Nomogram to predict dermatomyositis prognosis: a population-based study of 457 cases

Y. Li[1], Y. Li[1], Y. Wang[2], L. Shi[3], F. Lin[4], Z. Zhang[2], J. Zhang[5], F. Xu[6], X. Sun[1]

[1]Department of Rheumatology &Immunology, Beijing Key Laboratory for Rheumatism Mechanism and Immune Diagnosis (BZ0135), Peking University People's Hospital, Beijing;
[2]Department of Respiratory Medicine, Beijing Hospital of Traditional Chinese Medicine, Beijing;
[3]Department of Rheumatology, Peking University International Hospital, Beijing;
[4]Department of Rheumatology, People's Hospital of Jianyang City, Jianyang;
[5]Department of Rheumatology, Hongqi Hospital of Mudanjiang Medical University, Mudanjiang;
[6]R&D Management Department, China National Biotec Group, Beijing, China.

Abstract

Objective

Dermatomyositis (DM) is a systemic autoimmune disease, which typically affects the striated muscle with a variable involvement of the skin and other organs. Clinically amyopathic DM (CADM) is a combination of hypomyopathic DM (HDM) and amyopathic DM (ADM), with a characteristic of skin-predominant lesions. To date, large-scale studies on the prognostic factors of DM/CADM have been limited. The aim of this study is to evaluate the prognostic values of clinical manifestations in DM/CADM and to develop a prognostic nomogram for DM/CADM.

Methods

A development cohort (n =239), an internal validation cohort (n=128) and an external validation cohort (n=90) were included in this study. Overall survival (OS) was estimated by the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards regression analyses were performed. Cox proportional hazards model and forward stepwise selection with the Akaike information criterion were used for multivariate analysis of prognostic factors. The concordance index (C-index) and calibration curve were calculated to evaluate the predictive accuracy of the proposed nomogram.

Results

Rapidly progressive interstitial lung disease (RP-ILD) and erythrocyte sedimentation rate (ESR) were identified as risk independent prognostic factors, with antinuclear antibodies (ANA) was identified as protective independent prognostic factors, for DM/CADM. A prognostic nomogram was formulated based on these three predictors. The C-index of the proposed nomogram in the development cohort was 0.874 (95%CI, 0.819-0.929). The predictive accuracy of the proposed nomogram was further validated in the internal validation cohort, with a C-index of 0.799 (95%CI, 0.681-0.917). Furthermore, the C-index was 0.864 (95%CI, 0.699-1.000) in the external validation cohort, indicating a good calibration ability. This proposed nomogram showed a promising predictive accuracy on the prognosis of DM/CADM.

Conclusion

RP-ILD, ANA and ESR are prognostic factors for DM/CADM. The proposed nomogram based on these three factors could accurately predict the 10-year OS probabilities of patients with DM/CADM.

Key words

dermatomyositis, interstitial lung disease, prognosis

*Yimin Li, PhD**
*Yuhui Li, MD**
Yuguang Wang, PhD
Lianjie Shi, PhD
Fuan Lin, PhD
Zongxue Zhang, PhD
Jingli Zhang, PhD
Fangjingwei Xu, PhD
Xiaolin Sun, PhD

**Contributed equally as co-first authors.*

Please address correspondence to:
Xiaolin Sun,
11 Xizhimen South Street,
Beijing 100044, China.
E-mail: sunxiaolin_sxl@126.com

Yuhui Li,
11 Xizhimen South Street,
Beijing 100044, China.
E-mail: liyuhui84@163.com

Fangjingwei Xu,
R&D Management Department,
China National Biotec Group,
Beijing 100024, China.
E-mail: xufangjingwei@sinopharm.com

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Introduction

Dermatomyositis (DM) is a rare autoimmune disease. It is related to various amounts of systemic involvement, such as muscle, lung and other organs (1), characterised by proximal muscle weakness, elevation of muscle enzymes, myopathic changes on electromyography (EMG) and muscle pathological damage. Clinically amyopathic DM (CADM) is a combination of hypomyopathic DM (HDM) and amyopathic DM (ADM), with a characteristic skin-predominant lesions (2-5). For practical purpose, patients with HDM and ADM have been included in the same group defined as CADM. Diagnosis is based on the clinical examination in combination with laboratory values, including autoantibodies, EMG and the histopathology of the skeletal muscle (1, 6).

DM is one of the most lethal rheumatic diseases, its 10-year survival rates were reported to range from 42% to 85% (7-14) and the mortality rates of 10-year were as high as 42% to 74% (7-10). Prognosis associated with myositis-specific autoantibodies (MSAs), interstitial lung disease (ILD), skin ulceration and older age were evaluated in patients with DM/CADM (6, 15-21). Generally, anti-melanoma differentiation-associated gene (MDA5) antibody was strongly correlated with survival, since patients with MDA5 antibody had an increased risk of developing ILD, especially the rapidly progression ILD (RP-ILD) with higher mortality (18-20). So far, there is no prognostic model which integrated the aforementioned predictors together. Therefore, a more accurate model to predict individualised survival chance of DM/CADM patients is required.

Nomography has been widely used to predict the survival of various diseases (22-24). It can be used to calculate the survival probability for an individual patient (25). A nomogram can provide a user-friendly graphical interface, and it is convenient for clinical usage, so as to provide reference for clinical decision-making. However, nomography for DM/CADM has not been developed so far. The aim of our study is to establish an accurate nomogram for prognostic prediction of DM/CADM patients. The findings of this study will be helpful to optimise personalised treatment and follow-up strategies for DM/CADM patients.

Methods

Patients

A total of 434 DM/CADM patients were included consecutively in the department of Rheumatology and Immunology, Peking University People's Hospital from 2005 to 2019, and their clinical data were analysed in our study. External validation was based on retrospective demographic, clinical, and laboratory test data from 127 DM/CADM patients admitted in four other independent clinical centres (Peking University International Hospital, Beijing Hospital of Traditional Chinese Medicine, People's Hospital of Jianyang City, Hongqi Hospital of Mudanjiang Medical University) from 2010 to 2019. Patients (≥18 years old) were included according to a diagnosis of definite DM by Bohan and Peter or 2017 EULAR/ACR criteria (26, 27), and CADM was diagnosed according to criteria proposed by Sontheimer (5). Patients who had at least one follow-up visit were included. The patient exclusion criteria included: recent acute infection; pulmonary infarction; presence of heart failure; history of neoplasm; other connective tissue diseases concomitantly, including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA) and Sjögren's syndrome (SS); or insufficient demographic, clinical, and laboratory test data. ILD was diagnosed by the findings of high-resolution computed tomography (HRCT), according to the International Consensus Statement of Idiopathic Pulmonary Fibrosis of the American Thoracic Society (28) and defined as previously described (29). RP-ILD was defined as acute and progressive deterioration of dyspnoea requiring supplementary oxygen, hospitalisation, or subsequent respiratory failure within 3 months of the diagnosis of ILD; the evidence of abnormal gas exchange as defined by a low partial pressure of arterial oxygen (PaO_2)/percentage of inspired oxygen (FiO_2) ratio or a decrease in PaO_2; new radiographic opacities; with the exclusion of an alter-

native explanation, including infection, pulmonary embolism, left heart failure (28, 30), and RP-ILD was in the case of the occurrence of a respiratory worsening in 3 months of absent lung disease. Chest HRCT patterns were classified into non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), OP+NSIP and diffuse alveolar damage (DAD) according to the international classification created by American Thoracic Society/European Respiratory Society (31). Pulmonary function tests (PFT) and Bronchoalveolar lavage (BAL) examinations were performed to evaluate ILD. % predicted forced vital capacity (FVC), % predicted diffusing lung capacity for carbon monoxide (DLco), and total lung capacity (TLC) were recorded at the initial diagnosis.

Demographic and clinical information including age at onset, gender, and initial symptoms including: fever, proximal muscle weakness, Gottron's sign/papules, skin ulceration, periungual erythema, velcro rales, and ILD were assessed. Laboratory data including: aspartate aminotransferase (AST), alanine transaminase (ALT), erythrocyte sedimentation rate (ESR), and lactate dehydrogenase (LDH). Myositis-specific autoantibodies (antigen panel included Jo-1, PL-7, PL-12, EJ, OJ, KS, MDA5, NXP2, SAE, Mi-2, TIF-1γ), and myositis-associated autoantibodies (antigen panel included Ro-52, PM-Scl, antinuclear antibodies (ANA)) were screened in all patients by immunoblotting according to manufacturers' instructions (Euroimmun, Germany). All data were collected before initiating appropriate therapy. Overall survival (OS) and causes of death were recorded and analysed. The end point was defined as death of patients.

Development and validation cohorts

In order to develop and validate the nomogram, DM/CADM patients from 2005 to 2013 were included as the development cohort (n=239). The internal validation cohort was composed of the patients from 2014 to 2019 (n=128), and the external validation cohort was composed of the patients from the other four independent hospitals (n=90).

Table I. Comparison of clinical and laboratory manifestations among the development cohort and the validation cohort, the external validation cohort.

	DC (n=239)	IVC (n=128)	EVC (n=90)	*p*
Demographics				
Age at onset, years	48.0 ± 14.3	48.7 ± 13.5	57.4 ± 12.1	0.000
Female (n, %)	188 (78.7)	97 (75.8)	60 (66.7)	0.078
Subtype of IIM				0.000
DM (n, %)	113 (47.3)	64 (50.0)	77 (85.6)	
CADM (n, %)	126 (52.7)	64 (50.0)	13 (14.4)	
Clinical characteristics				
RP-ILD (n, %)	70 (29.3)	40 (31.3)	18 (20.0)	0.155
Gottron's sign/papules (n, %)	173 (72.4)	90 (70.3)	37 (41.1)	0.000
Mechanic's hands (n, %)	76 (31.8)	46 (35.9)	38 (42.2)	0.203
Heliotrope rash (n, %)	120 (50.2)	56 (43.8)	28 (31.1)	0.008
V sign (n, %)	113 (47.3)	52 (40.6)	22 (24.4)	0.001
Shawl sign (n, %)	64 (26.8)	28 (21.9)	19 (21.1)	0.426
Skin ulceration (n, %)	11 (4.6)	10 (7.8)	4 (4.4)	0.389
Periungual erythema (n, %)	48 (20.1)	17 (13.3)	7 (7.8)	0.016
Myalgia (n, %)	26 (10.9)	16 (12.5)	28 (31.1)	0.000
Myasthenia (n, %)	117 (49.0)	62 (48.4)	43 (47.8)	0.981
Velcro rales (n, %)	38 (15.9)	23 (18.0)	77 (85.6)	0.000
Fever (n, %)	100 (41.8)	53 (41.4)	15 (16.7)	0.000
Dysphagia (n, %)	4 (1.7)	1 (0.8)	8 (8.9)	0.001
Arthralgia (n, %)	111 (46.4)	65 (50.8)	13 (14.4)	0.000
Raynaud's phenomenon	10 (4.2)	7 (5.5)	4 (4.4)	0.852
Myositis-specific antibodies				
Anti-ARS positivity	53 (22.2)	29 (22.7)	57 (63.3)	0.000
Anti-Jo-1 positivity	19 (7.9)	6 (4.7)	14 (15.6)	0.016
Anti-MDA5 positivity	32 (13.4)	17 (13.3)	19 (21.1)	0.179
Myositis-associated antibodies				
Anti-Ro-52 positivity	68 (28.5)	42 (32.8)	30 (33.3)	0.568
Anti-PM/Scl-75/100 positivity	1 (0.4)	1 (0.8)	6 (6.7)	0.000
ANA	159 (66.5)	88 (68.8)	35 (38.9)	0.000
Laboratory features				
Arterial blood gas				
PaO_2, mean±SD mmHg	85.0 ± 14.4	71.3 ± 14.8	80.8 ± 26.8	0.000
HRCT				0.000
NSIP	5 (2.1)	9 (7.0)	6 (6.7)	
OP	215 (90)	69 (53.9)	47 (52.2)	
OP+NSIP	19 (7.9)	46 (35.9)	24 (26.7)	
UIP	0 (0)	3 (2.3)	3 (3.3)	
DAD	0 (0)	0 (0)	0 (0)	
Pulmonary function tests[a]				
FVC % predicted	83.9 ± 17.5	67.0 ± 18.1	85.2 ± 17.8	0.000
DLco % predicted	67.4 ± 19.6	53.5 ± 18.2	78.3 ± 22.1	0.000
TLC % predicted	85.7 ± 16.9	73.3 ± 17.3	102.3 ± 45.7	0.000
Bronchoalveolar lavage[b]				
Total cell number, 10^5/ml	0.40 ± 0.37	0.30 ± 0.28	0.17 ± 0.03	0.373
Macrophage, %	63.7 ± 21.6	48.0 ± 22.2	57.0 ± 13.7	0.000
Lymphocyte, %	27.4 ± 20.0	37.8 ± 23.1	36.0 ± 17.0	0.019
Neutrophil, %	7.4 ± 10.1	12.9 ± 18.3	5.7 ± 4.7	0.169
Eosinophil, %	1.5 ± 2.7	1.2 ± 2.8	1.3 ± 1.5	0.730
Elevated ALT (n, %)	95 (39.7)	54 (42.2)	34 (37.8)	0.800
Elevated AST (n, %)	106 (44.4)	66 (51.6)	38 (42.2)	0.305
Elevated LDH (n, %)	159 (66.5)	88 (68.8)	60 (66.7)	0.905
ESR	29.7 ± 25.4	29.2 ± 22.9	24.7 ± 21.5	0.232
Death	70 (29.3)	40 (31.3)	18 (20.0)	0.155
OS, years	5.2 ± 5.7	5.0 ± 5.5	2.3 ± 1.1	0.002

[a]Number of subjects with DC, n=106, Number of subjects with IVC, n=58, Number of subjects with EVC, n=17; [b]Number of subjects with DC, n=62, Number of subjects with IVC, n=80, Number of subjects with EVC, n=3. Categoric variables were reported as counts (%) and compared using the χ^2 test. Continuous variables were presented as the mean ± standard deviation, and compared by the Analysis of Variance or the Kruskal Wallis test. *P* values were two-sided, and values of < 0.05 were considered statistically significant.

DC: development cohort; IVC: internal validation cohort; EVC: external validation cohort; RP-ILD: rapidly progressive interstitial lung disease; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis; ARS include Jo-1, EJ, OJ, PL-7, PL-12, KS. ARS: aminoacyl-tRNA synthetase; MDA5: melanoma differentiation-associated 5; PM/Scl: polymyositis/scleroderma; ANA: antinuclear antibodies; RF: rheumatoid factor; ALT: alanine transaminase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

Table II. Risk factors for overall survival according to Cox proportional hazards regression model.

	Univariate analysis			Multivariate analysis		
Variables	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Subtype of IIM						
DM	1.50	1.02-2.20	0.038			
CADM	Reference					
RP-ILD	13.77	5.18-36.58	0.000	12.74	4.75-34.19	0.000
Fever	2.88	1.33-6.26	0.008			
Skin ulceration	4.29	1.49-12.41	0.007			
ANA	0.46	0.22-0.95	0.037	0.42	0.20-0.87	0.02
Anti-MDA5 antibody	2.62	1.10-6.21	0.029			
ESR	1.02	1.01-1.03	0.001	1.01	1.002-1.024	0.017

CI: confidence interval; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis; RP-ILD: rapidly interstitial lung disease; ANA: antinuclear antibody; MDA5: melanoma differentiation-associated gene 5; ESR: erythrocyte sedimentation rate.
The Cox proportional hazards model was used in univariate and multivariate analyses. *p*-values were two-sided, and values of <0.05 were considered statistically significant. Variables with statistical significance in the univariate analysis were included in the multivariate analysis, and the forward elimination process was used to select the variables to formulate the final model in SPSS 23.0.

Statistical analysis

Demographic and clinical characteristics of the development cohort and validation cohort were compared. Categoric variables were reported as counts (%) and compared using the χ^2 test. Continuous variables were presented as the mean ± standard deviation, and compared by the Analysis of Variance or the Kruskal Wallis test. The LSD of analysis of variance and chi square test were used in a pair-wise *post-hoc* analysis. The exploration of risk factors analysis was done through univariate and multivariate analyses, which were performed by using the Cox proportional hazards model. Variables with statistical significance in the univariate analysis were included in the multivariate analysis, and the forward elimination process was used to select the variables to formulate the final model.

The performance of the nomogram was measured by their discrimination ability using the Harrel concordance index (C-index), while the calibration ability was validated with calibration curve. Discrimination refers to the ability of a model to correctly distinguish non-events and events, and it can be quantified by calculating the C-index for the survival model (32). Larger C-index value denoted better predictive accuracy. The calibration measurement shows that the predicted probability is in good agreement with the actual result numerically (32).

p-values were two-sided, and values of <0.05 were considered statistically significant. All data were analysed using SPSS v. 23.0 and a nomogram was generated based on the multivariate prediction model using the package of rms (33) in R v. 3.6.3 (http://www.r-project.org/). To use the nomogram, for each variable, draw a line straight upward to the Points axis at the same vertical position. The total points were calculated. Draw a line straight down to survival axis to find the patient's probability of 10-year survival at the same vertical position.

Results

Patient characteristics

There was a total of 434 adult patients with DM/CADM in the ward of Peking University People's Hospital from 2005 and 2019. After excluding patients with other combined autoimmune diseases or without any follow-up, 367 patients were eventually included in the study. The development cohort includes patients from 2005 to 2013 (n=239), and the internal validation cohort includes the remaining patients from 2014 to 2019 (n=128). 90 patients from the other four independent hospitals were included for external validation. The flow chart of patient inclusion in Peking University People's Hospital was shown in Supplementary Fig. S1, and the flow chart of external validation set was shown in Supplementary Fig. S2. The demographic characteristics of the development cohort and the internal validation cohort, the external validation cohort are summarised in Table I. And we compare the clinical and laboratory manifestations of the three cohorts with a pair-wise *post-hoc* analysis in Supplementary Table S1.

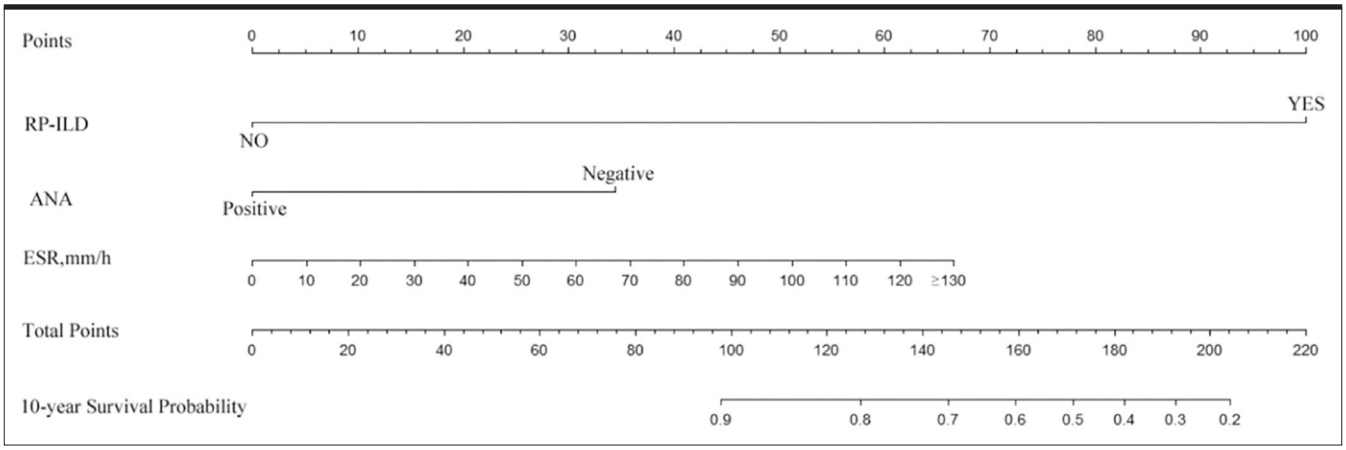

Fig. 1. Prognostic nomogram for overall survival of patients with DM.
RP-ILD: rapidly progressive interstitial lung disease; ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate.

Univariate and multivariate analysis for risk factors of the development cohort

All the clinical manifestations and laboratory parameters shown in Table I were included in univariate survival analysis. Univariate analysis showed that RP-ILD (p<0.001), Skin ulceration (p=0.007), Anti-MDA5 antibody (p=0.029), ESR (p=0.001), ANA (p=0.037), Subtype of IIM (p=0.038) and fever (p=0.008) were significant prognostic factors of OS (Table II). These variables were included in the multivariate model. RP-ILD has been reported as the most common and serious involvement in DM/CADM, which leads to a significant increase in mortality (34-36). After forward elimination process with the Akaike information criterion in multivariate analysis, RP-ILD (HR=12.74 [95%CI 4.75–34.19]), ANA (HR=0.42 [95%CI 0.20–0.87]), and ESR (HR=1.01 [95%CI 1.002–1.024]) were finally identified to construct the Cox proportional hazards regression model (Table II).

Establishment and validation of the prognostic nomogram

According to the results of multivariate analysis and the Cox proportional hazards regression model, the nomogram was established by RP-ILD, ANA and ESR in the development cohort (Fig. 1). To estimate the 10-year OS rates, score for each factor and the sum of the points were calculated based on the point scale in the nomogram. The calibration plot based on bootstrap resampling validation demonstrated good agreement between predicted and actual survival in development cohort (Fig. 2A) and internal validation cohort (Fig. 2B). In the external validation cohort, the OS for all patients is less than 10 years, so the calibration plot couldn't be performed. In the bootstrap resampling cohort, the C-index of the nomogram was 0.874 (95%CI, 0.819–0.929) in development cohort, 0.799 (95%CI, 0.681–0.917) in the internal validation cohort and 0.864 (95%CI, 0.699–1.000) in the external validation cohort, indicating an accurate prediction .

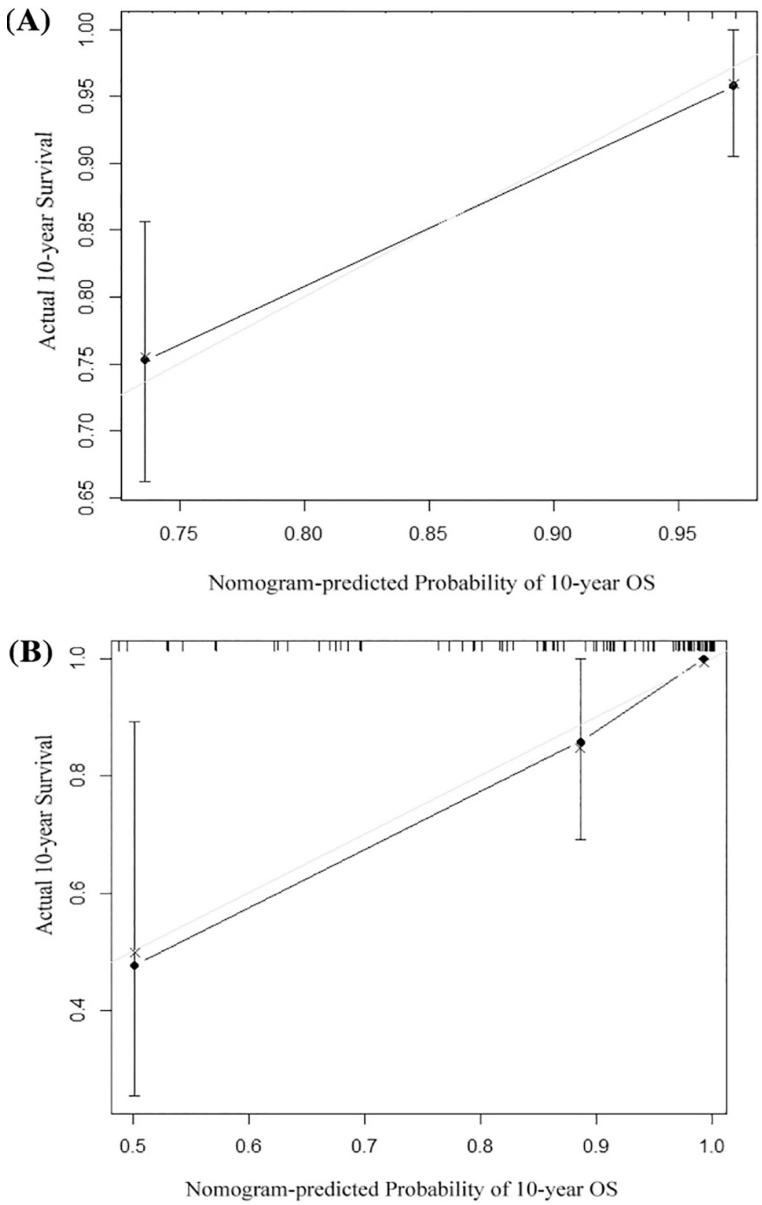

Fig. 2. The calibration curve of nomogram for predicting survival at 10 years in (**A**) the development cohort, (**B**) the internal validation cohort.
a. Nomogram-predicted survival probability is plotted on the x-axis while actual OS is plotted on the y-axis; b. Thin grey line represents the reference line; c. OS: overall survival.

Discussion

DM/CADM is a group of rare autoimmune diseases characterised by muscular involvement leading to muscle destruction, and frequent extra-muscular signs such as Gottron's sign/papules, skin ulceration, arthritis, Raynaud's phenomenon, mechanic's hands and ILD (6, 37). So far, the large-scale studies on the prognostic factors of DM/CADM have been very limited, and there is no prognostic model which integrated the aforementioned predictors together. Therefore, a more accurate model to predict individualised survival rate of DM/CADM patients is required. In this study, we demonstrated that RP-ILD, ANA and ESR were independent prognostic factors of DM/CADM. We formulated a nomogram with these factors to effectively predict the 10-year OS probabilities of patients with DM/CADM, which can guide clinical treatment better.

Amongst extra-muscular complications of DM/CADM, ILD is both the most frequent and severe involvement, and RP-ILD is a life-threatening subtype of DM/CADM-associated ILD which tends to be resistant to high-dose glucocorticoid and immunosuppressants associated with mortality rates ranging from 70% to 90% (38-40). Therefore, the evalu-

ation of RP-ILD is crucial in the management of DM/CADM, particularly in the anti-MDA5 antibody-associated myositis (41). A dose-dependent relationship between anti-MDA5 antibody and RP-ILD has been recently reported, unveiling a strong collinearity between anti-MDA5 antibodies and RP-ILD, which both are significant risk factors for poor prognosis (42). So, the results of our report demonstrated MDA5 was a significant prognostic factor in the univariate analysis but not in the multivariate analysis, causing Cox proportional hazards model analysis would automatically select the factors with strong collinearity for optimal elimination.

ANA testing is usually performed in patients with suspected DM/CADM, with 50% to 78% of confirmed patients being positive (43, 44). Unlike clinical correlation of myositis-specific antibody status, however, the clinical correlation of ANA status in DM/CADM is not clear. So far, there are few related studies, the results are contradictory and limited by the low statistical ability (3, 45). A recent study included 231 DM patients found ANA negative was related with increased risk of malignancy referred to worse prognosis for DM, which agreed with our results (46). Moreover, one study, which included a population of 90 patients with DM, reported raised ESR were identified as risk indicators for DM (39). Elevated ESR were also found to increase the risk of ILD associated with DM significantly, which referred to worse disease course (40, 41). In our study, the C-index of the proposed nomogram was 0.874 (95%CI, 0.819-0.929) in the development cohort, 0.799 (95%CI, 0.681-0.917) in the internal validation cohort and 0.864 (95%CI, 0.699-1.000) in the external validation cohort, indicating a good calibration ability. This proposed nomogram showed a promising predictive accuracy on the prognosis of DM/CADM.

In the present study, there are also several limitations. First, compared with previous studies, this study has a relatively large number of patients, but a lot of laboratory tests have not been widely applied in those patients, such as ferritin, cytokines and T lymphocyte subsets, so it is still not ideal for achieving more effective risk factor analysis; moreover, this study needs to be further validated by more multi-centre studies with enlarged patient cohorts. Second, this study is a retrospective study, which is suboptimal compared to prospective trials and might have biases in patient selection. In the future, prospective research should be done to further verify and optimise the predictive model.

Conclusion

In our study, we used three prognostic factors, including RP-ILD, ANA and ESR, to build a nomogram that can be used to predict the prognosis of DM/CADM patients. Our nomogram showed high predictive accuracy and more studies are required to validate the reliability and effectiveness of this predictive model. The use of nomogram in predicting the prognosis of DM/CADM patients to clinical treatment is a new concept.

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