The diagnostic value of serum YKL-40 for myocardial involvement in immune-mediated necrotising myopathy

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Abstract

Objective

This study aimed to determine the diagnostic value of YKL-40 for myocardial involvement in immune-mediated necrotising myopathy (IMNM).

Methods

We retrospectively analysed the data of patients with IMNM admitted to the Neurology Department at Tongji Hospital between April 2013 and August 2022. Clinical data including patients' demographics, clinical characteristics (disease duration, muscle strength, atrophy, rash, dysphagia, dyspnoea, and myalgia) and laboratory test results were collected from the electronic medical record system. Serum YKL-40 levels were measured using an enzyme-linked immunosorbent assay. A receiver operating characteristic (ROC) curve was drawn, and the area under the ROC curve was calculated to evaluate the diagnostic value of YKL-40 for cardiac involvement in IMNM.

Results

29 patients with IMNM and15 sex and age-matched volunteers without history of heart diseases were recruited for the study. Compared with the healthy controls, serum YKL-40 levels were notably up-regulated [96.3 (55.5 120.6) pg/ml vs. 19.6 (13.8 20.9) pg/ml; p=0.000] in patients with IMNM. We compared 14 patients with IMNM with cardiac abnormalities and 15 patients with IMNM without cardiac abnormalities. The most important finding was that serum YKL-40 levels were higher in the patients with IMNM with cardiac involvement based on cardiac magnetic resonance (CMR) examination [119.2 (88.4 185.69) pm/ml vs. 72.5 (35.7 98) pm/ml; p=0.002]. YKL-40 had a specificity and sensitivity of 86.7% and 71.4% respectively, at a cut-off value of 105.46 pg/ml for predicting myocardial injury in patients with IMNM.

Conclusion

YKL-40 could be a promising non-invasive biomarker for diagnosing myocardial involvement in IMNM. However, larger prospective study is warranted.

Key words

immune-mediated necrotising myopathy, myocardial involvement, YKL-40, myocardial markers

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Introduction

Immune-mediated necrotising myopathy (IMNM) is an important subtype of idiopathic inflammatory myopathies (IIMs). IMNM is clinically featured by acute or subacute proximal weakness and highly elevated creatine kinase (CK) values and histologically defined primarily by necrosis, regeneration and degenerative muscle fibres with rarely inflammatory infiltration (1, 2). It was subcategorised into three subgroups according to positive myositis-specific antibodies (MSAs) against IMNM: anti-signal recognition particle (SRP), anti 3-hydroxy-3-methylgluaryl-coenzyme A reductase (HMGCR), and seronegative (3, 4) IMNM. IMNM is characterised by severe proximal muscle weakness and is associated with severe cardiorespiratory events (5, 6). Cardiac involvement has been reported as one of the most leading causes of mortality in certain patients with IIM, with a 9-72% prevalence of cardiac abnormality (6, 7). Meanwhile, cardiac dysfunction was commonly listed as an extra-muscular symptoms in patients with IMNM (8). However, retrospective studies are rare, and the diagnostic method of cardiac dysfunction in patients with IMNM is not fully elucidated.

Although endomyocardial biopsy is the gold standard for definitive diagnosis of cardiac diseases, its clinical usefulness is not high, as it is an invasive examination. Electrocardiography (ECG) and echocardiography (Echo) are commonly used as non-invasive methods for assessing heart function. However, the diagnostic accuracy of these modalities is insufficient, particularly for detecting subclinical cardiac abnormalities. Cardiac magnetic resonance (CMR) could provide more details of cardiac tissue characteristics and function abnormalities (myocardial inflammation and fibrosis) (9). However, some patients cannot tolerate this non-invasive examination due to serious complications. Elevated serum troponin levels were found to be less sensitive biomarker for detecting cardiac dysfunction (10). Consequently, it is necessary to establish new biomarkers for assessing the diagnostic myocardial abnormalities due to IMNM.

YKL-40 also known as chitinase-3-like-1 protein, is a 40kDa heparin- and chitin-binding glycoprotein (11) produced by a variety of cells, such as macrophages, vascular smooth muscle cells, fibroblast-like cells, neutrophils and endothelial cells (12). YKL-40 participates in the activation of the innate immune system and tissue repair and remodelling, such as the Th1/Th2 inflammatory balance and macrophage differentiation (13). Previous studies have shown that high YKL-40 serum levels have been detected in patients with systemic autoimmune diseases (14), including inflammatory myopathies (15), rheumatoid arthritis (16), and systemic sclerosis (17) and could be a quantitative biomarker for disease presence and determining prognosis in patients with systemic autoimmune myopathies. In addition, YKL-40 has been found to be strongly associated with cardiovascular diseases, such as permanent atrial fibrillation (AF) (18), chronic heart failure (19), myocardial infarction (MI) and coronary artery disease (CAD) (20), correlating with severity of disease activity.

We hypothesized that YKL-40 could participate in the pathophysiology of cardiac dysfunction in patients with IMNM. Thus, we aimed to identify whether serum YKL-40 could serve as a diagnostic biomarker for myocardial involvement in IMNM.

Matieral and methods

Patients' selection and controls

All patients were enrolled in the study from the Department of Neurology at Tongji Hospital between April 2013 and August 2022. The diagnosis of IMNM was based on the criteria of the European Neuromuscular Centre International Workshop on Idiopathic Inflammatory Myopathies (3). The exclusion criteria were: (i) infection-, drug-, or toxin-induced myopathies (n=8); (ii) severe coronary artery disease (n=2); and (iii) insufficient clinical data (n=2) (data shown in Fig. 1).

Finally, 29 patients with IMNM and 15 sex and age-matched volunteers without history of heart diseases were recruited for the study. 29 patients with IMNM underwent CMR examinations.

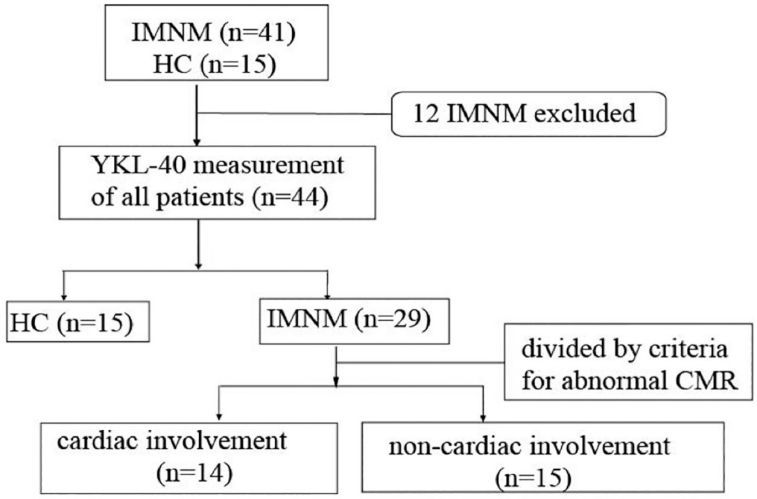

Fig. 1. Study flow of the clinical research.
IMNM: immune-mediated necrotising myopathy; HC: healthy control; YKL-40: chitinase-3-like-1 protein; CMR: cardiac magnetic resonance.

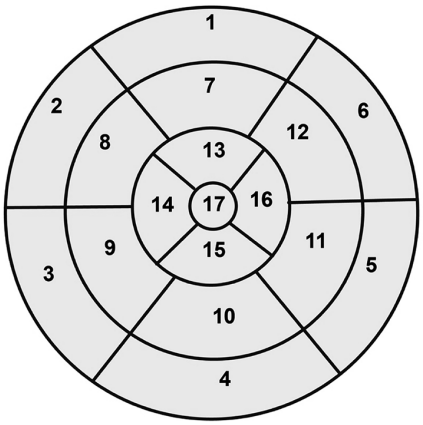

Fig. 2. American Heart Association (AHA) 17-segment model.

29 patients with IMNM were divided into two groups based on meeting the criteria for abnormal CMR (21): cardiac involvement (n=14) and non-cardiac involvement (n=15). We compared serum YKL-40 level between patients with IMNM and healthy controls and between IMNM patients with and without cardiac involvement.

Clinical data, including patients' demographic, clinical characteristics (including disease duration, muscle strength, atrophy, rash, dysphagia, dyspnoea, myalgia) and laboratory result, were collected from electronic medical record system.

Sera from all patients were tested for rheumatoid-related factors, MSAs and myositis- associated antibodies (MAAs). The rheumatoid-related factors were assayed at Tongji Hospital Laboratory, including anti-nuclear, anti-SSA/Ro60, anti-SSB/La, anti-Sm, anti-RNP, anti-mitochondrial, anti-ds-DNA antibodies. The following MSAs and MAAs were estimated using two commercial semi-quantitative line blot assays (D-Tek, Germany; Euroline, Germany): anti-SRP, anti-HMGCR, anti-Ro52, anti-Mi2α and β, anti-TIF1γ, anti-MDA5, anti-NXP2, anti-SAE1, anti-Jo1, anti-PL7, anti-PL12, anti-Ku, anti-EJ, anti-OJ, anti-cN-1A, anti-PM-Scl100 and anti-PMScl75 antibodies.

The study was approved by the Ethics Committee of Tongji Hospital (IRB ID: TJ-C20121221). All experiments were conducted in accordance with the Declaration of Helsinki and all patients provided written informed consents.

Cardiac magnetic resonance

The patients underwent cardiac magnetic resonance (CMR) imaging using on a 3-T scanner (MAGNETOM Skyra) with commercially available cardiac software, electrocardiographic triggering, and cardiac-dedicated surface coils. Late gadolinium enhancement (LGE) images were acquired 15 min after intravenous administration of gadopentetatedimeglumine (0.15 mmol/kg) in the same imaging planes by a T1-weighted inversion recovery gradient-echo sequence {repetition time (TR), 4.0ms; echo time (TE), 1.1ms; trigger delay (TD), 300ms; slice thickness (SL), 8 mm; gap, 0 mm; flip angle (FA), 20°; field of view (FOV), 48cm×38cm; and matrix, 256×192} as the cine-images. Cine-imaging was acquired using a balanced steady-state-free-procession sequence and a stack of short-axis slices completely covering the left ventricle (LV).

Ventricular volumes, ejection fraction and LV mass were derived by contouring the endo and epicardia borders on the short-axis cine images and indexed to the body surface area, which were measured by two experienced blinded diagnostic radiologists. Criteria for abnormal CMR were defined as either one of the following: (i) a LV ejection fraction (EF) <60%, and/or (ii) the presence of unexplained LV hypertrophy, and/or (iii) LGE presence in at least one myocardial segment (21).

We assessed LGE location using the 17-segment model according to the American Heart Association (22). This 17-segment model separated the left ventricular wall into three regions from the apex to base. Each region was further subdivided collectively into 16 total segments. The final 17th segment was placed at the true apex (Fig. 2).

Measurement of serum YKL-40 levels

Serum samples were obtained from the patients with IMNM (n=29) and healthy controls (n=15). The blood samples of all patients were collected in EDTA tubes during hospitalisation as well as other clinical information. After centrifugation at room temperature at 3000 rpm for 10min, the serum was isolated and stored at -40°C until analysis. Serum YKL-40 was measured by enzyme-linked immunosorbent assay (Human YKL-40 ELISA Kit, BOSTER, EK0974), according to the manufacturer's protocol. The assay range and sensitivity were 62.5–4000 pg/ml and 10 pg/ ml, respectively. Serum samples were tested in duplicates.

Statistical analysis

All analyses were performed using SPSS version 23.0.and figures were generated using the GraphPad PRISM software version 9.0 (Graph Pad Software Inc., San Diego, CA, USA, 2020). Categorical and continuous variables were ex-

pressed as frequencies and percentages respectively. Student's t-test and Mann-Whitney U-test were performed for continuous variable comparisons between patient and control parameters. Fisher's exact test or chi-square test was used for categorical variables. Spearman's or Pearson's correlation were used to identify all correlations. The diagnostic accuracy was calculated using a receiver operating characteristic (ROC) curve. A *p*-value less than 0.05 indicated statistical significance.

Results

Patient clinical characteristics

The demographic data and characteristics of patients with IMNM and healthy controls are summarised in Table I. A total of 29 patients with IMNM and 15 healthy volunteers were enrolled in this study. Both groups consisted a predominantly of females (65.5% *vs*. 60%, *p*=0.751). The median ages of the 29 patients with IMNM and 15 control individuals were 50 (38 58.5) and 42 (39 48) years, respectively (*p*=0.092). The median disease duration of IMNM was 5.5 (2 11.25) years.

Table I. Demographic data and baseline characteristics of patients with IMNM and healthy controls.

	IMNM (n=29)	HC (n=15)	*p*-value
Demographics			
Female, n (%)	19 (65.5)	9 (60)	0.751
Age, years, range	50 (38 58.5)	42 (39 48)	0.092
Disease duration, months	5.5 (2 11.25)		
Clinical manifestation			
Muscle strength			
Upper proximal limbs weakness (≤3, MRC)	11 (37.9)		
Upper distal limbs weakness (≤3, MRC)	3 (10.3)		
Lower proximal limbs weakness (≤3, MRC)	15 (51.7)		
Lower distal limbs weakness (≤3, MRC)	5 (17.2)		
Dysphagia	7 (24.1)		
Dyspnoea	2 (6.9)		
Myalgia	9 (31)		
Atrophy	9 (31)		
Rash	3 (10.3)		
YKL-40 (pg/mL)	96.3 (55.5 120.6)	19.6 (13.8 20.9)	**0.000****
Autoantibody profile			
SRP	11 (35.5)		
HMGCR	3 (10.3)		
Negative	9 (31)		
SS-A	9 (31)		
SS-B	1 (3.4)		
Mi-2	3 (10.3)		
PM-scl100	1 (3.2)		
PM-scl75	1 (3.4)		
PM-scl70	1 (3.4)		
Jo-1	1 (3.4)		
PL-12	1 (3.4)		
PL-7	1 (3.4)		

YKL-40: chitinase-3-like-1 protein; SRP: anti-signal recognition particle; HMGCR: anti 3-hydroxy-3-methylgluaryl-coenzyme A reductase.

Serum YKL-40 levels were significantly elevated in patients with IMNM

Serum YKL-40 level in patients with IMNM were significantly higher than those in healthy controls [96.3 (55.5 120.6) pg/ml *vs*. 19.6 (13.8 20.9) pg/ml; *p*=0.000] (data shown in Table I and Fig. 3). There was no correlation between serum YKL-40 levels and the clinical parameters (Supplementary Fig. S1).

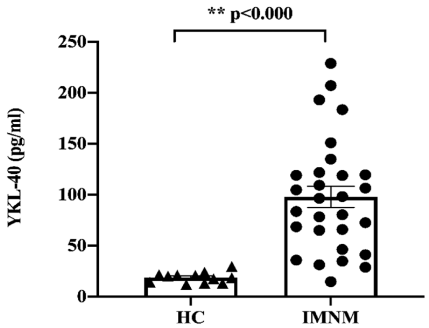

Fig. 3. Comparison of YKL-40 levels in healthy controls and patients with IMNM.
YKL-40: chitinase-3-like-1 protein; IMNM: immune-mediated necrotising myopathy

The clinical characteristics and YKL-40 levels of 29 patients with IMNM with and without cardiac involvement

To further explore serum YKL-40 expression in patients with IMNM with cardiac involvements, the patients with IMNM were divided into groups with and without cardiac involvement based on CMR examination. The clinical characteristics of 29 patients with IMNM are shown in Table II. Notably, serum YKL-40 levels [119.2 (88.4 185.69) pm/ml *vs*. 72.5 (35.798) pm/ml; *p*=0.002] (Fig. 4) and creatinine levels [39.5 (28.75 45.75) umol/L *vs*. 57 (38 61) umol/L; *p*=0.033] in patients with IMNM with cardiac involvement were significantly increased compared with those without cardiac involvement. In addition, serum myoglobin level [999 (252 1201) ng/ml *vs*. 129.8 (38.5 883.75) ng/ml; *p*=0.069], serum LDH levels [727 (403 1064) U/l *vs*. 285 (206 631.5) U/l; *p*=0.057] tended to have higher levels in patients with IMNM with cardiac involvement. No significant differences in demographic characteristics, disease duration, or other clinical indicators were found between the two groups.

Fourteen patients (48.2%, 14/29) exhibited varying degrees of cardiac involvement. All patients underwent, wherein 4 (28.6%) patients were found to have arrhythmia, including bradycardia, sinus tachycardia, conduction block, and premature atrial beats. 3 (21.4%) patients had acute coronary syndrome (ST elevation). Eight patients underwent cardiac echocardiography that detected atrial enlargement and decreased left ventricular ejection fraction in 2 (25%) and 3 (37.5%) patients, respectively. 2 (25%) patients showed ascending aortic enlargement. In addition, one patient showed pericardial effusion. All patients underwent cardiac MRI, 8 patients showed LGE abnormality sig-

Table II. The characteristics and YKL-40 of patients with IMNM between cardiac involvement and non-cardiac involvement.

Items	Cardiac involvement (n=14)	Non-cardiac involvement (n=15)	*p*-value
Demographics			
Sex(Female)	10 (71.4)	9 (60)	0.7
Age at myositis diagnosis(years)	48.5 (39.5 58.8)	54 (31 59)	0.72
Disease duration (months)	5 (2 16.5)	6 (2 12)	0.856
Clinical manifestation			
Upper proximal limbs weakness (≤3, MRC)	6 (42.9)	5 (33.3)	0.71
Upper distal limbs weakness (≤3, MRC)	2 (14.3)	1 (6.67)	0.598
Lower proximal limbs weakness (≤3, MRC)	6 (42.9)	9 (60)	0.466
Lower distal limbs weakness (≤3, MRC)	1 (7.1)	4 (26.7)	0.33
Dysphagia	5 (35.7)	2 (13.3)	0.215
Dyspnoea	2 (14.3)	0	0.224
Myalgia	4 (28.6)	5 (33.3)	>0.999
Atrophy	6 (42.9)	3 (20)	0.245
Rash	3 (21.4)	0	>0.999
Thyroid dysfunction	6 (42.9)	7 (46.7)	>0.999
ANA abnormality	9 (62.9)	10 (66.7)	0.696
Laboratory examinations			
CK (U/l)	2179 (633.7 5487)	549 (108 5283)	0.19
LDH (U/l)	727 (403 1064)	285 (206 631.5)	0.057
ESR (mm/H)	25.5 (6 29.25)	14.5 (5.75 30.75)	0.568
hsCRP (mg/L)	4 (1.7 10.7)	2.2 (0.9 3.85)	0.356
NI-PRO-BNP (pg/ml)	180 (51.8 383.8)	133 (85 393)	0.419
Alb (g/L)	37 (29 40.65)	37.9 (33.5 42.5)	0.809
Glb (g/L)	30.7 (2738.6)	30.4 (25.25 36.7)	0.774
cTnI (pg/ml)	17.75 (1.8 77.63)	6.3 (1.9 16)	0.263
CK-MB (ng/ml)	96.35 (33 202.2)	9.1 (3.2 175)	0.141
Myoglobin (ng/ml)	999 (252 1201)	129.8 (38.5 883.75)	0.069
GLU (mmol/L)	4.69 (4.14 5.51)	4.86 (4.555.21)	0.467
HbA1c (%)	5.6 (5.35 5.7)	5.5 (5.15 5.65)	0.462
ALT (U/l)	100 (34.25 165.25)	29 (12 134)	0.123
AST (U/l)	85 (31.25 161)	35 (20 109)	0.233
Cr (umol/L)	39.5 (28.75 45.75)	57 (38 61)	**0.033***
eGFR ((mL/min/1.73m^2)	114.6 (87.4 132.3)	99.4 (95.13 124.6)	0.781
C4 (g/L)	0.17 (0.16 0.22)	0.21 (0.16 0.24)	0.38
C3 (g/L)	0.81 (0.69 0.9)	0.91 (0.86 0.98)	0.08
IgA (g/L)	1.96 (1.4 3.18)	2.13 (1.9 2.71)	0.894
IgG (g/L)	13.3 (10.85 16.2)	11.95 (11.4 14.63)	0.873
IgM (g/L)	1.16 (0.78 1.73)	1.13 (0.99 1.88)	0.628
YKL-40 (pg/mL)	119.2 (88.4 185.69)	72.5 (35.7 98)	**0.002***
WBC	7.25 (5.34 11.42)	6.03 (4.65 7.36)	0.34
Neutro	3.82 (2.86 8.24)	3.93 (2.85 .49)	0.381
Lym	2.2 (1.59 2.54)	2.11 (1.01 2.28)	0.614
MSA positive			
anti-SRP	6 (42.9)	4 (26.7)	0.44
Negative	4 (28.6)	5 (33.3)	>0.999
anti-HMGCR	0 (0)	3 (20)	0.222
anti-Mi-2	1 (7.14)	2 (13.3)	>0.999
anti-ARS	1 (7.14)	1 (6.7)	>0.999
anti-PM-Scl70	1 (7.14)	0 (0)	0.481
anti-PM-Scl75	0 (0)	1 (6.7)	>0.999
anti-PM-Scl100	1 (7.14)	0 (0)	0.481
MAA positve			
anti-SSA	6 (42.9)	4 (26.7)	0.44
anti-SSB	1 (7.14)	0 (0)	0.481
Electrocardiogram			
PR interval (ms)	152 (141.5 160)	144 (132 156)	0.331
QRS interval (ms)	86 (80 93)	92 (78 100)	0.747
QTc (ms)	427.5 (416.3 434.3)	413 (399.2 432.8)	0.454
ST change,	3 (21.4)	1 (6.67)	0.33
Echocardiogram			
Left ventricular dysfunction	5 (35.7)	1 (6.7)	0.08
Other echo abnormality	2 (14.3)	1 (6.7)	0.224
CMR			
LAD (mm)	29 (26.8 31.5)	29.5 (28 37.5)	0.297
LVDd (mm)	48 (43.8 50)	44.5 (42 48)	0.118
LVDs (mm)	33 (29 39)	33.5 (28.5 43.8)	0.841
EF (%)	61.5 (51.3 70)	68 (65 71)	0.134
CMR abnormality (LVEF< 60%, and/or the presence of unexplained LV hypertrophy)	7 (50)	0 (0)	**0.002***
LGE	8 (61.5)	0 (0)	**0.029***
ILD	4 (28.6)	4 (26.7)	>0.999

YKL-40: chitinase-3-like-1 protein; MSA: myositis special antibody; ANA: anti-nuclear antibody; SRP: anti-signal recognition particle; HMGCR: anti 3-hydroxy-3-methylgluaryl-coenzyme A reductase; eGFR: estimated glomerular filtration rate; ILD: interstitial lung disease; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; CMR: cardiac magnetic resonance; ECG: electrocardiogram.

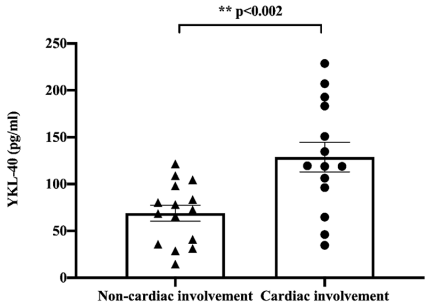

Fig. 4. Comparison of YKL-40 levels in patients with IMNM with and without cardiac involvement.
YKL-40: chitinase-3-like-1 protein.

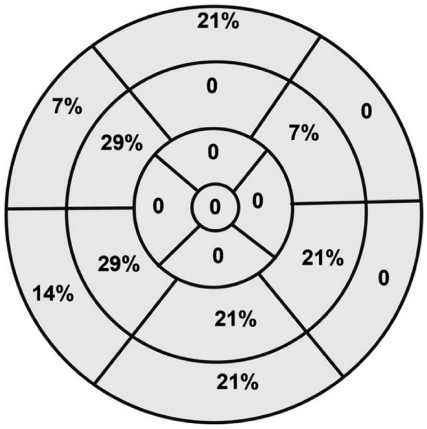

Fig. 5. Bull's eye plots demonstrate LGE distribution in the LV using the 17-segment model in patients with IMNM with cardiac involvement.

nals. Furthermore, 7 patients showed LVEF< 60% and/or the presence of unexplained LV hypertrophy (Table II and Fig. 5).

YKL-40 as an indicator of myocardial involvement in patients with IMNM

The clinical diagnostic value of serum YKL-40 for predicting myocardial involvement calculated by ROC Curve. The area under the ROC curve for YKL-40 in detecting myocardial involvement was 0.805. The cut-off value for YKL-40 was 105.46 pg/ml (Fig. 6). In addition, the AUC of cTnI for ROC curve analysis was relatively small (AUC 0.602), indicating that it may not accurately predict myocardial involvement.

Multi-variate logistic regression analysis showed that serum YKL-40 levels were independently associated with myocardial involvement in IMNM. The risk of myocardial injury in patients

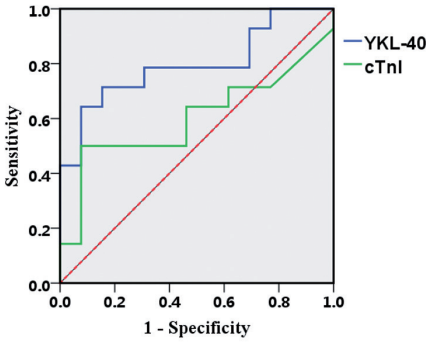

Fig. 6. ROC curve of serum YKL-40, cTnI in identifying myocardial injury of patients with IMNM.

Table III. Multivariate logistic regression analysis of patients with IMNM with myocardial injury.

Variables	β	SE	Wals	*p*	OR	95% Cl for Exp	
						Lower	Upper
Age	-0.034	0.039	0.743	0.389	0.967	0.895	1.044
Cr	-0.041	0.034	1.409	0.235	0.96	0.897	1.027
YKL-40	0.034	0.015	5.241	0.022	1.034	1.005	1.065

Cr: creatinine; YKL-40: chitinase-3-like-1 protein.

with IMNM was raised at average of 3.4% per increased unit of YKL-40 (OR = 1.034, 95% CI 1.005–1.065, Table III).

Discussion

To the best of our knowledge, this is the first study demonstrating the relevance of YKL-40 in patients with IMNM. In this study, serum YKL-40 levels were notably up-regulated in patients with IMNM compared with healthy controls. The most important finding was that serum YKL-40 levels were higher in patients with IMNM with cardiac involvement, based on the CMR examination. YKL-40 is a putative independent risk factor for IMNM with cardiac involvement. Therefore, YKL-40 may be a potential diagnostic biomarker for cardiac involvements in IMNM.

Cardiac involvement in patients with IIMs is a serious event because it is one of the most common causes of patient death (6). Our research team reported that patients with IMNM with dual-positive anti-SRP and MDA-5 achieved symptomatic relief with prednisone and tacrolimus only after the cardiac transplantation (23). Retrospective studies of cardiac involvement in IMNM were fewer than those of IIMs. In addition, previous retrospective or perspective studies have rarely reported their diagnostic methods. Manifestations of cardiac involvement in patients with IMNM were arrhythmia, myocardial ischaemia, myocardial infarction, left ventricular hypertrophy, decreased left ventricular diastolic function, decreased systolic function (decreased left ventricular ejection fraction), pericardial effusion and atrial enlargement (24). In our study, the cardiac involvement ratio and ECG/Echo manifestations of anti-SRP antibody positive (54.5%) and antibody-negative (44.4%) IMNM were quite similar to those of the recent study (24). Currently, CMR examinations are widely performed in patients with myositis and other autoimmune diseases (25, 26). A series case of patients with IMNM confirmed that cardiac involvement diagnosis by CMR was consistent with findings of endocardial biopsy (27, 28), CMR is a valuable and a non-invasive tool that facilitates the diagnosis of myocarditis. Additionally, LGE has been considered the gold standard for detecting irreversible myocardial injury associated with myocardial infarction, including necrosis and fibrosis (9). In our study, the proportion of LGE was 61.5%, which was consistent with previous studies showing the incidence of LGE in 56.3–62.2% of patients with IIMs (29). Images of patients with IMNM with cardiac involvement showed LGE most frequently in the mid-anteroseptal and infero-septal segments, followed by the basal anterior and inferior, mid-inferior and inferolateral sections. However, the LGE areas and patterns of cardiac involvement in patients with IMNMs require further research. Although CMR is a very safe test, there are some contraindications, such as severe respiratory muscle weakness, claustrophobia, presence of metal objects in the body, or sensitivity to sounds. Some patients with cardiac involvement are severely ill, and most are unable to undergo CMR.

Many reviews have demonstrated that YKL-40 was an important autoantigen in patients with autoimmune and rheumatic diseases immunopathology, such as rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and inflammatory bowel disease: correlated with disease severity (14). In our study, significantly greater serum YKL-40 levels were observed in patients with IMNM than in the controls. The most significant finding in this study was that the serum YKL-40 levels were higher in the patients with IMNM with cardiac involvement, which was consistent with that in a previous study (15).

YKL-40 levels increased in patients with coronary artery disease (CAD) and acute myocardial infarction (MI) (20). However, the exact mechanism remains unclear. YKL-40 is expressed and secreted by many cell types, including macrophages, fibroblast-like cells, neutrophils, hepatic stellate cells, endothelial cells, and cancer cells (13). Immune-mediated inflammation leads to the increased production of inflammatory cytokines and increased inflammatory cell infiltration, impairing the normal function of cardiomyocytes and leading to myocardial fibrosis (29). Although the mechanisms involved in this disease are not completely understood, we suggest that the possible mechanism of action of YKL-40 in patients with IMNM with myocardial injury is as follows: firstly, YKL40 was induced by classical activation and inhibited by alternative activation, which regulated Th1 and Th2 differentiation (30). In classically activated macrophages, Th1 cytokines (IFN-γ, TNF) enhanced YKL40 production, while and Th2 cytokines (IL-4 and IL-13) suppressed their production (31). A previous study demonstrated that patients with IMNM could display Th1/classically activated

macrophage M1 derived inflammation mediated immune response with detection of up-regulated IFN-γ (32-34). The presence of anti-SRP and anti-HMGCR Abs in patients with IMNM induced an increase in the production of pro-inflammatory molecules (IL-6, TNF, and ROS), while decreasing the levels of two anti-inflammatory cytokines (IL-4 and IL-13), which inhibited myoblast fusion (35). Based on the above mechanisms, we suggest that up-regulation of Th1 and down-regulation Th2 cytokines in patients with IMNM may augmented serum YKL-40 levels. Secondly, mechanistic studies have demonstrated that YKL-40 protein expression was expressed in injured smooth muscle and skeletal muscle cells (36) (37). A correlation study between heart and muscle pathology research suggested that the myocardium might share many features with the skeletal muscle, which could be affected by the same inflammatory processes during the different forms of IIMs (38). YKL-40 may inhibit Fas expression and induce protein kinase B (PKB)/Akt phosphorylation to achieve a pro-inflammatory effect, activate inflammatory cells, and inhibit the apoptosis/cell death of inflammatory cells (15). Thirdly, in a review study of patients with IIM with cardiac involvement, the manifestations of cardiac tissue was myocardial fibrosis (39). In our previous study, biopsied ventricular tissues showed that disarranged myofibrils, atrophic myofibres with remarkable interstitial fibrosis (23). Previous research has shown that YKL-40 was a novel biomarker for fibrosis in cardiovascular diseases, acting as a key factor in fibroblast proliferation and matrix deposition (20), and related to disease severity. This may be a promising indicator for the degree of cardiovascular diseases fibrosis (40). However, myocardial fibrosis is reversible, and serum YKL-40 may help detect myocardial fibrosis, which plays an important role in prevention and prognostic assessment (41). Serum YKL-40 levels were not correlated with clinical parameters, and we suggest that serum YKL-40 levels might be a qualitative biomarker for predicting cardiac involvement in IMNM but may not reflect the degree of myocardial injury. Therefore, we need to expand the sample size in future studies.

In the present study, YKL-40 was found to have a specificity and sensitivity of 86.7% and 71.4% respectively, at a cut-off value of 105.46 pg/ml for predicting myocardial injury in patients with IMNM. Compared with cTnI, YKL-40 had a higher accuracy in detecting cardiac involvement in IMNM. YKL-40 may aid clinicians in establishing diagnosis and can potentially be used as a gauge therapy.

Although these data are encouraging, there are several limitations to this study. First, the present study had a relatively small sample size from a single clinical centre. Therefore, our findings should be validated through prospective studies with larger number of participants from different clinical centres. In addition, this was a descriptive and observational study, and the complex mechanisms supporting these correlations were not unidentified.

Conclusion

In conclusion, patients with IMNM exhibited higher serum YKL-40 expression, indicating the possible involvement of YKL-40 in IMNM. We found that YKL-40 was promising for detecting cardiac involvements in IMNM with high sensitivity and specificity. YKL-40 was a promising non-invasive biomarker for diagnosing myocardial involvement in IMNM. Further studies are required to confirm these findings.

Take home messages

- Patients with IMNM presented with higher serum YKL-40 level.
- YKL-40 is a promising non-invasive biomarker for diagnosing myocardial involvement in IMNM.

References

1. MA X, XU L, JI S, LI Y, BU B: The clinicopathological distinction between seropositive and seronegative immune-mediated necrotizing myopathy in China. *Front Neurol* 2021; 12: 670784. https://doi.org/10.3389/fneur.2021.670784
2. DOURADO E, BOTTAZZI F, CARDELLI C *et al*.: Idiopathic inflammatory myopathies: one year in review 2022. *Clin Exp Rheumatol* 2023; 41(2): 199-213. https://doi.org/10.55563/clinexprheumatol/jof6qn
3. ALLENBACH Y, MAMMEN AL, BENVENISTE O *et al*.: 224th ENMC International Workshop: Clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. *Neuromuscul Disord* 2018; 28(1): 87-99. https://doi.org/10.1016/j.nmd.2017.09.016
4. RADEMACHER JG, GLAUBITZ S, ZECHEL S *et al*.: Treatment and outcomes in anti-HMG-CoA reductase-associated immune-mediated necrotising myopathy. Comparative analysis of a single-centre cohort and published data. *Clin Exp Rheumatol* 2022; 40(2): 320-8. https://doi.org/10.55563/clinexprheumatol/2ao5ze
5. TANBOON J, URUHA A, STENZEL W, NISHINO I: Where are we moving in the classification of idiopathic inflammatory myopathies? *Curr Opin Neurol* 2020; 33(5): 590-603. https://doi.org/10.1097/wco.0000000000000855
6. JAYAKUMAR D, ZHANG R, WASSERMAN A, ASH J: Cardiac manifestations in idiopathic inflammatory myopathies: an overview. *Cardiol Rev* 2019; 27(3): 131-7. https://doi.org/10.1097/crd.0000000000000241
7. OPINC AH, MAKOWSKI MA, LUKASIK ZM, MAKOWSKA JS: Cardiovascular complications in patients with idiopathic inflammatory myopathies: does heart matter in idiopathic inflammatory myopathies? *Heart Fail Rev* 2021; 26(1): 111-25. https://doi.org/10.1007/s10741-019-09909-8
8. TRIPLETT J, KASSARDJIAN CD, LIEWLUCK T *et al*.: Cardiac and respiratory complications of necrotizing autoimmune myopathy. *Mayo Clin Proc* 2020; 95(10): 2144-9. https://doi.org/10.1016/j.mayocp.2020.03.032
9. FRIEDRICH MG, SECHTEM U, SCHULZ-MENGER J *et al*.: Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. *J Am Coll Cardiol* 2009; 53(17): 1475-87. https://doi.org/10.1016/j.jacc.2009.02.007
10. SUN J, YIN G, XU Y *et al*.: Phenotyping of myocardial involvement by cardiac magnetic resonance in idiopathic inflammatory myopathies. *Eur Radiol* 2021; 31(7): 5077-86. https://doi.org/10.1007/s00330-020-07448-7
11. HAKALA BE, WHITE C, RECKLIES AD: Human cartilage gp-39, a major secretory product of articular chondrocytes and synovial cells, is a mammalian member of a chitinase protein family. *J Biol Chem* 1993; 268(34): 25803-10.
12. HOZUMI H, FUJISAWA T, ENOMOTO N *et al*.: Clinical Utility of YKL-40 in Polymyositis/dermatomyositis-associated interstitial lung disease. *J Rheumatol* 2017; 44(9): 1394-401. https://doi.org/10.3899/jrheum.170373
13. ZHAO T, SU Z, LI Y, ZHANG X, YOU Q: Chitinase-3 like-protein-1 function and its role in diseases. *Signal Transduct Target Ther* 2020; 5(1). https://doi.org/10.1038/s41392-020-00303-7
14. TIZAOUI K, YANG JW, LEE KH *et al*.: The role of YKL-40 in the pathogenesis of autoimmune diseases: a comprehensive review. *Int J Biol Sci* 2022; 18(9): 3731-46. https://doi.org/10.7150/ijbs.67587
15. TANG Y, DU M, QIAN W *et al*.: The diagnostic

value of serum YKL-40 for myocardial involvement in idiopathic inflammatory myopathy. *Clin Chim Acta* 2022; 537: 167-72. https://doi.org/10.1016/j.cca.2022.10.022
16. JOHANSEN JS, STOLTENBERG M, HANSEN M *et al*.: Serum YKL-40 concentrations in patients with rheumatoid arthritis: relation to disease activity. *Rheumatology* 1999; 38(7): 618-26. https://doi.org/10.1093/rheumatology/38.7.618
17. LA MONTAGNA G, D'ANGELO S, VALENTINI G: Cross-sectional evaluation of YKL-40 serum concentrations in patients with systemic sclerosis. Relationship with clinical and serological aspects of disease. *J Rheumatol* 2003; 30(10): 2147-51
18. HENNINGSEN KM, THERKELSEN SK, JOHANSEN JS, BRUUNSGAARD H, SVENDSEN JH: Plasma YKL-40, a new biomarker for atrial fibrillation? *Europace* 2009; 11(8): 1032-6. https://doi.org/10.1093/europace/eup103
19. BILIM O, TAKEISHI Y, KITAHARA T *et al*.: Serum YKL-40 predicts adverse clinical outcomes in patients with chronic heart failure. *J Card Fail* 2010; 16(11): 873-9. https://doi.org/10.1016/j.cardfail.2010.05.029
20. KUCUR M, ISMAN FK, KARADAG B, VURAL VA, TAVSANOGLU S: Serum YKL-40 levels in patients with coronary artery disease. *Coron Artery Dis* 2007; 18(5): 391-6. https://doi.org/10.1097/MCA.0b013e328241d991
21. FLORIAN A, LUDWIG A, STUBBE-DRAEGER B *et al*.: Characteristic cardiac phenotypes are detected by cardiovascular magnetic resonance in patients with different clinical phenotypes and genotypes of mitochondrial myopathy. *J Cardiovasc Magn Reson* 2015; 17(1): 40. https://doi.org/10.1186/s12968-015-0145-x
22. BROWNSTEIN J, AFZAL M, OKABE T *et al*.: Method and atlas to enable targeting for cardiac radioablation employing the american heart association segmented model. *Int J Radiat Oncol Biol Phys* 2021; 111(1): 178-85. https://doi.org/10.1016/j.ijrobp.2021.03.051
23. MA X, XU L, LI Y, BU B: Immunotherapy reversed myopathy but not cardiomyopathy in a necrotizing autoimmune myopathy patient with positive anti-SRP and MDA-5 autoantibodies. *BMC Cardiovasc Disord* 2021; 21(1): 88. https://doi.org/10.1186/s12872-021-01900-2
24. LIU M, LIN Y, QIAO L, CHEN J, SHI Q: Characteristics of cardiac involvement in immune-mediated necrotizing myopathy. *Front Immunol* 2023; 14. https://doi.org/10.3389/fimmu.2023.1094611
25. MAVROGENI SI, KITAS GD, DIMITROULAS T *et al*.: Cardiovascular magnetic resonance in rheumatology: Current status and recommendations for use. *Int J Cardiol* 2016; 217: 135-48. https://doi.org/10.1016/j.ijcard.2016.04.158
26. ROSENBOHM A, BUCKERT D, GERISCHER N *et al*.: Early diagnosis of cardiac involvement in idiopathic inflammatory myopathy by cardiac magnetic resonance tomography. *J Neurol* 2015; 262(4): 949-56. https://doi.org/10.1007/s00415-014-7623-1
27. POLTE CL, BERGH N, OLDFORS A, HANNA B, BOLLANO E: Cardiac involvement in immune-mediated necrotizing myopathy: insights from CMR and somatostatin receptor PET/CT. *Eur Heart J Cardiovasc Imaging* 2022; 23(5): E237. https://doi.org/10.1093/ehjci/jeab262
28. TAKEGUCHI-KIKUCHI S, HAYASAKA T, KATAYAMA T *et al*.: Anti-signal recognition particle antibody-positive necrotizing myopathy with secondary cardiomyopathy: the first myocardial biopsy- and multimodal imaging-proven case. *Intern Med* 2019; 58(21): 3189-94. https://doi.org/10.2169/internalmedicine.2564-18
29. MAVROGENI S, BRATIS K, KARABELA G, STAVROPOULOS E, SFENDOURAKI E, KOLOVOU G: Myocarditis during acute inflammatory myopathies: evaluation using clinical criteria and cardiac magnetic resonance imaging. *Int J Cardiol* 2013; 164(1): e3-4. https://doi.org/10.1016/j.ijcard.2012.09.109
30. BONNEH-BARKAY D, BISSEL SJ, KOFLER J, STARKEY A, WANG G, WILEY CA: Astrocyte and macrophage regulation of YKL-40 expression and cellular response in neuroinflammation. *Brain Pathol* 2012; 22(4): 530-46. https://doi.org/10.1111/j.1750-3639.2011.00550.x
31. KZHYSHKOWSKA J, MAMIDI S, GRATCHEV A *et al*.: Novel stabilin-1 interacting chitinase-like protein (SI-CLP) is up-regulated in alternatively activated macrophages and secreted via lysosomal pathway. *Blood* 2006; 107(8): 3221-8. https://doi.org/10.1182/blood-2005-07-2843
32. PREUSSE C, GOEBEL HH, HELD J *et al*.: Immune-mediated necrotizing myopathy is characterized by a specific Th1-M1 polarized immune profile. *Am J Pathol* 2012; 181(6): 2161-71. https://doi.org/10.1016/j.ajpath.2012.08.033
33. ALLENBACH Y, AROUCHE-DELAPERCHE L, PREUSSE C *et al*.: Necrosis in anti-SRP+ and anti-HMGCR(+)myopathies: role of autoantibodies and complement. *Neurology* 2018; 90(6): E507-E17. https://doi.org/10.1212/wnl.0000000000004923
34. MA X, BU B-T: Anti-SRP immune-mediated necrotizing myopathy: A critical review of current concepts. *Front Immunol* 2022; 13. https://doi.org/10.3389/fimmu.2022.1019972
35. AROUCHE-DELAPERCHE L, ALLENBACH Y, AMELIN D *et al*.: Pathogenic role of anti-signal recognition protein and anti-3-Hydroxy-3-Methylglutaryl-CoA reductase antibodies in necrotizing myopathies: myofiber atrophy and impairment of muscle regeneration in necrotizing autoimmune myopathies. *Ann Neurol* 2017; 81(4): 538-48. https://doi.org/10.1002/ana.24902
36. RATHCKE CN, VESTERGAARD H: YKL-40--an emerging biomarker in cardiovascular disease and diabetes. *Cardiovasc Diabetol* 2009; 8: 61. https://doi.org/10.1186/1475-2840-8-61
37. LI F, SHENG Z, LAN H, XU J, LI J: Down-regulated CHI3L1 alleviates skeletal muscle stem cell injury in a mouse model of sepsis. *IUBMB Life* 2020; 72(2): 214-25. https://doi.org/10.1002/iub.2156
38. PRISCO F, PAPPARELLA S, PACIELLO O: The correlation between cardiac and skeletal muscle pathology in animal models of idiopathic inflammatory myopathies. *Acta Myol* 2020; 39(4): 313-9. https://doi.org/10.36185/2532-1900-035
39. LIU X-H, FENG X-J, SHI J-Y *et al*.: The quest for diagnostic approaches of cardiac involvement in polymyositis and dermatomyositis. *Ann Palliat Med* 2020; 9(4): 2256-70. https://doi.org/10.21037/apm-19-650
40. MAROTT SCW, BENN M, JOHANSEN JS, JENSEN GB, TYBJAERG-HANSEN A, NORDESTGAARD BG: YKL-40 levels and atrial fibrillation in the general population. *Int J Cardiol* 2013; 167(4): 1354-9. https://doi.org/10.1016/j.ijcard.2012.04.006
41. DIEZ J, QUEREJETA R, LOPEZ B, GONZALEZ A, LARMAN M, UBAGO JLM: Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. *Circulation* 2002; 105(21): 2512-7. https://doi.org/10.1161/01.Cir.0000017264.66561.3d