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

Beibei Cui
Sichuan University

Yuehong Chen
Sichuan University

Fengming Luo
Sichuan University

Sang Lin
Sichuan University

Huan Liu
Sichuan University

Yupeng Huang
Sichuan University

Yueyuan Zhou
Sichuan University

Yunru Tian
Sichuan University

Geng Yin
Sichuan University

Qibing Xie (✉ xieqibing1971@163.com)
Sichuan University

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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. In the cross-sectional study, a total of 65 DM patients with mean age 47.71 years and 30 healthy controls with mean age 47.73 years were included. Serum YKL-40 level was detected using enzyme-linked immunosorbent assay, and its association with clinical and laboratory parameters was analyzed by Spearman correlation analysis. The diagnostic value of serum YKL-40 in patients with DM was assessed by receiver operating characteristic (ROC) curve analysis. 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 vs 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 4 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.

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 [1]. PM/DM are associated with malignant tumors, pulmonary fibrosis, and cardiac abnormalities, which are risk factors for poor prognosis, as low as 62% [2]. 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 [3-5]. However, the prevalence of currently available traditional or myositis-specific autoantibodies is low, as it ranges from rare prevalence to about 50% in patients [6-8]; furthermore, the currently available disease-specific autoantibodies only cover 70% of patients [7]. 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 [9]. Several studies have investigated the clinical use of YKL-40 in patients with PM/DM [10-13]. 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 [14]. 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 [15].

Materials And Methods

**Methods for cross-sectional study**

**Study population**

Patients with a definite diagnosis of DM on the basis of the EULAR/ACR 2017 classification criteria [8-9,13,14], 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) [16]. Scores ≥ 4 were considered moderate or severe, while scores ≤ 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. In total, and 30 healthy volunteers were enrolled as controls. 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.

**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 intra-assay % coefficient of variation (CV%) and inter-assay CV% were less than 10% and less than 12%, respectively.
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.

**Statistical analysis**

IBM SPSS Statistics version 22.0 and GraphPad Prism version 6.0 were used to analyze and organize the data. 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.

**Methods for systematic review**

**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.

**Search strategy**

Electronic databases of OVID Medline, OVID EMBASE, and Web of science were searched on July 26, 2021, without language limitation and using both Mesh terms and keywords. Search terms were “polymyositis,” “dermatomyositis,” “myositis,” “chitinase-3-like-1 protein.” The detailed search strategy can be found in the supplementary document. Reference lists of included studies were manually checked to identify the potentially eligible studies.

**Study selection**

Studies went through two-step screening. In the first step, studies were screened by titles and abstracts. After excluding the irrelevant studies, the remaining studies with full-texts underwent the second round of screening based on study selection criteria. Microsoft Office Access 2013 was used to manage study selection. Reference lists were manually checked. Two reviewers independently conducted the study screening. Any disagreement was resolved via discussion or adjudication by a third reviewer if necessary.

**Data extraction**

Two authors independently collected data on the family name of the first author, year of publication, disease condition of patients, number of patients and controls, age, diagnostic criteria of patients, serum level of YKL-40, diagnostic value of YKL-40, correlation with clinical characteristics. Any disagreement on data extraction was resolved via discussion or adjudication by a third reviewer if necessary.

**Methodological quality assessment**

All included studies were cross-sectional studies. Therefore, the agency for healthcare research and quality (ARHQ) assessment tool was used to assess the methodological quality of included studies [1724]. ARHQ includes 11 items. For each item, “yes,” “no,” and “unclear” can be used to judge whether the item is correctly used and described. The quality of all included studies was judged on the basis of overall quality assessment results. Methodological quality assessment was independently performed by two authors, any disagreement was resolved via discussion or adjudication by a third reviewer if necessary.

**Data processing**

We intended to pool data from different studies with the same study objectives and measures. However, several studies were included with inconsistent research objectives and different subgroup populations. Therefore, we systematically reviewed the results of included studies instead of synthesizing extracted data.

**Results**

**Results for cross-sectional study**

**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 fluimucil (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.

### Table 1

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

### 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 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) (Fig. 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 vs 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 (Fig. 2B-C).

### Effect of anti-MDA5 antibodies on serum YKL-40 level

Previously published studies have reported that the presence of anti-melanoma differentiation-associated gene 5 (MDA5) body was associated with poor prognosis in patients with DM [1825]. Therefore, we analyzed the serum YKL-40 level in patients with DM based on the presence or absence of anti-MDA5 antibodies. Results showed that in patients with DM, those who presented with anti-MDA5 antibodies 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 antibodies.

### 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 Supplemental Table 2. 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 (Supplemental Table 3). 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 =
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 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 (Fig. 3).

Results For Systematic Review

Baseline characteristics

A total of 31 studies were found from electronic databases. After excluding irrelevant studies, 4 studies were included in our systematic review [10–13], and by adding our study results, a total of 5 studies reported the clinical value of YKL-40 in patients with PM/DM (Fig. 1). 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 [10]. 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 (Supplemental Table 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>number of participants</th>
<th>Age (years)</th>
<th>Serum level of YKL-40 (ng/mL)</th>
<th>Diagnostic value of serum YKL-40</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Our study 2021</td>
<td>China</td>
<td>DM: 65</td>
<td>30</td>
<td>47.71 ± 10.88</td>
<td>47.73 ± 7.64</td>
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<tr>
<td></td>
<td></td>
<td>control</td>
<td>PM/DM</td>
<td>84.09 (52.72–176.4)</td>
<td>27.37 (12.30–53.58)</td>
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<tr>
<td></td>
<td></td>
<td>DM</td>
<td>40.71</td>
<td>0.7</td>
<td>0.844</td>
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<td></td>
<td></td>
<td>control</td>
<td>PM/DM</td>
<td>0.84</td>
<td>0.835, 95% CI (0.751–0.920)</td>
</tr>
<tr>
<td>Carboni 2021</td>
<td>Brazil</td>
<td>antisynthetase syndrome: 64</td>
<td>64</td>
<td>44.8 ± 11.8</td>
<td>42.6 ± 10.4</td>
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<td></td>
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<td>control</td>
<td>PM/DM</td>
<td>0.54 (0.36–0.85)</td>
<td>0.27 (0.20–0.45)</td>
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<tr>
<td></td>
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<td>None</td>
<td>PM/DM</td>
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<td></td>
<td></td>
<td>None</td>
<td>PM/DM</td>
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<td>None</td>
</tr>
<tr>
<td>Gao 2019</td>
<td>China</td>
<td>PM: 58, DM: 41</td>
<td>87</td>
<td>62 (51, 69) median (quartile)</td>
<td>51.6 (36.4–63.8)</td>
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<tr>
<td></td>
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<td>PM/DM</td>
<td>27.8 (22.6–35.0)</td>
<td>ILD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DM</td>
<td>55.9</td>
<td>0.91, 95% CI (0.72–0.99)</td>
<td>0.72, 95% CI (0.61–0.82)</td>
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<td></td>
<td></td>
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<td>PM/DM</td>
<td>None</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td>None</td>
<td>PM/DM</td>
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<td>None</td>
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<tr>
<td>Jiang 2019</td>
<td>China</td>
<td>MDA5 + DM: 105</td>
<td>44</td>
<td>47.5 ± 12.1</td>
<td>45.6 ± 12.1</td>
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<tr>
<td></td>
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<td>PM/DM</td>
<td>48.75 (27.30–89.23)</td>
<td>14.94 (10.49–22.22)</td>
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<tr>
<td></td>
<td></td>
<td>DM</td>
<td>50.0</td>
<td>0.51</td>
<td>0.83</td>
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<td></td>
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<td>PM/DM</td>
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<td></td>
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<td>PM/DM</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>number of participants</th>
<th>Age (years)</th>
<th>Serum level of YKL-40 (ng/mL)</th>
<th>Diagnostic value of serum YKL-40</th>
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<tr>
<td>PM/DM control</td>
<td>PM/DM control</td>
<td>PM/DM control</td>
<td>Identifying</td>
<td>cutoff</td>
<td>sensitivity</td>
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<tr>
<td>death within 6 months from admission</td>
<td>death within 2 years from diagnosis</td>
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<tr>
<td>PM/DM</td>
<td>control</td>
<td>PM/DM</td>
<td>control</td>
<td>PM/DM</td>
<td>control</td>
</tr>
<tr>
<td>Hozumi 2017 [13]</td>
<td>Japan</td>
<td>PM/DM-ILD: 69</td>
<td>34</td>
<td>53 (32–77)</td>
<td>53 (27–71)</td>
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<tr>
<td>death within 2 years from diagnosis</td>
<td>105</td>
<td>0.75</td>
<td>0.83</td>
<td>0.78</td>
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</tr>
</tbody>
</table>

**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 ng/mL to 84 ng/mL, which was higher than that in the controls, which varied from 0.27 ng/mL to 27.8 ng/mL (Table 2).

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

Results of the systematic review reported that serum YKL-40 was associated with TNFα 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 ($r = 0.33, p < 0.01$), PaO₂ ($r = 0.40, p < 0.001$), and %DLCO ($r = 0.41, p = 0.01$) (Table 2).

**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).

### Table 3

Spearman correlations ($r$) between serum levels of YKL-40 and disease activity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Sample size</th>
<th>$r$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional disease activity</td>
<td>64</td>
<td>0.503</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cutaneous disease activity</td>
<td>64</td>
<td>0.509</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Skeletal disease activity</td>
<td>64</td>
<td>0.078</td>
<td>0.539</td>
</tr>
<tr>
<td>Gastrointestinal disease activity</td>
<td>64</td>
<td>0.381</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulmonary disease activity</td>
<td>64</td>
<td>0.095</td>
<td>0.457</td>
</tr>
<tr>
<td>Cardiovascular disease activity</td>
<td>64</td>
<td>0.329</td>
<td>0.008</td>
</tr>
<tr>
<td>Muscle disease activity</td>
<td>64</td>
<td>0.425</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Global disease activity</td>
<td>64</td>
<td>0.628</td>
<td>&lt; 0.001</td>
</tr>
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</table>

Bold font of numbers indicate statistic significant.

### Discussion

#### 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 TNFα 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.
Higher serum YKL-40 level (> 80 ng/mL) was related to a lower survival rate as compared to low serum YKL-40 level (≤ 80 ng/ml) (67% vs 89%, p < 0.01) [12]. When the cutoff was at 105 ng/mL, a higher YKL-40 level was associated with a lower 5-year survival rate than the lower YKL-40 level (41.6% vs 93.6%, p < 0.001) [13]. The association of serum YKL-40 level with survival rate may be explained by the fact that YKL-40 is associated with ILD which is a risk factor for poor prognosis, especially RPLILD, and a major cause of death in clinically amyopathic DM patients within 6 months [19]. Similarly, Jiang et al. reported that the serum level of YKL-40 in DM patients with RP-ILD was higher than that in patients without RP-ILD (non RP-ILD) (80.3 [28.7–107.7] vs 42.4 [26.6–73.1] ng/mL, p = 0.011) [12].

Our study reported serum level of YKL-40 was associated with disease activities, including 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), and muscle disease activity (r = 0.425, p < 0.001), and was related to several laboratory indicators, such as CRP (r = 0.303, p = 0.043), CK (r = 0.263, p = 0.037), LDH (r = 0.460, p < 0.001), and HBDH (r = 0.435, p < 0.001), which were consistent with the reports by Gao 2019, Jiang 2019, and Hozumi et al. that YKL-40 had relationships with 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), KL-6 (r = 0.33, p < 0.01), and ferritin (r = 0.61, p < 0.01; r = 0.46, p < 0.001) [11–13]. However, this is not confirmed by the results reported by Carboni 2021 et al. [10]. These 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 antibody was lower than that in the absence of the anti-MAD5 antibodies (76.15 ng/mL vs 118.84 ng/mL, p = 0.0449) and the presence of ILD did not have an effect on the serum levels of YKL-40 (84.09 ng/mL vs 85.24 ng/mL, p = 0.97). This could be explained by the fact that the sample size was small, and the study population was from a different medical center. Moreover, we only enrolled patients with DM, which is a microvasculopathy. As YKL-40 is involved in angiogenesis, the markedly increased YKL-40 level in the presence of severe skin lesions might cover the slightly elevated YKL-40 level due to ILD, as demonstrated by the severity of skin lesions affecting the serum level of YKL-40. Furthermore, this was a cross-sectional study in which all patients were alive and there was no follow-up. Thus, the alive DM-ILD patients who had lower YKL-40 levels might mostly be the subtypes of rheumatoid and vasculopathic clusters, rather than the RP-ILD pattern [20].

**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.

**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. YKL-40 can possibly be used to identify ILD in patients with PM/DM and RPLILD in MDA5+DM and to predict poor prognosis, highlighting its clinical importance. Owing to the limited study population and study number, more participants are needed to confirm the findings.

**Declarations**

**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. 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 drifted and revised the manuscript.

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None.

**Ethics 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.

### Availability of data and material

All data are presented in tables or can be found in supplementary documents.

### Code availability

Not applicable.

### Study registration

The systematic review was registered in PROSPERO (CRD42021270316).

### References

Figure 1
Study selection flow chart.

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.

Supplementary Files

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