

# A multi-predictor model to predict risk of scleroderma renal crisis in systemic sclerosis: a multicentre, retrospective, cohort study

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## ABSTRACT

**Objective.** Scleroderma renal crisis (SRC) is a life-threatening syndrome. The early identification of patients at risk is essential for timely treatment to improve the outcome. Therefore, it is of great interest to provide a personalised tool to predict risk of SRC in systemic sclerosis (SSc).

**Methods.** We tried to set up a SRC prediction model based on the PKUPH-SSc cohort of 302 SSc patients. The least absolute shrinkage and selection operator (Lasso) regression was used to optimise disease features. Multi-variable logistic regression analysis was applied to build a SRC prediction model incorporating the features of SSc selected in the Lasso regression. Then, a multi-predictor nomogram combining clinical characteristics was constructed and evaluated by discrimination and calibration, with further assessment by external validation in a validation cohort composed of 400 consecutive SSc patients from other 4 tertiary hospitals.

**Results.** A multi-predictor nomogram for evaluating the risk of SRC was successfully developed. In the nomogram, four easily available predictors were contained, including disease duration <2 years, cardiac involvement, anaemia and corticosteroid >15mg/d exposure. The nomogram displayed good discrimination with an area under the curve (AUC) of 0.843 (95% CI: 0.797–0.882) and good calibration. High AUC value of 0.854 (95% CI: 0.690–1.000) could still be achieved in the external validation. The model is now available online for research use.

**Conclusion.** The multi-predictor nomogram for SRC could be reliably and conveniently used to predict the individual risk of SRC in SSc patients, and be a step towards more personalised medicine.

## Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterised by vasculopathy and fibrosis of multiple organ systems (1, 2). Scleroderma renal crisis (SRC) is the most serious complication, affecting approximately 11% of diffuse and 4% of limited cutaneous SSc patients (3). Although with the advent of angiotensin-converting enzyme (ACE) inhibitors, mortality rates decreased significantly, the survival rate of SRC is still as low as 70–82% at 1 year, and decreases to 50–60% at 5 years despite dialysis support (4). Early and accurate prediction and identification of high-risk SRC patients is of great significance to improving the outcome of patients with SSc (5). Several studies have reported different predicting variables associated with SRC including diffused SSc, cardiac involvement, presence of anti-RNA-polymerase III antibodies, and the use of corticosteroid especially in higher doses above 15 mg/day (6–8). However, a prediction tool synthesising patients' clinical characteristics to predict the probability of SRC accurately is not available yet. Nomograms is an emerging method to support accurate clinical decision-making, which combines several predictors instead of analysing a single predictor based on multivariable logistic analysis (9). In this study, we aimed to establish a multi-predictor nomogram to evaluate the risk of SRC by selecting significant predictors from clinical characteristics easily obtained from SSc patients.

## Methods

### Study cohorts

We used the Peking University People's Hospital Systemic Sclerosis Cohort (PKUPH-SSc) as a derivation cohort.

This cohort included 302 subsequent patients recruited from Department of Rheumatology and Immunology, Peking University People's Hospital, China, from January 1999 to March 2020. To test the generalisation of our multi-predictor nomogram, we collected 400 consecutive SSc patients from four tertiary medical centres from January 2010 to March 2020 as a validation cohort. They covered wide geographic regions, two from southern China (Kunming and Shenzhen) and two from northern China (Beijing and Shijiazhuang). All patients fulfilled the 1980 and/or 2013 American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria (10). The patients were subdivided into diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) according to the subclassification criteria of LeRoy *et al.* (11). Cases of SRC were identified based on the International Scleroderma Renal Crisis Study criteria (12). Written consents from all participants were collected according to the Declaration of Helsinki and with the approval of the Ethics Committee of Peking University People's Hospital. All relevant medical records were reviewed in detail to obtain the following data: age, gender, disease duration, disease subsets, Raynaud's phenomenon, digital ulcer, telangiectasia, SSc-related organ involvement, laboratory results, and medications. SSc-related cardiac involvement included (i) presence of pericardial effusion on echocardiogram (excluding infectious, malignancy, congenital and other causes), (ii) myocardial disease attributable to SSc based on a constellation of clinical features and supportive investigations, for example, syncope secondary to conduction abnormality, arrhythmia requiring defibrillator, heart block requiring permanent pacemaker or ablation, systolic or diastolic dysfunction on echocardiogram, (iii) moderate-to-severe right ventricular dysfunction noted on echocardiogram. Pulmonary arterial hypertension (PAH) was defined as a resting mean pulmonary artery pressure greater than 25 mmHg and pulmonary capillary wedge pressure (PCWP)  $\leq$ 15 mmHg measured by right heart cath-

**Table I.** Demographic and clinical characteristics of SSc patients with and without SRC in the PKUPH-SSc cohort for derivation and internal validation.

Characteristics	SRC (n=15)	without SRC (n=287)	p-value
<b>Demographic characteristics</b>			
Sex, female	12 (80.0%)	244 (85.0%)	0.874
Age, years	61 (54-68)	53 (44-62)	0.03
Disease duration, months	28 (14-78)	71 (24-168)	0.054
<b>Subtypes of SSc</b>			
Limited SSc	6 (40.0%)	130 (45.3%)	0.688
Diffuse SSc	9 (60.0%)	157 (54.7%)	0.688
<b>Clinical symptoms</b>			
Raynaud's phenomenon	11 (73.3%)	242 (84.3%)	0.444
Digital ulcer	1 (6.7%)	52 (18.1%)	0.430
Telangiectasia	3 (20.0%)	34 (11.8%)	0.593
Joint involvement	4 (26.7%)	131 (45.6%)	0.150
Myalgias and myopathy	6 (40.0%)	53 (18.5%)	0.086
Interstitial lung disease	10 (66.7%)	123 (42.9%)	0.07
PAH	5 (33.3%)	35 (12.2%)	0.05
Cardiac involvement	7 (46.7%)	43 (15.0%)	0.004
GI involvement	9 (60.0%)	144 (50.2%)	0.458
<b>Prior medications</b>			
CS use	11 (73.3%)	171 (59.6%)	0.298
Mean duration of CS use, months	9 (3-21)	12 (3-36)	0.789
CS use >15 mg/day	9 (60.0%)	52 (18.1%)	<0.001
ACE inhibitors	2 (13.3%)	15 (5%)	0.184
CCB	1 (6.7%)	29 (10.1%)	1.000
Immunosuppressants	11 (73.3%)	166 (57.8%)	0.235
<b>Laboratory features</b>			
ANA	13/14 (92.9%)	226/235 (96.2%)	0.446
Anti-CENP A	1/7 (14.3%)	34/115 (29.6%)	0.662
Anti-CENP B	1/7 (14.3%)	34/106 (32.1%)	0.573
Anti-Scl70	3/11 (27.3%)	70/224 (31.3%)	1.000
Anti-RP 11	2/7 (28.6%)	8/110 (7.3%)	0.110
Anti-RP 155	2/7 (28.6%)	6/103 (5.8%)	0.081
Anti-NOR90	2/5 (40.0%)	2/107 (1.9%)	0.009
Anti-Th/To	2/5 (40.0%)	2/107 (1.9%)	0.009
Anti-PM-Scl-100	0/7 (0%)	2/114 (1.8%)	1.000
Anti-PM-Scl-75	0/7 (0%)	7/107 (6.5%)	1.000
Anti-Ku	0/7 (0%)	3/112 (2.7%)	1.000
Anti-RNP	1/11 (9.1%)	39/231 (16.9%)	0.792
Anti-Sm	0/12 (0.0%)	6/236 (2.5%)	1.000
Anti-SSA	3/13 (23.1%)	43/242 (17.8%)	0.909
Anti-SSB	1/12 (8.3%)	11/242 (4.5%)	0.448
Serum creatinine, $\mu$ mol/l	110.5 (90.5-271.8)	59.0 (49.0-68.5)	<0.001
BUN, mmol/l	10.1 (6.5-23.4)	4.6 (3.7-5.7)	<0.001
Alb, g/l	35.3 (32.1-38.2)	38.4 (35.2-41.5)	0.008
ESR, % elevated	7 (46.7%)	107 (37.3%)	0.465
CRP, % elevated	6 (40.0%)	79 (27.5%)	0.865
IgG, g/l	10.35 (8.23-18.0)	13.3 (10.4-16.3)	0.147
IgA, g/l	2.24 (1.23-3.08)	2.37 (1.68-3.30)	0.444
IgM, g/l	0.87 (0.61-1.22)	1.05 (0.76-1.51)	0.181
C3	0.83 (0.74-1.01)	0.93 (0.80-1.06)	0.186
C4	0.22 (0.20-0.24)	0.20 (0.16-0.24)	0.181
Proteinuria	6 (40.0%)	19 (6.6%)	<0.001
Haematuria	7 (46.7%)	45 (15.7%)	0.006
WBC, $\times 10^9$ /l	7.6 (6.3-11.3)	6.0 (4.7-7.7)	0.003
Platelets, $\times 10^9$ /l	214.0 (181.0-229.0)	202.0 (159.0-248.0)	0.775
Hb, g/l	98.0 (94.0-121.0)	123.0 (108.0-135.0)	0.011
Anaemia	10 (66.6%)	60 (20.9%)	<0.0001

Data are presented as median (IQR) for continuous variables and number (frequency) (%) for categorical variables.

SSc: systemic sclerosis; SRC: scleroderma renal crisis; PAH: pulmonary arterial hypertension; GI involvement: gastrointestinal involvement; CS: corticosteroid; ACE inhibitors: angiotensin converting enzyme inhibitors; CCB: calcium channel blocker; Immunosuppressants included cyclophosphamide, azathioprine, mycophenolate mofetil or methotrexate; Alb: albumin; ANA: antinuclear antibody; BUN: blood urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; IgG: immunoglobulin G; WBC: white blood cell.

eterisation or considered present when systolic pulmonary arterial pressure (sPAP) was >40 mmHg, as determined by echocardiogram (13). SSc-related interstitial lung disease (ILD) was established by thoracic high-resolution CT scan, with pulmonary function tests and clinical assessment of respiratory symptoms as supporting diagnostic tools. SSc-related gastrointestinal (GI) involvement included (i) oesophageal dysmotility defined as distal dysphagia refractory to treatment with differential diagnoses (*e.g.* oesophageal stricture or malignancy) excluded by endoscopy, (ii) pseudo-obstruction with symptoms such as vomiting or constipation, with dilatation of the small and/or large bowel on imaging, (iii) gastro-oesophageal reflux disease or gastric antral vascular ectasia confirmed on endoscopy, (iv) oesophageal stricture confirmed on testing such as endoscopy or barium swallow, (v) low body mass index of <18.5 kg/m<sup>2</sup> or weight loss of >10% in the last 12 months (14). We also measured myalgia and myopathy assessed by proximal muscle weakness and elevated creatine kinase, as well as joint involvement including arthralgia, synovitis, joint contracture, and/or tendon friction rubs.

Laboratory results were recorded including the presence of anti-nuclear (ANA), anti-centromere proteins (CENP A and B), anti-topoisomerase I (Scl-70), anti-RNAP III (RP 11 and RP155), anti-NOR90, anti-Th/To, anti-PM-Scl-100, anti-PM-Scl-75, anti-Ku, anti-RNP, anti-Sm, anti-SSA, and anti-SSB antibodies; concentration of serum creatinine, blood urea nitrogen (BUN), albumin (Alb), sedimentation rate (ESR), C-reactive protein (CRP), complement (C3 and C4) and immunoglobulin G/A/M (IgG/A/M); white blood cell (WBC), hemoglobin (Hb) and platelet count; Proteinuria and haematuria are assessed by urinalysis (UA). Categorical variables were established for elevated ESR (>20mm/h), elevated CRP (>8mg/l), proteinuria (>2+ on UA) and haematuria (>2+ on UA or >10 RBCs/HPF). Anaemia was defined as Hb levels <130 g/l for males and <120 g/l for females. Anaemia was further categorised into three grades based on the Hb levels, as follows: mild anaemia (110 g/l-normal

**Table II.** Demographic and clinical characteristics of SSc patients with and without SRC in four validation cohorts composed of four rheumatology centres.

Characteristics	SRC (n=12)	without SRC (n=388)	p-value
Demographic characteristic			
Sex, female	11 (91.7%)	319 (82.2%)	0.643
Age, years	58.00 (47.75, 64.00)	52.00 (43.00, 59.00)	0.083
Disease duration, months	36.00 (21.50, 168.00)	60.00 (24.00, 144.00)	0.793
Subtypes of SSc			
Limited SSc	2 (16.7%)	79 (20.4%)	1.000
Diffuse SSc	10 (83.3%)	309 (79.6%)	1.000
Clinical symptoms			
Raynaud's phenomenon	11 (91.7%)	349 (89.9%)	1.000
Joint involvement	6 (50.0%)	127 (32.7%)	0.347
Interstitial lung disease	9 (75.0%)	290 (74.7%)	1.000
PAH	1 (8.3%)	48 (12.4%)	1.000
Cardiac involvement	6 (50.0%)	45 (11.6%)	<0.001
GI involvement	7 (58.3%)	144 (37.1%)	0.234
Prior medications			
CS use	11 (91.7%)	295 (76.0%)	0.362
CS >15 mg/day	4 (33.3%)	28 (7.2%)	0.006
Laboratory features			
Serum creatinine, umol/l	240.95 (123.75, 473.05)	59.00 (51.18, 69.78)	<0.001
BUN, mmol/l	14.19 (8.87, 22.45)	4.54 (3.60, 5.53)	<0.001
Alb, g/l	34.60 (30.32, 36.15)	38.20 (35.38, 41.20)	<0.001
Proteinuria	6 (50.0%)	20 (5.2%)	<0.001
Haematuria	7 (58.3%)	37 (9.5%)	<0.001
WBC, *10 <sup>9</sup> /l	9.56 (7.59, 11.57)	6.31 (4.91, 8.12)	0.002
Hb, g/l	89.00 (82.75, 103.50)	125.50 (116.00, 137.00)	<0.001
Anaemia	10 (83.3%)	59 (15.2%)	<0.001

Data are presented as median (IQR) for continuous variables and number (frequency) (%) for categorical variables.

SSc: systemic sclerosis; SRC: scleroderma renal crisis; GI involvement: gastrointestinal involvement; PAH: pulmonary arterial hypertension; CS: corticosteroid; Alb: albumin; BUN: blood urea nitrogen; Hb: haemoglobin; WBC: white blood cell.

**Table III.** Prediction factors for SRC in SSc patients.

Intercept and variable	Predicting model		
	$\beta$	Odds ratio (95% CI)	p-value
Intercept	-6.152	0.002 (0.000-0.010)	<0.001
Age >60 years old	0.746	2.109 (0.581-7.893)	0.254
Disease duration <2 years	1.376	3.958 (1.085-14.898)	0.036
Cardiac involvement	1.580	4.853 (1.281-19.107)	0.020
ILD	0.287	1.332 (0.345-5.376)	0.676
PAH	1.249	3.486 (0.790-15.048)	0.090
Anaemia	1.671	5.320 (1.593-19.923)	0.002
Corticosteroid exposure >15mg/d	2.101	8.176 (2.445-33.869)	0.008

$\beta$  is the regression coefficient. CI: confidential interval; ILD: interstitial lung disease; PAH: pulmonary artery hypertension; SSc: systemic sclerosis; SRC: scleroderma renal crisis.

levels), moderate anaemia (80-110 g/l) and severe anaemia (Hb<80 g/l). Anaemia was also categorised into three types based on mean corpuscular volume (MCV<80, 80-100, and >100 fl). Medications included corticosteroid, immunosuppressants (cyclophosphamide, azathioprine, mycophenolate mofetil or methotrexate), angiotensin converting enzyme (ACE) inhibitors and cal-

cium channel blocker (CCB) therapies. The use of corticosteroid, immunosuppressants, ACE inhibitors or CCB was defined as present if it was used at any time prior to event (renal crisis in SSc patients or the latest visit in SSc patients without SRC). Since previous studies have shown that the development of SRC is associated with antecedent high-dose corticosteroid therapy, especially

**Table IV.** The comparison of grading and types of anaemia between SSc patients with SRC and without SRC.

	SSc with SRC (n=15)	SSc without SRC (n=287)	p-value
Anaemia	10 (66.6%)	60 (20.9%)	<0.0001
Grading			
Mild	4 (40.0%)	37 (61.7%)	0.299
Moderate	5 (50.0%)	19 (31.7%)	0.294
Severe	1 (10.0%)	4 (6.6%)	0.549
Types			
Microcytosis (MCV <80fL)	1 (10.0%)	14 (23.3%)	0.678
Normocytic (MCV 80-100fL)	8 (80.0%)	42 (70.0%)	0.713
Macrocytosis (MCV >100fL)	1 (10.0%)	4 (6.7%)	0.549

SSc: systemic sclerosis; SRC: scleroderma renal crisis; MCV: mean corpuscular volume.

more than 15 mg/day, we also analysed the use of high-dose corticosteroid (over 15 mg/day) (6, 15).

#### Development and validation of a multi-predictor nomogram

Clinical characteristics were described and compared between SRC and non-SRC by univariate analyses. Variables associated with SRC ( $p < 0.1$ ) were included in further analyses. The least absolute shrinkage and selection operator (Lasso) method was used to screen

the optimal predictive features in risk factors of SRC (16). Features with non-zero coefficients in the Lasso regression model were selected. Then, a prediction model is established using multivariable logistic regression analysis. Variables with the  $p$ -value  $< 0.05$  were included in the model.

A multi-predictor nomogram was built to calculate the probability of occurrence of SRC in each patient by summing up all scores of predictors and then a conversion function between the

score and the probability. In addition, we validated the nomogram by evaluating the discrimination and calibration in the validation cohort.

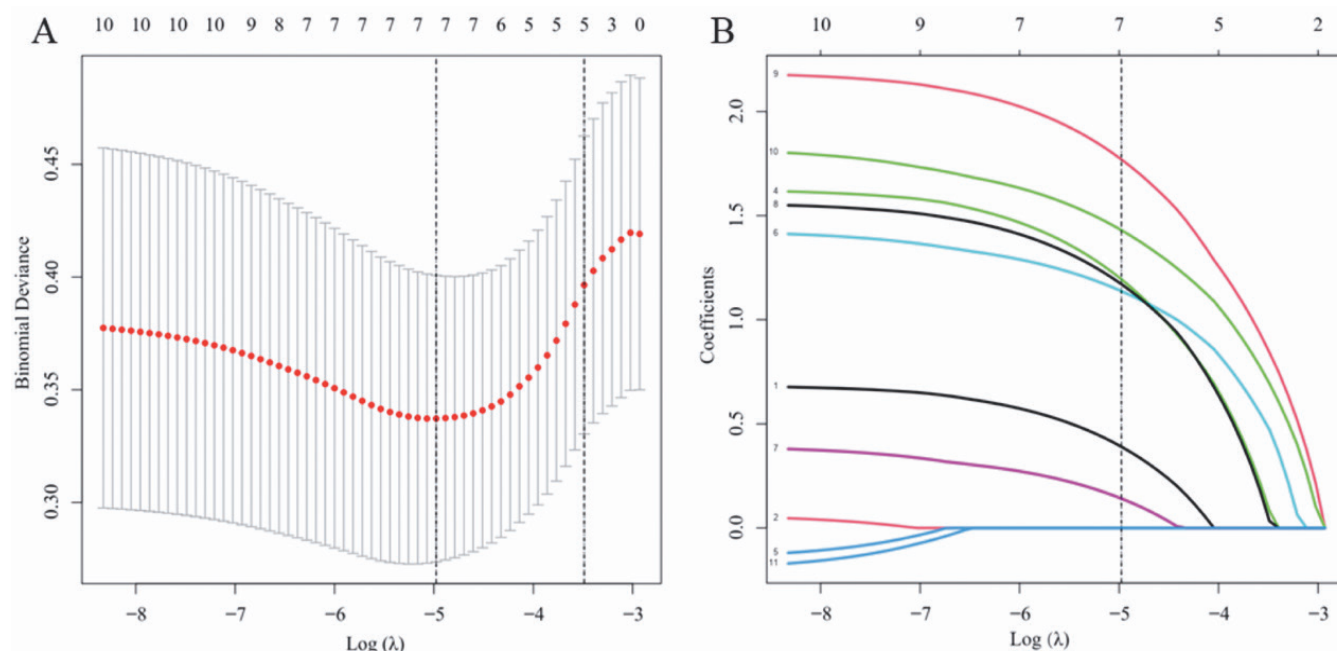
#### Statistical analysis

Continuous variables were reported as median [interquartile range, (IQR)] values. Categorical variables were summarised as counts (%). The independent sample  $t$ -test, Mann-Whitney  $U$ -test, Chi-square test and Fisher's exact test were conducted, as appropriate. All statistical analyses were performed with SPSS Statistics (v. 22) and R software (v. 3.6.3).

#### Results

##### Study patients

In the derivation cohort, 4.97% patients were identified as SRC. SRC patients had significantly higher proportions of cardiac involvement, ILD and PAH compared with controls. Notably, more SRC patients had received high-dose corticosteroid (over 15mg/day) before SRC onset. For the validation cohort, 3.0% SSc patients were complicated with SRC. The

**Fig. 1.** Demographic and clinical feature selection using the Lasso binary logistic regression model.

**A:** Optimal parameter ( $\lambda$ ) selection in the Lasso model via minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted versus  $\log(\lambda)$ . Dotted vertical lines were drawn at the optimal values by using the minimum criteria and the 1-SE criteria.

**B:** Lasso coefficient profiles of the 10 features: age >60 years old, disease duration <2 years, myalgia and myopathy, cardiac involvement, ILD, PAH, elevated WBC, anaemia, reduced albumin, and corticosteroid >15mg/d exposure. A coefficient profile plot was produced against the  $\log(\lambda)$  sequence. A vertical line was drawn at the optimal  $\lambda$ . As a result, 7 features including age >60 years old, disease duration <2 years, cardiac involvement, ILD, PAH, anaemia, and corticosteroid >15mg/d exposure with non-zero coefficients were selected.

Lasso: least absolute shrinkage and selection operator; SE: standard error.

detailed clinical characteristics are provided in Tables I, II and IV.

### Features selection

Of the clinical characteristics, univariate comparison between SRC and non-SRC in the derivation cohort identified 10 features related to SRC: age >60 years old, disease duration <2 years, myalgia and myopathy, cardiac involvement, ILD, PAH, elevated WBC, anaemia, reduced albumin, and corticosteroid >15mg/day exposure. With Lasso analysis, all the above variables were then reduced to 7 potential predictors (Fig. 1A-B).

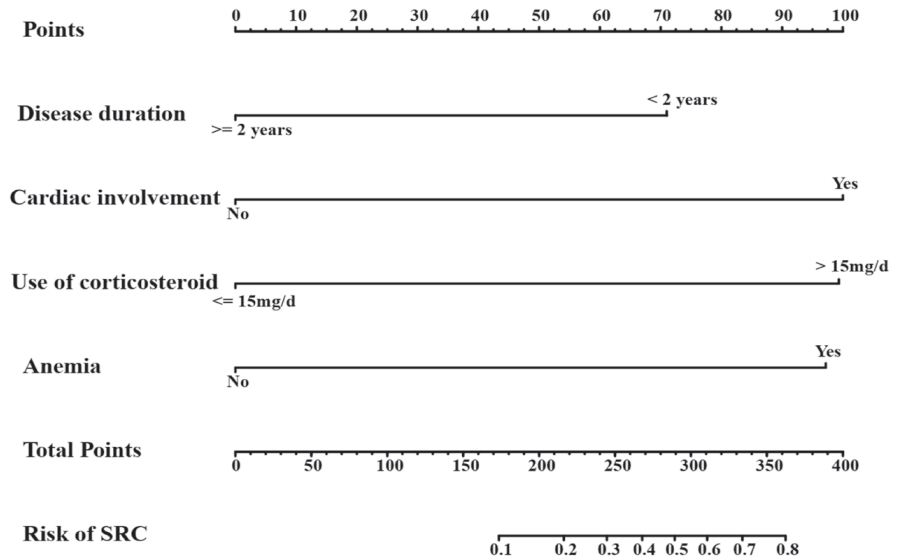
### Development of an individualised prediction model

Seven features above were further analysed in the multivariable logistic analysis, and three items (age, ILD and PAH) were removed at this stage as they were not statistically significant. Finally, four independent predictors including disease duration <2 years, cardiac involvement, anaemia and corticosteroid >15mg/day exposure remained in the final multivariable logistic model (Table III) and were presented as the nomogram (Fig. 2). An online version of our nomogram can be accessed at <https://predicting-risk-of-src.shinyapps.io/dynomapp/>.

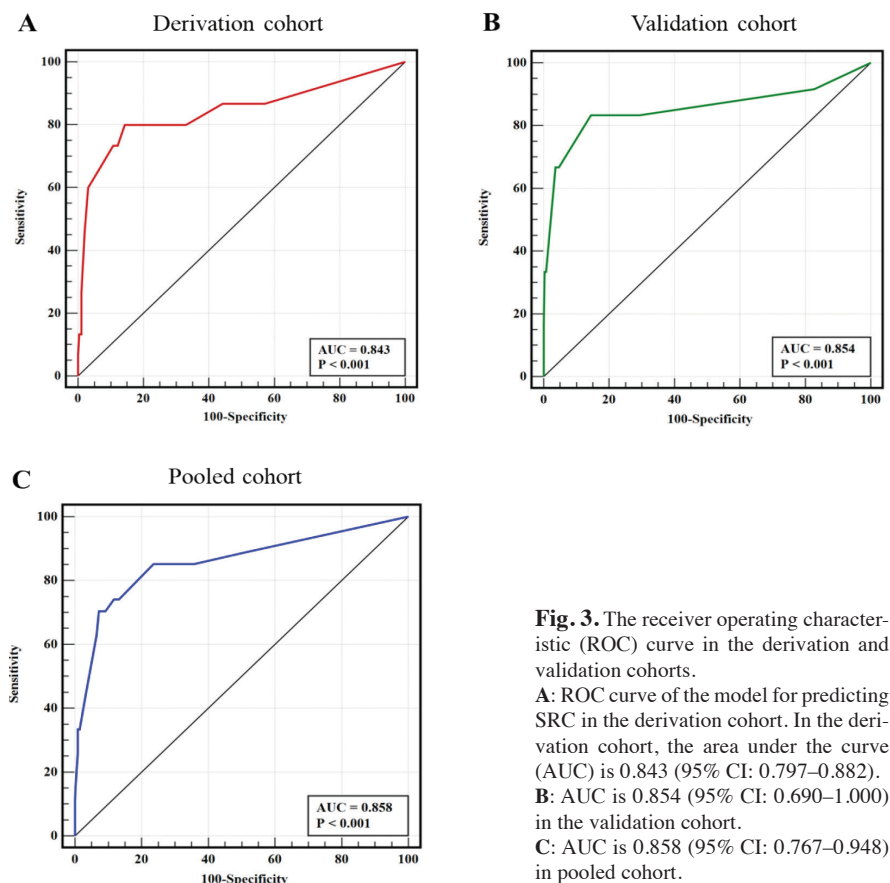
### Performance of the SRC risk nomogram

For the nomogram development, we first performed an internal validation to test the performance of our model. In the derivation cohort, the AUC for the prediction nomogram was 0.843 (95% CI: 0.797–0.882), indicating good discrimination capability (Fig. 3A). The Hosmer-Lemeshow test used to calibrate SRC risk nomogram also demonstrated good consistency ( $\chi^2=6.788$ ,  $p=0.237$ ).

We further validated our model in the validation cohort. The AUC of the SRC risk nomogram was 0.854 (95% CI: 0.690–1.000) in the validation cohort (Fig. 3B) and 0.858 (95% CI: 0.767–0.948) in pooled cohort (Fig. 3C). The Hosmer-Lemeshow test for calibration of the SRC risk nomogram showed relatively good agreement between the actual and predicted risk. ( $\chi^2=8.947$ ,



**Fig. 2.** A prediction nomogram integrates four clinical predictors including disease duration <2 years, cardiac involvement, anaemia, corticosteroid >15mg/d exposure.



**Fig. 3.** The receiver operating characteristic (ROC) curve in the derivation and validation cohorts.

**A:** ROC curve of the model for predicting SRC in the derivation cohort. In the derivation cohort, the area under the curve (AUC) is 0.843 (95% CI: 0.797–0.882).

**B:** AUC is 0.854 (95% CI: 0.690–1.000) in the validation cohort.

**C:** AUC is 0.858 (95% CI: 0.767–0.948) in pooled cohort.

$p=0.111$  in validation cohort;  $\chi^2=7.363$ ,  $p=0.195$  in pooled cohort).

### Discussion

Here, we have developed and optimised a feasible multi-predictor nomogram for SRC. This SRC risk predic-

tion tool was derived from real-life data, and may assist clinicians with early identification of patients at high risk of SRC and taking interventions in time to prevent the occurrence of life-threatening renal failure.

In this multi-variable prediction model,

all included variables were independently correlated with SRC. Consistent with previous studies, we found SRC was most common in the early stage of SSc. The mean disease duration of symptoms prior to the diagnosis of SRC was 3.2 and 1.9 years in previous studies (6, 17), and 2.3 years in the present report. Our results showed disease duration <2 years contributes 71 points for the risk of SRC in the nomogram with a maximum possible total score of 367 points, and an approximately 4-fold higher risk of SRC was found in early SSc subjects.

Cardiac involvement is the only visceral symptom included in the prediction model and contributes as high as 100 points for the risk of SRC in the nomogram. Cardiac involvement may lead to the decrease of renal blood flow and cause hyperplasia of the juxtaglomerular apparatus and release of renin, which may contribute to SRC.

Although the presence of anaemia is often ominous in SSc, Steen *et al.* reported that anaemia occurred frequently in SSc patients with renal involvement (6). In our study, anaemia is present in approximately two thirds of SRC patients and contributes 97 points in the nomogram. There are two possible reasons for this. The well-established relationship between inflammation and anaemia was confirmed in this study by significant associations between lower haemoglobin concentrations and higher level of ESR ( $r = -0.287$ ,  $p < 0.001$ ) or CRP ( $r = -0.125$ ,  $p = 0.046$ ). Another reason is thrombotic microangiopathy (TMA), and the exact pathogenesis of TMA in SRC is still unclear.

The use of corticosteroid >15 mg/day was also included as a potent risk factor for SRC. Corticosteroid therapy, especially in high doses, triggers SRC by favoring the vasoconstriction of renal arteries and altered perfusion of the juxtaglomerular apparatus. From the current literature and our study (18), corticosteroid dose is related to the risk of SRC, and we strongly suggest avoiding medium to high dose corticosteroid

therapy for SSc patients, especially in early SSc patients with anaemia and cardiac involvement.

There are also several limitations of our current study. First, the sample size is still small, which is a common issue for a rare disorder. A further collaboration with other SSc cohorts to widely validate the nomogram is warranted. Second, we did not include all reported potential risk factors for SRC in our nomogram, such as the presence of anti-RNA-polymerase-III antibodies. The presence of anti-RNA-polymerase-III antibodies in SSc is about 7% in Asia (19). As a fact, the detection rate of anti-RNA-polymerase-III antibodies is quite low in China because many hospitals have no facilities for the test. Remarkably, our model has a certain tolerance for the missing of anti-RNA-polymerase-III antibodies, as we still achieved high performance on the external validation cohort.

In conclusion, we used four easily available clinical characteristics to develop a multi-predictor nomogram that predicts individual risk of SRC in patients with SSc. By submitting clinical information online, medical staff can further screen for patients most at risk for SRC at the time of diagnosis or adjusting treatments of SSc.

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