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Clinical science

Preliminary nomogram model for predicting irreversible organ damage of patients with systemic sclerosis

Xiaocong Huo[1], Xinxiang Huang[1], Yanting Yang[1], Chengcheng Wei[1], Danli Meng[1], Rongjun Huang[1], Jinying Lin[1,*]

[1]The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences, Nanning, Guangxi, China

*Correspondence to: Jinying Lin, The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Academy of Medical Sciences, No.6 Taoyuan Road, Nanning, Guangxi 530021, China. E-mail: yy201450040@163.com

Abstract

Objective: To investigate predictive factors for irreversible organ damage in systemic sclerosis (SSc) and establish a nomogram model.

Methods: This retrospective study included patients with SSc who were treated at our hospital between March 2013 and March 2023. Irreversible organ damage included heart failure, respiratory failure, renal failure, and gangrene of the hands and feet. Cox and LASSO regression analyses were performed to determine the predictive factors. Based on the results, a nomogram model was developed. The model was evaluated using the C-indices, calibration plots and DCA.

Results: A total of 361 patients with systemic sclerosis were randomly divided into the development ($n = 181$) and validation ($n = 180$) groups. Multivariate Cox regression analysis showed that age ≥65 years, weight loss, digital ulcers, mRSS ≥16, elevated creatinine, elevated myoglobin, elevated C-reactive protein, renal involvement and cardiac involvement were independent risk factors. Based on the LASSO analysis, a nomogram model of irreversible organ damage was established. The C-indices of the development group at 24, 60 and 96 m were 96.7, 84.5 and 85.7, whereas those of the validation group at 24, 60 and 96 m were 86.6, 79.1 and 78.5, respectively. The results of the DCA showed that the nomogram can be used as a valuable tool to predict irreversible organ damage in patients with SSc.

Conclusion: We included commonly used clinical indicators. According to the nomogram, the probability of irreversible organ damage can be calculated and high-risk patients can be identified.

Keywords: hormone, renal, cardiovascular, gastrointestinal, skin, biomarker, observational study.

Rheumatology key messages

- Age, weight loss, DUs, mRSS, myoglobin, CRP, renal and cardiac involvements are predictors for irreversible organ damage of patients with SSc.
- According to the nomogram, the probability of irreversible organ damage and high-risk patients can be identified.
- Multi-centre studies and the inclusion of more quantitative indicators may lead to better predictive models.

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown aetiology, characterized by fibrosis of the skin, blood vessels and internal organs [1, 2]. Its pathogenesis is complex and involves the interaction of multiple cells, inflammatory factors and signalling molecular pathways. The clinical manifestations of SSc are complex and its mortality rate is high.

Currently, no effective treatment for SSc is available [3–5], and the disease inevitably progresses, resulting in the failure of one or more involved organs and death [6]. The clinical manifestations of SSc are highly heterogeneous, and there is no clinical tool that can accurately predict the prognosis and guide treatment decision making. Accurate disease stratification will allow clinicians to better distinguish between patients who are at risk of rapid progression and need urgent treatment, and those who are indolent and can undergo conservative treatment.

Although recent studies have revealed that some novel biomarkers can be used to predict disease progression [7–9], these biomarkers may not represent the entire complexity of the disease, are still in the scientific research stage and cannot be directly used in clinical treatment. Currently, no adequate biomarkers for early diagnosis, activity assessment and prognosis of SSc exist. Modified Rodnan skin score (mRSS) is one of the commonly used clinical predictors. It is non-invasive and cost-effective, but it possesses several shortcomings, including the subjectivity of skin palpation, difficulty of marginal skin sclerosis scoring and confounding effect caused by tissue inflammation or oedema [10, 11]. Therefore, there is

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an urgent need for reliable, safe and feasible markers that can accurately predict disease progression and treatment response in order to provide more accurate and personalized treatments for patients with SSc.

This study included patients with diffuse SSc admitted to our hospital over the past 10 years, investigated the predictive factors for irreversible organ damage in SSc and established a nomogram model. The results of this study may help with the early diagnosis of high-risk patients, provide personalized and accurate treatment and improve outcomes.

Methods

Study population

First, this was a retrospective study. Patients with SSc treated at the People's Hospital of Guangxi Zhuang Autonomous Region between March 2013 and March 2023 were included in this study. Inclusion criteria were as follows: patients with SSc who met the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc [12] were evaluated for organ involvement and had follow-up data. The exclusion criteria were as follows: follow-up <6 months, irreversible organ damage at baseline, limited SSc, sine scleroderma, classified undetermined connective tissue disease, local scleroderma and patients with SSc without major organ evaluation.

This study was approved by the Ethics Committee of the People's Hospital of Guangxi Zhuang Autonomous Region (ethics approval number: KY-SY-2021–9). Informed consent was obtained from all the patients prior to the commencement of the study.

Data collection

By consulting the electronic medical records of the patients, the details regarding demographic information, laboratory test results, and patient treatments were collected in detail. Except for the treatments, all the variables mentioned were collected at baseline and treatments were recorded during follow-up. The course of disease was defined as the time from the date of the first non-Raynaud phenomenon symptom to the baseline visit. Weight loss was defined as an unintentional weight loss of 5% or more over the previous year according to Fried's criteria [13]. Pulmonary arterial hypertension (PAH) was defined as a mean pulmonary arterial pressure exceeding 25 mmHg at rest or exceeding 30 mmHg during exercise coupled with a pulmonary capillary wedge pressure exceeding 15 mmHg, as determined using a right echocardiogram. Alternatively, a pulmonary artery systolic pressure exceeding 40 mmHg at rest, as indicated by an echocardiogram test, was also indicative of PAH [14]. Interstitial lung disease (ILD) was diagnosed qualitatively based on chest CT findings. The normal ranges of other qualitative data were pro-BNP, 0.0–300.0 pg/ml; creatine kinase, 40.0–200.0 U/l; myoglobin, 25.0–58.0 ng/ml; troponin, 0.0–0.1 ng/ml; C-reactive protein (CRP), 0.0–10.0 mg/l; immunoglobulin G, 7.0–16.6 g/l; and rheumatoid factor, 0.0–14.0 IU/ml.

All the data were collected at the first visit of the patients. If the patient had acute infection at the first visit, ESR and CRP data were retested and recorded after the acute infection was improved; the serum was collected and stored in the refrigerator at −80°C, and the serum Krebs von den Lungen (KL)-6 was detected according to Ruixin biological instructions.

According to Kelly's Textbook of Rheumatology and related literature [15], myositis is defined as myalgia, myasthenia, and creatine kinase and myoglobin elevation. Cardiac involvement was defined as arrhythmia, myocardial involvement, pericardial effusion, elevated troponin levels, valvular regurgitation or pulmonary hypertension. Further, the involvement of the digestive system was defined as gastroesophageal reflux, constipation, hiccups, swallowing obstruction and intestinal obstruction. Renal involvement was defined as history of SRC (scleroderma renal crisis), creatinine ≥1.5 mg/dl (132.6 μmol/l), 24-h urinary protein ≥0.5 g/24 h and microscopic hematuria, among others.

Clinical outcomes

Irreversible organ damage included heart failure, respiratory failure, renal failure and gangrene of the hands or feet.

Irreversible heart failure was defined as heart failure caused by SSc, which is characterized by the major symptoms or signs (such as dyspnea, ankle swelling, fatigue, enlargement of heart boundary, dull heart sound, elevated jugular vein pressure, lung wet rales). Additionally, a decrease in left ventricular ejection fraction [heart failure with mildly reduced ejection fraction (HFmrEF) LVEF of 41–49%, heart failure with reduced ejection fraction (HFrEF), LVEF ≤40%] and an increase in pro-BNP were also indicative of heart failure caused by SSc [16]. If heart failure was caused by coronary heart disease, hypertension, dilated cardiomyopathy, rheumatic valvular heart disease, congenital heart disease or other diseases, it was not recorded as an end event. If transient heart failure was caused by infection, arrhythmia, blood volume increase, excessive physical exertion, and other reasons and after active treatment, LVEF exceeded 50% and symptoms and signs disappeared, it was not recorded as an end event. As there is no distinct standard duration for acute and chronic heart failure, the duration of heart failure was not limited in this study.

Irreversible respiratory failure was defined as arterial oxygen partial pressure exceeding 60 mmHg caused by SSc- ILD for >1 month [17]. Respiratory failure due to pneumoconiosis, drugs, other rheumatic diseases or idiopathic ILD was not recorded as an end event. Transient respiratory failure due to pulmonary infection, post anti-infection therapy and arterial oxygen partial pressure exceeding 60 mmHg was not recorded as an end event. As there is no distinct standard duration for acute and chronic respiratory failure, the duration of respiratory failure was not limited in this study.

Irreversible renal failure was defined as a glomerular filtration rate exceeding 60 mL/(min·1.73 m^2) for >3 months [18]. Renal failure caused by hypertensive nephropathy, diabetic nephropathy, infection or drugs was not recorded as an end point event.

During the follow-up period, organ damage was assessed and the occurrence of irreversible organ damage was recorded as a positive end event.

Statistical analysis and construction of the nomogram model

Data analysis was conducted using SPSS 22.0, and the R-studio platform (version 4.0.4). Measurement data conforming to a normal distribution were expressed as mean (standard deviation), and the independent sample *t* test was used for inter-group comparison. Non-normally distributed data were expressed as medians (P25, P75), and the rank sum

(Mann–Whitney) test was used for comparison between groups. Categorical variables were expressed as the number of cases and percentages, and $\chi 2$ or Fisher's test was used for comparison between groups. Univariate and multivariate Cox regression analyses were used to investigate risk factors for irreversible organ damage in patients with SSc. The Kaplan–Meier curve was used for survival analysis (log-rank test). Lasso and Cox regression analyses were used to screen the indicators and prepare for subsequent development of the nomogram model. The identification and calibration of the model were evaluated using C-indices, calibration plots and DCA. Statistical significance was set at $P < 0.05$.

Results

General clinical data of patients

After strict screening, 361 patients with SSc were randomly divided into development ($n = 181$) and validation ($n = 180$) groups in a 5:5 ratio. See Table 1. There were no statistically significant differences in various indicators between the

Table 1. Clinical characteristics between irreversible organ damage group and without irreversible organ damage group

	Primary group	Without irreversible organ damage group	Irreversible organ damage group	*P*	t/χ2/U
Number of patients	361	281	80		
Gender (female, %)	239 (66.2)	192 (68.3)	47 (58.8)	0.110	0.200
Age (years, mean (SD))	55.5 (10.9)	54.8 (10.5)	57.7(12.0)	0.034	0.259
Course of disease (months, median [IQR])	10.0 [6.0, 14.0]	9.0 [6.0, 12.0]	11.0 [6.0, 15.0]	0.169	0.604
Smoking (%)	48 (13.3)	37 (13.2)	11 (13.8)	0.892	0.017
Overlap syndrome (%)	36 (10.0)	23 (8.2)	13 (16.2)	0.034	0.248
Weight loss (%)	85 (23.5)	43 (15.3)	42 (52.5)	<0.001	0.855
mRSS (median [IQR])	15.0 [10.0, 22.0]	13.0 [9.0, 19.0]	23.0 [16.0, 34.5]	<0.001	1.000
Raynaud phenomenon (%)	347 (96.1)	270 (96.1)	77 (96.2)	0.946	0.009
Arthritis (%)	166 (46.0)	133 (47.3)	33 (41.2)	0.336	0.123
DUs (%)	112 (31.0)	61 (21.7)	51 (63.7)	<0.001	0.939
Tuberculosis (%)	16 (4.4)	13 (4.6)	3 (3.8)	0.737	0.044
ANA (%)	353 (97.8)	277 (98.6)	76 (95.0)	0.055	0.204
Scl-70 (%)	296 (82.0)	231 (82.2)	65 (81.2)	0.844	0.025
ACA (%)	28 (7.8)	19 (6.8)	9 (11.2)	0.185	0.157
Elevated CRP (%)	60 (16.6)	28 (10.0)	32 (40.0)	<0.001	0.740
Elevated ESR (%)	97 (26.9)	80 (28.5)	17 (21.2)	0.199	0.168
Elevated IgG (%)	85 (23.5)	68 (24.2)	17 (21.2)	0.583	0.070
Elevated RF (%)	32 (8.9)	26 (9.3)	6 (7.5)	0.627	0.063
Velcro crackles (%)	78 (21.6)	44 (15.7)	34 (42.5)	<0.001	0.619
ILD (%)	264 (73.1)	200 (71.2)	64 (80.0)	0.116	0.207
KL-6 (U/mL, median [IQR])	689.0 [458.0, 962.0]	658.0 [413.0, 856.0]	1080.0 [821.8, 1368.0]	<0.001	0.967
Cardiac involvement (%)	96 (26.6)	55 (19.6)	41 (51.2)	<0.001	0.702
PAH (%)	63 (17.5)	33 (11.7)	30 (37.5)	<0.001	0.627
Elevated pro-BNP (%)	89 (24.7)	49 (17.4)	40 (50.0)	<0.001	0.734
Renal involvement (%)	34 (9.4)	5 (1.8)	29 (36.2)	<0.001	0.978
Elevated creatinine (%)	40 (11.1)	8 (2.8)	32 (40.0)	<0.001	1.016
Elevated BUN (%)	37 (10.2)	11 (3.9)	26 (32.5)	<0.001	0.797
Digestive system involvement (%)	104 (28.8)	65 (23.1)	39 (48.8)	<0.001	0.554
Coombs test positive (%)	45 (12.5)	23 (8.2)	22 (27.5)	<0.001	0.521
Haemoglobin (mean (SD))	116.7 (21.2)	120.4 (18.8)	103.5 (23.8)	<0.001	0.790
Myositis (%)	77 (21.3)	64 (22.8)	13 (16.2)	0.209	0.165
Elevated creatine kinase (%)	108 (29.9)	78 (27.8)	30 (37.5)	0.093	0.209
Elevated myoglobin (%)	101 (28.0)	61 (21.7)	40 (50.0)	<0.001	0.617
Hormone (%)				0.262	0.280
Corticosteroids pulse therapy	25 (6.9)	23 (8.2)	2 (2.5)		
High dose corticosteroids	99 (27.4)	73 (26.0)	26 (32.5)		
Moderate dose corticosteroids	109 (30.2)	84 (29.9)	25 (31.2)		
Low dose corticosteroids	128 (35.5)	101 (35.9)	27 (33.8)		
Immunosuppressive (%)				0.356	0.351
CTX	217 (60.1)	160 (56.9)	57 (71.2)		
MTX	108 (29.9)	92 (32.7)	16 (20.0)		
AZA	3 (0.8)	3 (1.1)	0 (0.0)		
CSA	4 (1.1)	3 (1.1)	1 (1.2)		
MMF	8 (2.2)	6 (2.1)	2 (2.5)		
RTX	17 (4.7)	14 (5.0)	3 (3.8)		
Tocilizumab	4 (1.1)	3 (1.1)	1 (1.2)		

AZA: azathioprine; CSA: ciclosporin; CTX: cyclophosphamide; DUs: digital ulcers; ILD: interstitial lung disease; KL-6: serum Krebs von den Lungen; MMF: mycophenolate mofetil; mRSS: Modified Rodnan Skin Score; MTX: methotrexate; PAH: pulmonary arterial hypertension; RTX: rituximab. Corticosteroids pulse therapy: (≥250 mg/d of prednisone or equivalent doses of methylprednisolone, dexamethasone or hydrocortisone); high-dose corticosteroids: (>30–100 mg/d of prednisone or equivalent doses of methylprednisolone, dexamethasone or hydrocortisone); moderate-dose corticosteroids: (>7.5–30 mg/d of prednisone or equivalent doses of methylprednisolone, dexamethasone or hydrocortisone); low-dose corticosteroids: (≤7.5 mg/d of prednisone or equivalent doses of methylprednisolone, dexamethasone or hydrocortisone). Except for treatments, the variables mentioned were all collected at baseline, treatments were recorded during follow-up.

development and validation groups ($P > 0.05$). See Table S1, available at *Rheumatology* online.

Cox analysis

Cox regression analysis was performed on patients in the development group. Considering irreversible organ damage as a dependent variable, from baseline visit to the onset of irreversible organ damage as follow-up time, irreversible organ damage, age exceeding 65 years, mRSS exceeding 16, KL-6 exceeding 945 U/ml, haemoglobin exceeding 103 g/l, and the course of disease exceeding 11 months were all assigned a score of 1. Multivariate Cox regression analysis showed that age exceeding 65 years, DUs, mRSS exceeding 16, weight loss, elevated CRP, elevated creatinine, elevated myoglobin, cardiac involvement and renal involvement were independent risk factors for irreversible organ damage in patients with SSc ($P < 0.05$). See Table 2.

Survival analysis

Survival analysis of patients in the development group showed an increased incidence of irreversible organ damage in patients with age exceeding 65 years, weight loss, mRSS exceeding 16, digital ulcers (Dus), renal involvement, cardiac involvement, elevated myoglobin and CRP ($P < 0.05$). See Fig. 1.

Construction and validation of the nomogram model

Based on the Lasso analysis, a nomogram model of irreversible organ damage was established. Indicators included age, weight loss, DUs, mRSS, elevated myoglobin level, elevated CRP level, renal involvement and cardiac involvement. See Fig. 2.

The nomogram was evaluated and validated in development and validation groups. The calibration curve shows that the predicted probability of the model agrees well with the

Table 2. Univariate and multivariate Cox analysis of SSc irreversible organ damage

	Crude HR (95%CI)	uni-*P* value	Adj HR (95%CI)	multi-*P* value
Gender (female)	0.642 [0.349, 1.181]	0.154	—	—
Age (≥65 years)	2.792 [1.537, 5.072]	0.001	6.233 [2.647, 14.676]	<0.001
Course of disease (≥11 months)	0.728 [0.400, 1.324]	0.298	—	—
Smoking	0.832 [0.297, 2.334]	0.727	—	—
Overlap syndrome	1.212 [0.522, 2.810]	0.655	—	—
Weight loss	5.129 [2.823, 9.319]	<0.001	1.704 [1.087, 5.725]	0.032
mRSS (≥16)	4.882 [2.415, 9.870]	<0.001	2.748 [1.051, 7.186]	0.039
Raynaud phenomenon	0.767 [0.105, 5.613]	0.794	—	—
Arthritis	0.673 [0.365, 1.241]	0.205	—	—
DUs	4.259 [2.220, 8.172]	<0.001	3.828 [1.569, 9.340]	0.003
Tuberculosis	3.157 [0.956, 10.421]	0.059	—	—
ANA	0.562 [0.200, 1.580]	0.275	—	—
Scl-70	0.742 [0.366, 1.503]	0.408	—	—
ACA	1.941 [0.815, 4.626]	0.134	—	—
Elevated CRP	5.440 [2.758,10.728]	0.000	2.596(1.126,6.368)	0.024
Elevated ESR	0.951 [0.459, 1.969]	0.892	—	—
Elevated IgG	0.902 [0.399, 2.037]	0.803	—	—
Elevated RF	0.384 [0.114, 1.293]	0.122	—	—
Velcro crackles	2.414 [1.322, 4.405]	0.004	0.774 [0.253, 2.369]	0.653
ILD	1.617 [0.753, 3.475]	0.218	—	—
KL-6 (≥945 U/mL)	3.950 [2.121, 7.355]	<0.001	0.567 [0.167, 1.926]	0.363
Cardiac involvement	4.199 [2.303, 7.654]	<0.001	2.259 [1.208, 8.087]	0.018
PAH	3.916 [2.144, 7.153]	<0.001	2.145 [0.781, 5.887]	0.139
Elevated pro-BNP	3.860 [2.140, 6.962]	<0.001	0.315 [0.084, 1.185]	0.088
Renal involvement	7.436 [4.101, 13.484]	<0.001	3.952 [1.919, 16.993]	0.035
Elevated creatinine	7.782 [4.272, 14.177]	<0.001	3.832 [1.959, 15.322]	0.037
Elevated BUN	9.794 [5.378, 17.835]	<0.001	1.478 [0.230, 9.508]	0.681
Digestive system involvement	2.751 [1.529, 4.950]	0.001	1.211 [0.471, 3.114]	0.691
Coombs test positive	3.434 [1.711, 6.892]	0.001	0.467 [0.158, 1.381]	0.169
Haemoglobin (≥103 g/L)	5.287 [2.915, 9.590]	<0.001	1.007 [0.272, 3.731]	0.991
Myositis	1.042 [0.462, 2.353]	0.920	—	—
Elevated creatine kinase	1.476 [0.792, 2.751]	0.220	—	—
Elevated myoglobin	3.440 [1.871, 6.324]	<0.001	2.976 [1.242, 7.131]	0.014
Hormone	—	—	—	—
Corticosteroids pulse therapy				
High-dose corticosteroids	2.731 [0.615, 12.122]	0.187	—	—
Moderate-dose corticosteroids	1.571 [0.344, 7.167]	0.56	—	—
Low-dose corticosteroids	2.018 [0.464, 8.772]	0.349	—	—
Immunosuppressive	—	—	—	—
CTX				
MTX	0.437 [0.209, 0.917]	0.029	0.790 [0.313, 1.995]	0.618
AZA	0.000 [0.000, Inf]	0.997	—	—
CSA	2.294 [0.310, 16.968]	0.416	—	—
MMF	1.430 [0.193, 10.609]	0.726	—	—
RTX	0.248 [0.034, 1.818]	0.170	—	—
Tocilizumab	0.000 [0.000, Inf]	0.999	—	—

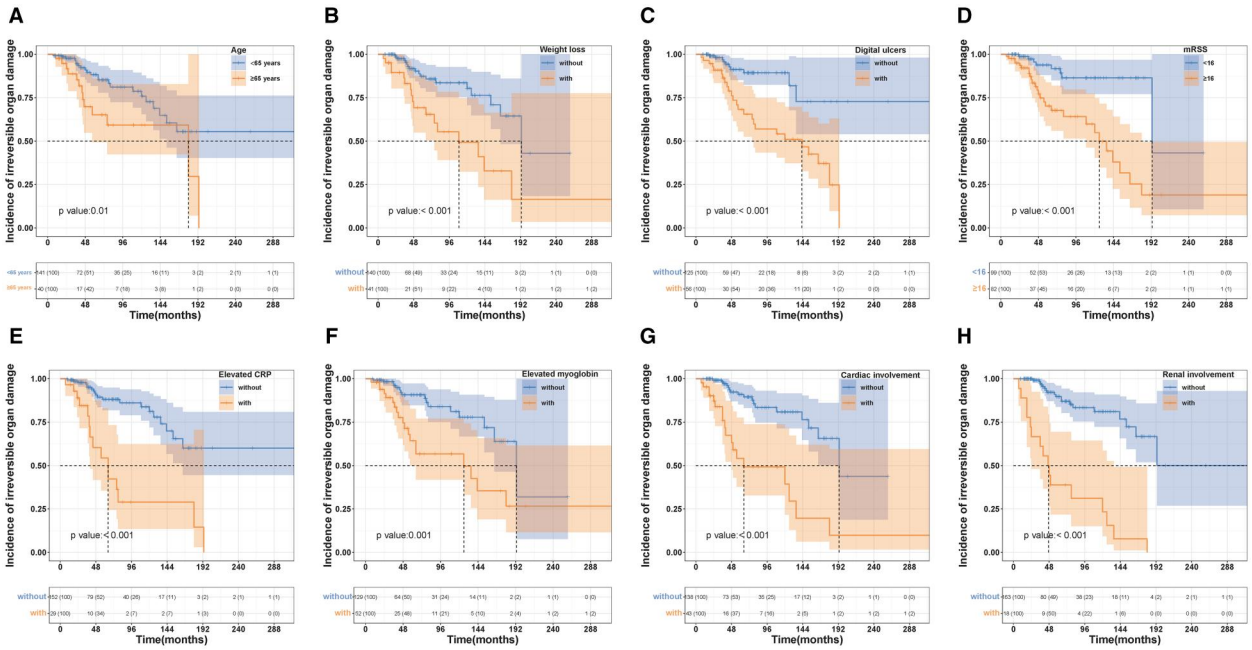

Figure 1. Kaplan–Meier Survival Curve Analysis of irreversible organ damage in patients with SSc. (**A**) is the comparison of different age groups, (**B**) is the comparison of the group with or without weight loss, (**C**) is the comparison of the group with or without digital ulcers, (**D**) is the comparison of different mRSS groups, (**E**) is the comparison of different CRP groups, (**F**) is the comparison of the group with or without elevated myoglobin, (**G**) is the comparison of the group with or without cardiac involvement and (**H**) is the comparison of the group with or without renal involvement. The log-rank test was used to determine significant differences between Kaplan–Meier curves

actual probability in the development and validation groups. The C-indices of the development group at 24 m, 60 m and 96 m were 96.7, 84.5 and 85.7, respectively, whereas those of the validation group at 24 m, 60 m and 96 m were 86.6, 79.1 and 78.5, respectively. See Fig. 3. The results of the ROC curve analysis showed that in the development group, the areas under the curve were 0.965, 0.872 and 0.843, whereas in the validation group, the areas under the curve were 0.900, 0.738 and 0.794, respectively. The results of the DCA showed that the nomogram can be used as a valuable tool to predict irreversible organ damage in patients with SSc and has good clinical value. See Fig. 4.

Discussion

SSc is a serious systemic autoimmune disease with high mortality that affects multiple organs and systems, including the lungs, heart, kidneys, skin and the microvascular system [19]. The clinical manifestations of SSc are highly heterogeneous, and no clinical tool can accurately predict the prognosis and guide treatment decisions.

Irreversible organ damage such as renal, heart or respiratory failure as well as hand or foot gangrene seriously affects the quality of life of patients and poses a heavy medical burden. SSc is a heterogeneous disease characterized by various clinical manifestations and organ involvement. A single prognostic index cannot fully capture the entire complexity of the disease. Therefore, this study collected common clinical data in our hospital over the past 10 years and established a nomogram model of irreversible organ damage in SSc to provide a basis for clinicians to make treatment plans.

Based on Cox and LASSO analyses, we determined the following eight indices: age, weight loss, DUs, mRSS, elevated myoglobin, CRP, renal involvement and cardiac involvement. We established a nomogram model and verified that it is a valuable tool for predicting irreversible organ damage in patients with SSc and has good clinical application value. These eight indices correspond to the general condition of the patients and reflect the important characteristics of vascular disease and autoimmunity and the involvement of important organs. Our results showed that patients with advanced age, vascular lesions such as DUs, high mRSS scores, inflammation (elevated CRP level) and major organ involvement (heart, kidneys and muscles) had a higher risk of irreversible organ damage.

This study found 85 cases (23.5%) of weight loss in all patients and 42 cases (52.5%) in the irreversible organ damage group. The incidence of weight loss was higher in the irreversible organ damage group and weight loss was an independent risk factor for irreversible organ damage. Studies on the incidences of weight loss and malnutrition in patients with SSc have varied significantly. Reportedly, 12% of patients are at a high risk and 14% are at a moderate risk of malnutrition [20]. Another study reported that 61.2%, 15.3% and 23.5% of patients were at low, medium and high risks of malnutrition, respectively [21]. Malnutrition is associated with interstitial lung disease and digestive system involvement [21]. Unintentional weight loss was positively correlated with disease severity [20]. Malnutrition is associated with a poor prognosis of SSc [22]. Chronic inflammation and progressive multiple-organ involvement in SSc are risk factors for malnutrition [23]. Malnutrition can impair immune function and increase the risk of opportunistic infections, particularly in patients treated with immunosuppressants. Weight loss is associated with digestive system involvement; >90% of patients with scleroderma have esophageal involvement; however, owing to hidden gastrointestinal symptoms in some patients, they often do not receive the required medical attention [24]. Some studies have suggested

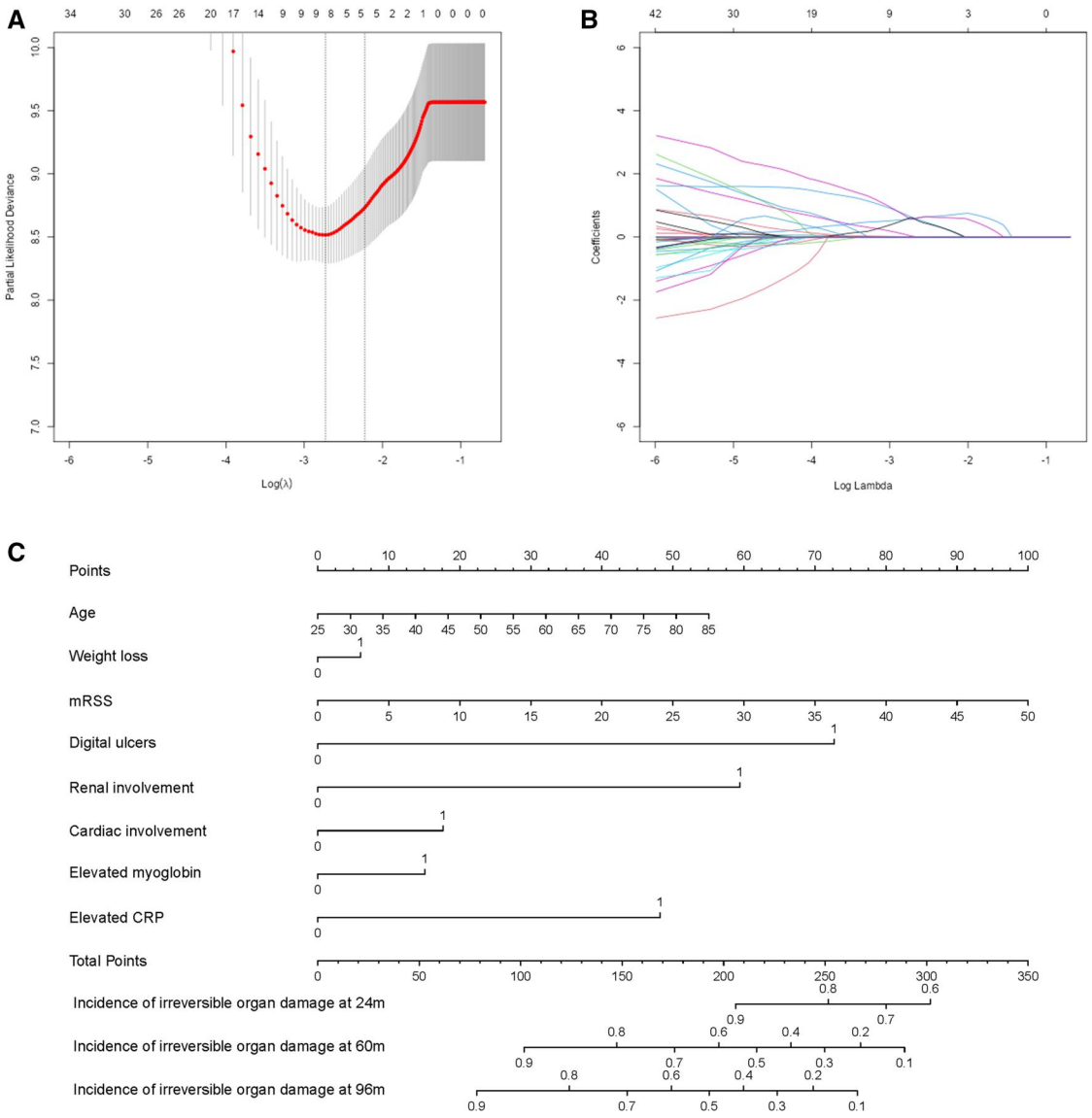

Figure 2. Screening of variables and nomogram for irreversible organ damage of patients with systemic sclerosis. (**A**) The selection process of the optimum value of the parameter λ in the Lasso regression model by cross-validation method. (**B**) The variation characteristics of the coefficient of variables. (**C**) Nomogram for irreversible organ damage of patients with systemic sclerosis

that individualized medical nutrition therapy can improve the symptoms of patients with SSc with digestive system involvement and reduce the risk of myasthenia; however, whether nutritional support therapy can improve the prognosis of SSc remains to be further studied [25].

In this study, we found that the incidence of DUs was higher in the irreversible organ damage group and that DUs were an independent risk factor for irreversible organ damage. DUs are a part of the vascular lesions in SSc, and ∼50% of patients develop DUs [26]. Microangiopathy-induced tissue hypoxia is the main cause of DUs in patients with SSc. DUs may be the result of 'severe Raynaud phenomenon' and the manifestation of advanced vascular lesions [26]. Patients with DUs had higher levels of mRSS and FVC and higher positive rates of diffuse diseases, interstitial lung diseases and anti-scl-70 antibodies [27]. DUs were associated with severe infections in patients with SSc [28]. SRC and DUs share a common pathophysiological process, fibroproliferative angiopathy [29]. SRC often occurs in the first few years of diffuse SSc [30], whereas 75% of patients with SSc develop DUs within 5 years after disease onset [31]. In general, DU is associated with ischaemia [26]. However, DUs of the extensor muscle of the hand may be associated with recurrent microtrauma and skin fibrosis [26]. We believe that DU is a clinical manifestation of SSc vascular disease and the progression of Raynaud's phenomenon. DU indicates vascular disease progression, and clinicians should pay attention to the evaluation and treatment of vascular diseases to avoid irreversible organ damage.

This study found that there was no statistical difference in the incidence of interstitial pneumonia between the irreversible organ damage and control groups and that interstitial pneumonia was not an independent risk factor for irreversible organ damage. There was a statistically significant difference in KL-6 levels between the two groups; however, the KL-6 level was not an independent risk factor for irreversible organ damage. This finding is inconsistent with the findings of previous studies. Previous studies have found that KL-6 is

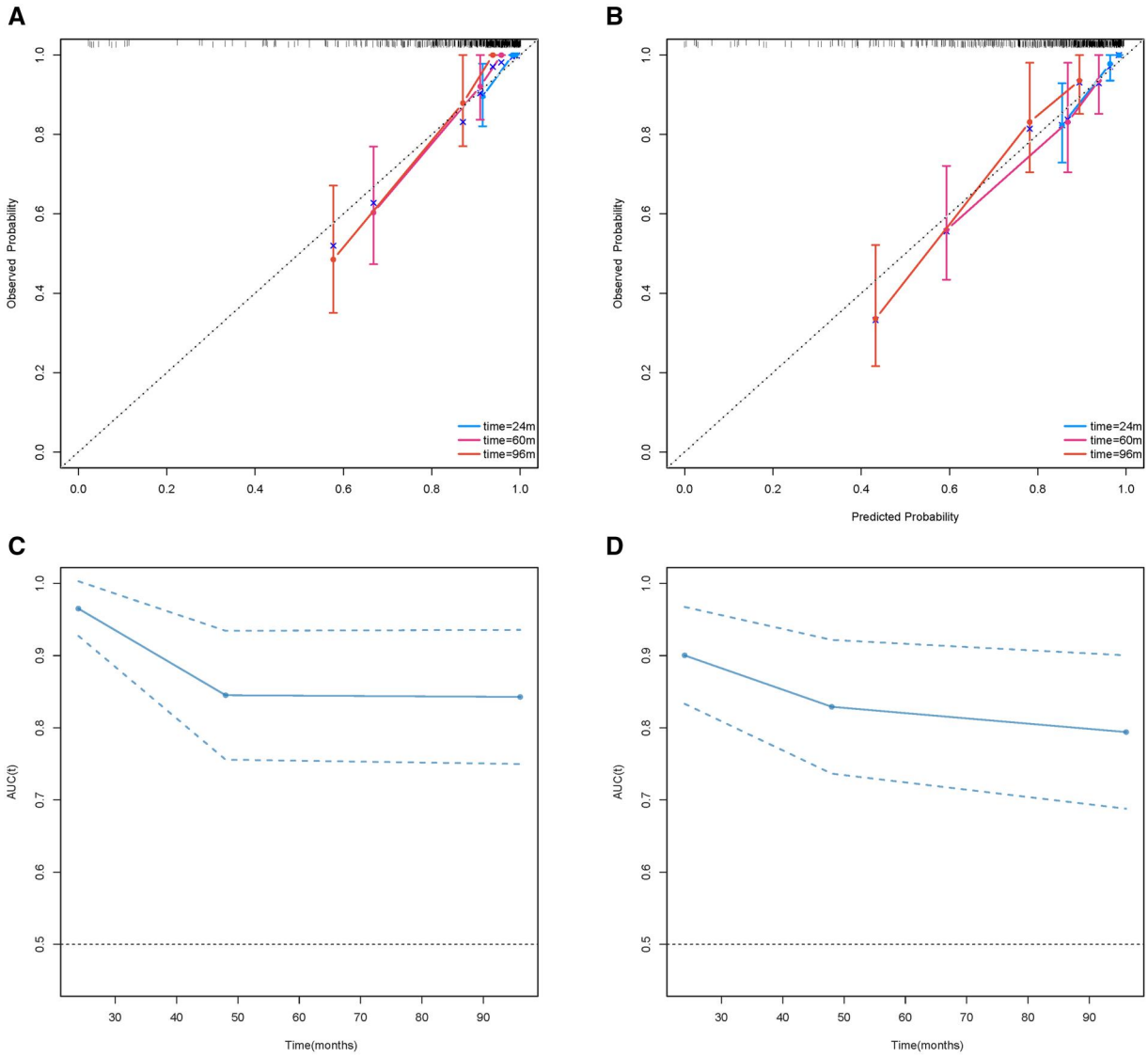

Figure 3. Calibration plots and calibration curve in the development and validation group of the nomogram. Calibration in the development group (**A**) and validation group (**B**); calibration curve in the development group (**C**) and validation group (**D**)

a reliable biomarker for SSc-ILD [32]; an increased level of KL-6 at baseline can predict the risk of ILD progression [33], and the progressive increase in KL-6 levels during follow-up is associated with disease progression in patients with SSc-ILD [34]. However, this study did not confirm the predictive ability of KL-6 as a biomarker. One of the primary endpoints of this study was respiratory failure, and the inclusion of ILD as a predictor may have led to outcome bias. Our findings did not indicate that ILD is a predictor of end-stage organ damage. A possible reason for our analysis is that the diagnosis of ILD was based on lung CT, which is only a qualitative diagnosis, without a semi-quantitative stratified analysis of ILD, and that the severity of ILD has a notable impact on irreversible organ damage. The study end point we selected was all organ damage, including the heart, lungs and kidneys, and hand and foot gangrene, whereas KL-6 could only reflect the severity of lung lesions but could not comprehensively predict the organ damage of SSc. The results of this study may be useful for predicting irreversible damage to the heart, kidney, hand and feet; however, the ability to predict lung damage may be limited. In the future, we will include more quantitative and semi-quantitative indicators, such as HRCT scores and lung function, to develop a better predictive model.

This study had some limitations. First, the data used in this study were from single-centre cases, and multicentre verification was not performed. Second, this study was a retrospective analysis; therefore, the medical records of patients, especially the description of physical signs, may not be very comprehensive. Third, the effect of different treatment regimens on irreversible organ damage failed to obtain positive results. If more patients were subsequently included, there might have been different outcomes for more innovative treatment regimens, such as rituximab and tuzumab. Fourth, the diagnosis of PAH in this study was mostly based on echocardiography, and a small number of patients underwent right heart catheterization, which may have led to a diagnostic bias. Finally, this study only included patients with diffuse SSc, whereas limited SSc, local scleroderma and sine scleroderma were excluded; therefore, the findings cannot be generalized to all patients with SSc.

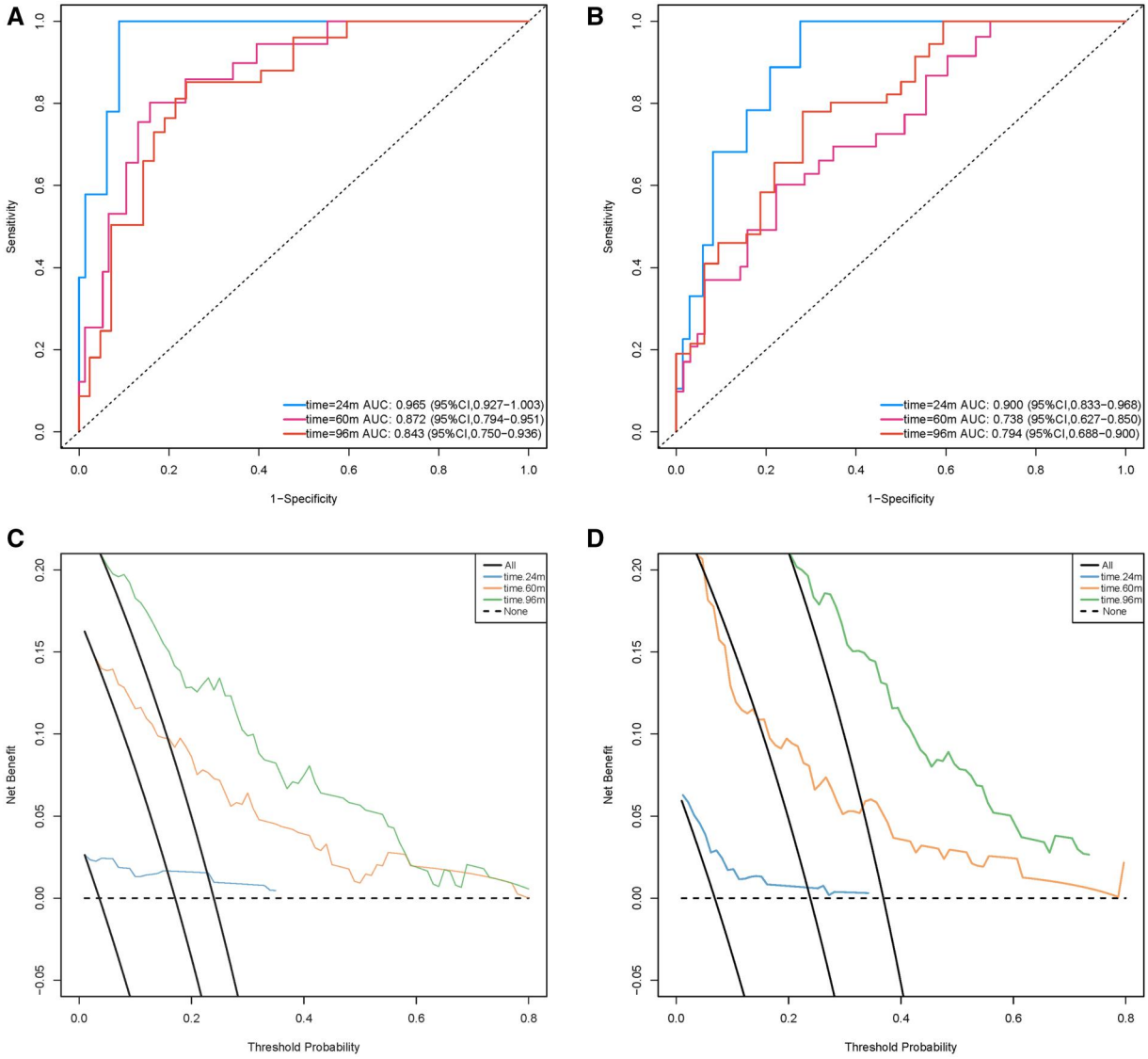

Figure 4. ROC and DCA of the nomogram ROC in the development group (**A**) and validation group (**B**); DCA in the development group (**C**) and validation group (**D**). AUC: area under roc curve; DCA: decision curve analysis; ROC: receiver operating characteristic curve

Conclusions

In summary, we included commonly used clinical indicators and constructed a nomogram with discriminant ability and accurate corrections to predict the risk of irreversible organ damage in patients with SSc. Based on the nomogram, the probability of irreversible organ damage in each patient was calculated using common clinical data to identify high-risk patients. Therefore, individualized treatment and management plans should be developed to improve prognosis.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data and material are available from the corresponding author upon reasonable request.

Contribution statement

Huo Xiaocong participated in the data collection and analysis and wrote the manuscript. Lin Jinying participated in study design and manuscript revision. The other authors contributed to data collection.

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