$ ) (Figure 2A). Further analysis revealed that the serum levels of YKL-40 in patients with DM who had severe cutaneous disease activity (severe vs mild: 170.5 [82.17–265.5] ng/mL versus 72.06 [51.09–127.8] ng/ml,  $p = 0.0056$ ) and global disease activity (moderate and severe vs mild: 128.3 [71.01–237.4] ng/ml vs 52.24 [37.65–72.63] ng/ml,  $p = 0.0014$ ) were higher as compared to the levels in patients with mild disease activity (Figure 2B–C).

### 3.1.3 | Effect of anti-MDA5 autoantibodies on serum YKL-40 level

Previously published studies have reported that the presence of anti-melanoma differentiation-associated gene 5 (MDA5) autoantibodies was associated with poor prognosis in patients with DM.<sup>18</sup> Therefore, we analyzed the serum YKL-40 level in patients with DM based on the presence or absence of anti-MDA5 autoantibodies. Results showed that in patients with DM, those who presented with anti-MDA5 autoantibodies had a lower YKL-40 level (76.15 ng/ml vs 118.84 ng/ml,  $p = 0.0449$ ) than patients who did not present with anti-MDA5 autoantibodies.

### 3.1.4 | Effect of ILD on serum YKL-40 level

We also assessed the influence of ILD on the serum levels of YKL-40 in patients with DM. The results showed that the presence of ILD

(84.09 [52.01–169.2] ng/ml vs 85.24 [53.61–190.4] ng/mL,  $p = 0.97$ ) did not influence the serum levels of YKL-40.

### Correlation between serum level of YKL-40 and clinical characteristics

Detailed MITAX scores of individual organ systems were listed in Table S2. Serum levels of YKL-40 in patient with DM were positively associated with the constitutional disease activity ( $r = 0.503$ ,  $p < 0.001$ ), cutaneous disease activity ( $r = 0.509$ ,  $p < 0.001$ ), gastrointestinal disease activity ( $r = 0.381$ ,  $p = 0.002$ ), cardiovascular disease activity ( $r = 0.329$ ,  $p = 0.008$ ), muscle disease activity ( $r = 0.425$ ,  $p < 0.001$ ), and global disease activity ( $r = 0.628$ ,  $p < 0.001$ ) (Table 3). Nevertheless, serum levels of YKL-40 were not associated with the pulmonary function (Table S3).

Serum levels of YKL-40 were associated with the course of DM ( $r = -0.469$ ,  $p < 0.001$ ) and correlated with several laboratory tests, including, CRP ( $r = 0.303$ ,  $p = 0.043$ ), CK ( $r = 0.263$ ,  $p = 0.037$ ), LDH ( $r = 0.460$ ,  $p < 0.001$ ), HBDH ( $r = 0.435$ ,  $p < 0.001$ ), ALT ( $r = 0.393$ ,  $p < 0.001$ ), AST ( $r = 0.508$ ,  $p < 0.001$ ), TnT ( $r = 0.533$ ,  $p = 0.001$ ), CKMB ( $r = 0.547$ ,  $p = 0.001$ ), and FT3 ( $r = -0.316$ ,  $p = 0.029$ ) (Table S4).

### 3.1.5 | Diagnostic value of serum YKL-40

As serum levels of YKL-40 in patients with DM were much higher than in healthy controls, we assessed the diagnostic value of YKL-40 in DM. The area under the ROC curve for YKL-40 was 0.835 (95% confidence interval [CI] 0.751–0.920). The diagnostic accuracy

TABLE 2 Characteristics of included study in systematic review

Study	number of participants		Serum level of YKL-40 (ng/ml)		Identifying	Cutoff	Diagnostic value of serum YKL-40		Spearman correlation with clinical variables	
	Country	PM/DM	control	PM/DM			control	sensitivity		specificity
Our study 2021	China	DM: 65	30	84.09 (52.72–176.4)	DM	40.71	0.7	0.844	0.835, 95%CI (0.751–0.920)	It is associated with constitutional disease activity ( $r = 0.503, p < 0.001$ ), cutaneous disease activity ( $r = 0.509, p < 0.001$ ), gastrointestinal disease activity ( $r = 0.381, p = 0.002$ ), cardiovascular disease activity ( $r = 0.329, p = 0.008$ ), muscle disease activity ( $r = 0.425, p < 0.001$ ), global disease activity ( $r = 0.628, p < 0.001$ ), and laboratory tests, including CRP ( $r = 0.303, p = 0.043$ ), CK ( $r = 0.263, p = 0.037$ ), LDH ( $r = 0.460, p < 0.001$ ), HBDH ( $r = 0.435, p < 0.001$ ), ALT ( $r = 0.393, p < 0.001$ ), AST ( $r = 0.508, p < 0.001$ ), TnT ( $r = 0.533, p = 0.001$ ), CKMB ( $r = 0.547, p = 0.001$ ), and FT3 ( $r = -0.316, p = 0.029$ )
Carboni 2021 [10]	Brazil	antisynthetase syndrome: 64	64	0.54 (0.36–0.85)	None	None	None	None	It is not correlate with any clinical, laboratory, disease status, or therapeutic parameters, but correlated with TNF $\alpha$ serum levels ( $r = 0.382, p = 0.007$ )	
Gao 2019 [11]	China	PM: 58, DM: 41	87	51.6 (36.4–63.8)	ILD	55.9	0.91, 95%CI (0.72–0.99)	0.72, 95%CI (0.61–0.82)	0.82, 95%CI (0.74–0.91)	It is correlated with MYOACT ( $r = 0.64, p < 0.01$ ), CRP ( $r = 0.34, p < 0.01$ ), ESR ( $r = 0.61, p < 0.01$ ) and ferritin ( $r = 0.61, p < 0.01$ )
Jiang 2019 [12]	China	MDA5+ DM: 105	44	48.75 (27.30, 89.23)	RPILD	80	0.51	0.83	0.648, 95%CI (0.535–0.760)	It is correlated with age ( $r = 0.278, p = 0.004$ ), ESR ( $r = 0.251, p = 0.011$ ), CRP ( $r = 0.332, p = 0.001$ ), CD3 + T cell counts ( $r = -0.231, p = 0.021$ ), but not associated with ferritin
Hozumi 2017 [13]	Japan	PM/DM-ILD: 69	34	56.7 (1.3–233)	death within 6 months from admission	105	0.75	0.83	0.658, 95%CI (0.499–0.817)	It is correlated with age ( $r = 0.41, p < 0.001$ ), KL-6 ( $r = 0.33, p < 0.01$ ), ferritin ( $r = 0.46, p < 0.001$ ), PaO2 ( $r = -0.40, p < 0.001$ ), %DLCO ( $r = -0.41, p = 0.01$ )

**TABLE 3** Spearman correlations (*r*) between serum levels of YKL-40 and disease activity

Characteristics	Sample size	<i>r</i>	<i>p</i> value
Constitutional disease activity	64	<b>0.503</b>	<b>&lt;0.001</b>
Cutaneous disease activity	64	<b>0.509</b>	<b>&lt;0.001</b>
Skeletal disease activity	64	0.078	0.539
Gastrointestinal disease activity	64	<b>0.381</b>	<b>0.002</b>
Pulmonary disease activity	64	0.095	0.457
Cardiovascular disease activity	64	<b>0.329</b>	<b>0.008</b>
Muscle disease activity	64	<b>0.425</b>	<b>&lt;0.001</b>
Global disease activity	64	<b>0.628</b>	<b>&lt;0.001</b>

Note: Bold font of numbers indicate statistic significant.

for YKL-40 was 79.8%. At a cutoff of 40.71 ng/ml and Youden index = 0.544, the sensitivity and specificity were 0.7 and 0.844, respectively (Figure 3).

## 3.2 | Results for systematic review

### 3.2.1 | Baseline characteristics

A total of 31 studies were found from electronic databases. After excluding irrelevant studies, four studies were included in our systematic review, and by adding our study results, a total of 5 studies reported the clinical value of YKL-40 in patients with PM/DM (Figure 1).<sup>10-13</sup> No eligible studies were included by manually checking references. The diagnostic criteria for patients was the Bohan and Peter classification criteria in all included studies, except for Carboni 2021 which used the modified ASSD criteria classification.<sup>10</sup> The included patients included PM/DM, MDA5+ DM, PM/DM-ILD, and patients with antisynthetase syndrome. The number of patients per study ranged from 64 to 105. Controls were all healthy controls, and the number of controls per study ranged from 30 to 87. The average age of patients and controls varied from 44.8 and 42.6 to 62 and 53, respectively (Table 2). Overall, the quality of included studies was moderate to high (Table S1).

### 3.2.2 | Serum level of YKL-40

The systematic review reported that the detection method of serum level of YKL-40 was ELISA in all studies. The median serum level of YKL-40 in patients with PM/DM ranged from 0.54 to 84 ng/ml, which was higher than that in the controls, which varied from 0.27 to 27.8 ng/ml (Table 2).

### 3.2.3 | Correlation between serum level of YKL-40 and clinical characteristics

Results of the systematic review reported that serum YKL-40 was associated with TNF $\alpha$  serum levels ( $r = 0.382$ ,  $p = 0.007$ ), MYOACT ( $r = 0.64$ ,  $p < 0.01$ ), CRP ( $r = 0.34$ ,  $p < 0.01$ ;  $r = 0.332$ ,  $p = 0.001$ ), ESR ( $r = 0.61$ ,  $p < 0.01$ ;  $r = 0.251$ ,  $p = 0.011$ ), ferritin

( $r = 0.61$ ,  $p < 0.01$ ;  $r = 0.46$ ,  $p < 0.001$ ), age ( $r = 0.278$ ,  $p = 0.004$ ;  $r = 0.41$ ,  $p < 0.001$ ), CD3+T cell counts ( $r = -0.231$ ,  $p = 0.021$ ), KL-6 ( $r = 0.33$ ,  $p < 0.01$ ), PaO<sub>2</sub> ( $r = -0.40$ ,  $p < 0.001$ ), and %DL<sub>CO</sub> ( $r = -0.41$ ,  $p = 0.01$ ) (Table 2).

### 3.2.4 | Diagnostic value of serum YKL-40

The systematic review suggested that serum level of YKL-40 could be used to identify ILD in patients with PM/DM (cutoff = 55.9 ng/ml, sensitivity = 0.91, specificity = 0.72, AUC = 0.82), rapid progress ILD in patients with MDA5+DM (cutoff = 80 ng/ml, sensitivity = 0.51, specificity = 0.83, AUC = 0.65), death within 6 months from admission in patients with MDA5+DM (cutoff = 80 ng/ml, sensitivity = 0.59, specificity = 0.75, AUC = 0.66), and death within 2 years from diagnosis in patients with PM/DM-ILD (cutoff = 105 ng/ml, sensitivity = 0.75, specificity = 0.83, AUC = 0.78) (Table 2).

## 4 | DISCUSSION

### 4.1 | Main findings

Our study reports that the serum level of YKL-40 is significantly increased in patients with DM, associated with cutaneous disease activity and global disease activity, and possibly has diagnostic value for DM. Results of the systematic review suggest that YKL-40 is correlated with several clinical lab tests, such as ESR, CRP, KL-6, ferritin, and serum TNF $\alpha$  level, and has clinical values for diagnosing PM/DM, identifying PM/DM patients with ILD or rapid progress ILD, and predicting death. These findings suggest that YKL-40 has possible value as a biomarker in clinical use.

According to previous reports, YKL-40 is mainly secreted by macrophages, vascular endothelial smooth muscle cells, alveolar epithelial cells, neutrophils, and chondrocytes.<sup>19-21</sup> YKL-40 plays important roles in several aspects, including participating in reorganizing endothelial cells, regulating fibroblast proliferation, remodeling chronic inflammatory microenvironment.<sup>20-21</sup> Although the role of YKL-40 in myositis remains unclear, the elevated YKL-40 might be associated with vascular endothelial cells impairment, macrophage activation, inflammatory process, and fibroblast proliferation.<sup>12-14</sup>

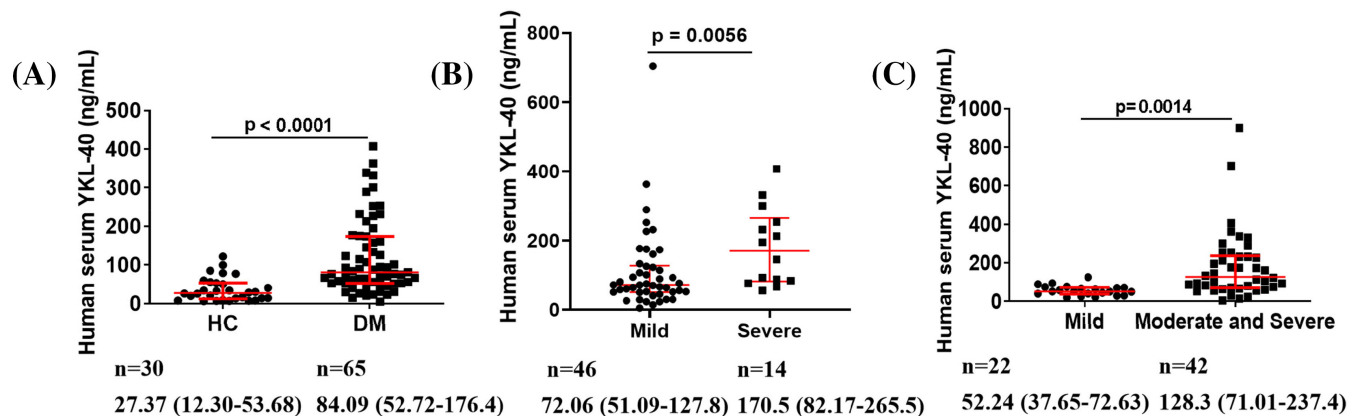


FIGURE 2 (A) Serum levels of YKL-40 in healthy controls (HC) and patients with DM. (B) Serum levels of YKL-40 in patients with DM affected by cutaneous disease activity. (C) Serum levels of YKL-40 in patients with DM affected by global disease activity. Data were expressed as median (quartile)

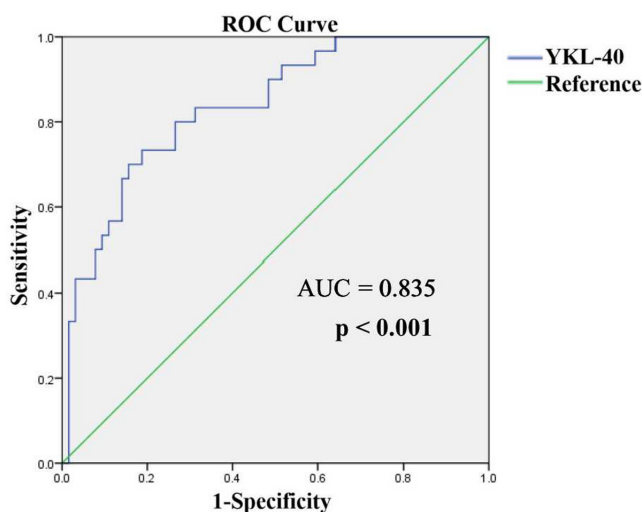


FIGURE 3 Diagnostic value of YKL-40 in patients with DM

Our study reported serum level of YKL-40 was associated with disease activities, including cutaneous disease activity, gastrointestinal disease activity, cardiovascular disease activity, and muscle disease activity, and was related to inflammatory biomarkers, which were consistent with the reports reported by Gao 2019, Jiang 2019, and Hozumi et al. that YKL-40 had relationships with MYOACT, CRP, ESR, KL-6, and ferritin.<sup>11-13</sup> However, this is not confirmed by the results reported by Carboni 2021 et al.<sup>10</sup> Those inconsistent results might be explained by the fact that study population was small, patients were from different study groups, and patients were with different subgroup diagnosis.

Our study results demonstrated that the serum YKL-40 level in DM patients in the presence of anti-MAD5 autoantibodies was lower than that in the absence of the anti-MAD5 autoantibodies and the presence of ILD did not have an effect on the serum levels of YKL-40. This could be explained by the fact that the sample size was small. Moreover, we only enrolled patients with DM, which is a microvasculopathy. The elevated YKL-40 caused by skin damage or other vasculitis may offset the effect of ILD on YKL-40. Furthermore, according to

the systemic review, patients with positive anti-MDA5 autoantibodies and RP-ILD may present elevated YKL-40, but in our cross-sectional study, due to the lack of follow-up data, we did not do subgroup analysis in patients with positive MDA5 autoantibodies.<sup>22</sup> Thus, further studies are warranted to analyze the association between the level of YKL-40 and anti-MDA5 autoantibodies positive population.

## 4.2 | Limitations

This study has several limitations. First, serum YKL-40 was found to be an acute-phase inflammation associated biomarker, which negatively correlated to the disease course of DM or ILD. However, we did not classify the onset of ILD as chronic, subacute, or acute owing to the limited study population and lack of follow-up for the change in the serum level of YKL-40. Second, our study is a cross-sectional and systematic review study with a relatively small study population, which limits the reliability of study results. Thus, prospective cohort studies with larger populations are needed to confirm the results. Finally, we only performed Spearman correlation analysis to investigate the possible effect factors of YKL-40 level or disease activity owing to the small study population, which limited us from performing multifactor analysis. Thus, to eliminate the mutual influence between etiologies, further studies with a larger study population are needed.

## 5 | CONCLUSION

Serum level of YKL-40 is elevated in patients with PM/DM, associated with the severity of disease activity, and correlated with several lab tests. Based on the results of our systematic review, YKL-40 can possibly be used to identify ILD in patients with PM/DM and RPILD in MDA5+ DM and to predict poor prognosis, highlighting its clinical importance. Owing to the limited study population and study number, studies with more participants are needed to confirm the findings.

## AUTHOR CONTRIBUTIONS

CBB, CYH, YG, and XQB conceived and designed the study. LFM, YG, and XQB guided the study. LH, LS, HYP, ZYY, and TYR collected clinical samples and assessed the disease activity. CBB, CYH, LH, LS, ZYY, and TYR performed ELISA and analyzed data. CBB, CYH, LS, LH searched the study, extracted the information. HYP, ZYY, TYR assessed the study quality. All authors drafted and revised the manuscript.

## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## DATA AVAILABILITY STATEMENT

All data are presented in tables or can be found in [Appendix S1](#).

## ETHICAL APPROVAL

The cross-sectional study was conducted in compliance with the Declaration of Helsinki and is approved by the ethics committee of West China Hospital (NO. 246 in 2019). Written informed consent was obtained from all participants.

## STUDY REGISTRATION

This systematic review was registered in PROSPERO (CRD42021270316).

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## REFERENCES

- Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362:971-982.
- Schiopu E, Phillips K, MacDonald PM, et al. Predictors of survival in a cohort of patients with polymyositis and dermatomyositis: effect of corticosteroids, methotrexate and azathioprine. *Arthritis Res Ther*. 2012;14:R22.
- Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. *J Intern Med*. 2016;280:8-23.
- DeWane ME, Waldman R, Lu J. Dermatomyositis: clinical features and pathogenesis. *J Am Acad Dermatol*. 2020;82:267-281.
- Cassius C, Le Buanec H, Bouaziz JD, et al. Biomarkers in adult dermatomyositis: tools to help the diagnosis and predict the clinical outcome. *J Immunol Res*. 2019;2019:9141420.
- Yang WM, Chen JJ. Advances in biomarkers for dermatomyositis. *Clin Chim Acta*. 2018;482:172-177.
- Fujimoto M, Watanabe R, Ishitsuka Y, Okiyama N. Recent advances in dermatomyositis-specific autoantibodies. *Curr Opin Rheumatol*. 2016;28:636-644.
- Lundberg IE, Tjälrlund A, Bottai M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. *Arthritis Rheumatol*. 2017;69:2271-2282.
- Pinto B, Janardana R, Nadig R, et al. Comparison of the 2017 EULAR/ACR criteria with Bohan and Peter criteria for the classification of idiopathic inflammatory myopathies. *Clin Rheumatol*. 2019;38:1931-1934.
- Carboni RCS, Behrens Pinto GL, Shinjo SK. High YKL-40 serum levels and its expression in the muscle tissues of patients with antisynthetase syndrome. *Adv Rheumatol*. 2021;61:44.
- Gao MZ, Wei YY, Xu QW, Ji R, Han ZJ, Jiang TW. Elevated serum YKL-40 correlates with clinical characteristics in patients with polymyositis or dermatomyositis. *Ann Clin Biochem*. 2019;56:95-99.
- Jiang L, Wang Y, Peng Q, Shu X, Wang G, Wu X. Serum YKL-40 level is associated with severity of interstitial lung disease and poor prognosis in dermatomyositis with anti-MDA5 antibody. *Clin Rheumatol*. 2019;38:1655-1663.
- Hozumi H, Fujisawa T, Enomoto N, et al. Clinical utility of YKL-40 in polymyositis/dermatomyositis-associated interstitial lung disease. *J Rheumatol*. 2017;44:1394-1401.
- Chai KX, Chen YQ, Fan PL, Yang J, Yuan X. STROBE: the correlation of Cyr61, CTGF, and VEGF with polymyositis/dermatomyositis. *Medicine (Baltimore)*. 2018;97:e11775.
- Moher D, Liberati A, Tetzlaff J, Altman DG, For the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
- Sultan SM, Allen E, Oddis CV, et al. Reliability and validity of the myositis disease activity assessment tool. *Arthritis Rheum*. 2008;58:3593-3599.
- Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8:2-10.
- Li L, Wang Q, Yang F, et al. Anti-MDA5 antibody as a potential diagnostic and prognostic biomarker in patients with dermatomyositis. *Oncotarget*. 2017;8(16):26552-26564.
- Deng Y, Li G, Chang D, Su X. YKL-40 as a novel biomarker in cardio-metabolic disorders and inflammatory diseases. *Clin Chim Acta*. 2020;511:1-31.
- Arain F, Abraitte A, Bogdanova M, et al. YKL-40 (chitinase-3-like protein 1) serum levels in aortic stenosis. *Circ Heart Fail*. 2020;13(10):509-517.
- Sun Y, Shi Z, Liu B, et al. YKL-40 mediates airway remodeling in asthma via activating FAK and MAPK signaling pathway. *Cell Cycle*. 2020;19(11):1-14.
- Allenbach Y, Uzunhan Y, Toquet S, et al. Different phenotypes in dermatomyositis associated with anti-MDA5 antibody: Study of 121 cases. *Neurology*. 2020;95:e70-e78.

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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