THERAPEUTIC ADVANCES in
Chronic Disease

Original Research

Predicting cardiovascular risk in a Chinese primary Sjögren's syndrome population: development and assessment of a predictive nomogram

Ther Adv Chronic Dis

2023, Vol. 14: 1–12

DOI: 10.1177/20406223231181490

Jincheng Pu*, Jiamin Song*, Shengnan Pan, Shuqi Zhuang, Ronglin Gao, Yuanyuan Liang, Zhenzhen Wu, Yanqing Wang, Youwei Zhang, Lufei Yang, Fang Han, Huihong Wu, Jianping Tang and Xuan Wang

Abstract

Background: Patients with primary Sjögren's syndrome (pSS) are at increased risk of cardiovascular morbidity as compared with the general population.

Objectives: A retrospective study on 349 Chinese patients with pSS was conducted to identify potential risk factors for cardiovascular events and develop a cardiovascular risk nomogram.

Design: This is a retrospective observational study.

Methods: The study included 349 patients who were diagnosed with pSS at Tongji Hospital, School of Medicine, Tongji University, China from January 2010 to March 2022. The least absolute shrinkage and selection operator (LASSO) was used to select features for the cardiovascular risk model. The features selected in LASSO were used to build the cardiovascular risk model in a multivariate logistic regression analysis. C-index, receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis were used to assess the predictive model. Internal validation was performed by bootstrapping.

Results: Sex, joint pain as an initial symptom, dry mouth, oral ulcers, dental caries, Raynaud's phenomenon, fatigue, diabetes, elevated thyroid-stimulating hormone (TSH) level, and elevated systolic blood pressure were included in the nomogram for the prediction of cardiovascular risk. Our model had good discrimination (C-index: 0.824, 95% confidence interval: 0.712–0.936) and good calibration (C-index in the interval validation: 0.8). Decision curve analysis indicated that our nomogram demonstrated clinical usefulness for intervention in a cardiovascular disease possibility threshold of 3%.

Conclusion: The cardiovascular risk nomogram incorporating sex, initial joint pain, dry mouth, oral ulcer, dental caries, Raynaud's phenomenon, fatigue, diabetes, elevated TSH, and systolic blood pressure could be used in the prediction of cardiovascular risk in patients with pSS and the guidance of further treatment.

Keywords: cardiovascular events, nomogram, predictive model, primary Sjögren's syndrome, risk

Received: 18 October 2022; revised manuscript accepted: 24 May 2023.

Correspondence to:
Jianping Tang
Department of Rheumatology and Immunology, Tongji Hospital, School of Medicine, Tongji University, No.389 Xincun Road, Shanghai 200065, China.
tangjp6512@126.com

Xuan Wang
Department of Rheumatology and Immunology, Tongji Hospital, School of Medicine, Tongji University, No.389 Xincun Road, Shanghai 200065, China.
xuan2018@tongji.edu.cn

Jincheng Pu
Jiamin Song
Shengnan Pan
Shuqi Zhuang
Ronglin Gao
Yuanyuan Liang
Zhenzhen Wu
Yanqing Wang
Youwei Zhang
Lufei Yang
Fang Han
Huihong Wu
Department of Rheumatology and Immunology, Tongji Hospital, School of Medicine, Tongji University, Shanghai, China

*Jincheng Pu and Jiamin Song contributed equally to this work.

Introduction

Primary Sjögren's syndrome (pSS), a chronic rheumatic disease, is characterized by a dry mouth and eyes caused by the lymphocytic infiltration of the salivary and lachrymal glands, accompanied by autoantibody production.[1] The prevalence of pSS in different studies and ethnic populations ranges from 0.1% to 4.8%.[2] Extra-glandular involvement occurs in at least one-third of patients with pSS, including thyroid, lung, gastrointestinal, vasculitis, kidney, hematological, central nervous, and peripheral nervous systems.[1]

Patients with pSS are more likely to have cardiovascular events than healthy people, which might be mainly associated with a higher prevalence of vasculitis and atherosclerosis caused by multiple metabolic abnormalities.[3] Several studies showed that acute systemic inflammation and chronic systemic vasculitis might be associated with endothelial cell abnormalities.[4] Patients with pSS may develop moderate vasculitis similar to polyarteritis nodosa.[5] The association between pSS chronic systemic vasculitis and atherosclerosis is unclear. The incidence of subclinical atherosclerosis (anomalies of carotid intima-media thickness or pulse wave velocity) in patients with pSS is higher.[6–8] Atherosclerosis in patients with pSS might be a major cause of death similar to that in systemic lupus erythematosus and rheumatoid arthritis.[9]

In addition to atherosclerosis, other traditional risk factors for cardiovascular events (hypertension, metabolic syndrome, periodontitis, and immune modulators, such as glucocorticoids) seem to have some relationships with pSS. Several studies found that diabetes, hypertension, and hyperlipidemia were more common in patients with SS than in the general population.[10–13]

Although disease-modifying antirheumatic drugs were thought to reduce cardiovascular events by inhibiting inflammatory processes, they may also produce cardiotoxicity. Hydroxychloroquine has superior effects on hypoglycemia, lipid control, and as an antithrombotic,[14] but may cause macular degeneration, restrictive cardiomyopathy, and conduction abnormalities.[15,16] Glucocorticoid is an effective anti-inflammatory drug, but hypertension, hyperlipidemia, insulin resistance, and central obesity induced by it could increase the risk of myocardial infarction and heart failure.[17–19] Rituximab also has the potential to cause hypotension, arrhythmias, and angina.[20]

Considering the number of associated risk factors, an accurate prediction of cardiovascular risk in patients with pSS and corresponding intervention measures might prevent cardiovascular events and improve outcomes. Although previous studies of cardiovascular events have identified several risk-related variables, there is no predictive model of cardiovascular risk in patients with pSS. An effective tool to predict cardiovascular risk using features available at the beginning of the treatment and to allow patients to adjust their lifestyles and medication accordingly should be built.

Materials and methods

Participants

Patients with pSS were diagnosed and followed at the Department of Rheumatology and Immunology, Tongji Hospital, School of Medicine, Tongji University in Shanghai, China from January 2010 to March 2022.

Inclusion criteria: All patients included met the ACR/EULAR 2016 classification criteria, which included symptoms (dry mouth and eyes), eye examination (corneal staining test, Schirmer's test), Sjögren's syndrome A (SSA) antibody in the blood, and a biopsy of salivary glands.[21]

Exclusion criteria: Patients developed other autoimmune diseases secondary to pSS that may affect the outcome, such as systemic lupus erythematosus. Patients were missing critical data, such as cardiovascular events and blood pressure.

This study was conducted in accordance with the approval of the Ethics Committee of Tongji Hospital, School of Medicine, Tongji University (Approval No. K-W-2023-001) and the Declaration of Helsinki, and informed consent forms were verbally obtained from all patients at the time of the patient's visit to our clinic. Since this was a retrospective study, we could not obtain written informed consent of patients at the first visit. After confirming the study protocol, we conducted a simple telephone follow-up with the participants. First, we verified the participants' identity, briefly stated information related to the clinical trial, including design and the consent of the Ethics Committee, and obtained oral informed consent. After obtaining informed consent, we collected participants' information and conducted relevant research. Those participants who did not agree to participate were excluded, and no related information was collected.

Characteristics

As a retrospective observational study, the sociodemographic and clinical features of our patients were obtained from interviews and physical examinations. Details of age at the first diagnosis, sex, smoking, symptoms, age at symptoms onset, duration of symptoms, initial symptoms, systems involved, and other diseases at the first visit were collected from the medical history. Weight, height, and blood pressure were collected from the nursing

system of our hospital. Symptoms mainly include dry mouth, dry eyes, oral ulcers, dental caries, Raynaud's phenomenon (RP), and fatigue. In our study, feeling a dry mouth every day for more than 3 months and swallowing dry food with frequent water assistance was defined as a dry mouth. Eye dryness was defined as repeated sand and gravel sensation in the eyes, dry eyes lasting more than 3 months, or requiring artificial tears three or more times a day. Dental caries, commonly known as wormwood and tooth decay, is a bacterial disease. The presence, quantity, and time of dental caries were recorded. Oral ulcers were defined as the repeated occurrence of oral ulcers within 1 year, and impacting life. RP manifests as a limb-end skin color change characterized by pain and paresthesia caused by paroxysmal spasm of the acral artery, temporary reduction or interruption of blood flow, and subsequent expansion and congestion. Fatigue was defined as non-specific conscious fatigue, limb weakness, and weakness. Body mass index (BMI) was calculated by dividing weight by height in square meters. Blood pressure was measured twice and the average value was determined.

The laboratory data of these patients were collected from the standardized tests of the clinical laboratory in Tongji Hospital, School of Medicine, Tongji University, which have all been verified. The laboratory data included blood routine, blood biochemistry, liver and kidney function, antibody, urine routine, etc. Myocardial ischemia, heart failure, cerebral infarction, and stroke were recorded as cardiovascular events during the follow-up. The time of cardiovascular events was recorded. The treatment of patients at the initial visit and subsequent follow-up were also recorded. The data were all stored in an electronic and secure database.

The EULAR Sjögren's Syndrome Disease Activity Index Score (ESSDAI) was used to assess disease activity in SS by weighing 12 specific physical aspects to get a score ranging from 0 to 123.[21] The 12 aspects were systemic condition, lymphadenopathy, gland involvement, skin manifestations, joint abnormalities, muscle involvement, respiratory system, urinary system, peripheral nervous system, central nervous system, blood system abnormalities, and biological index abnormalities. Each system in the ESSDAI was evaluated using medical records and laboratory results. The ESSDAI score of each aspect was scored by two people separately and checked by a third person. Finally, the total ESSDAI score was calculated by two people.

Classification of patients with pSS

Our previous analysis of patients with pSS found that the frequency of dyslipidemia in pSS patients was higher than that in the healthy population, and most pSS patients were middle-aged women. Therefore, we defined myocardial ischemia, heart failure, cerebral infarction, and stroke related to atherosclerosis as cardiovascular disease (CVD). Our patients were divided into the CVD group and non-CVD group according to whether there were subsequent cardiovascular events during the follow-up.

Statistical analysis

The sociodemographic and clinical features of our patients were represented as the mean (SD), median (interquartile range), or count (percentage) and analyzed by R software (version 3.5.1; https://www.R-project.org). The characteristics between the two groups were compared by the *t*-test, Mann–Whitney *U* test, or chi-square test. The features were assessed by odds ratio (OR) with a 95% confidence interval (CI) and *p*-value (two-tailed). For the sample size and the number of independent variables required for logistic regression analysis, it is generally believed that the number of samples should be 5–10 times the number of independent variables. The result is statistically significant if the two-tailed *p*-value is less than 0.05.

We used the least absolute shrinkage and selection operator (LASSO) regression model to choose nonzero characteristics that best predict cardiovascular events in patients with pSS.[22–24] Then, we used characteristics selected in the LASSO to develop a prediction model *via* multivariable logistic regression for further analysis. The model included all sociodemographic and clinical characteristics with *p*-values less than 0.05.[25] Other potential predictors were included in the predictive model for cardiovascular risk.[26,27]

A receiver operating characteristic (ROC) curve and a calibration curve were used to assess the cardiovascular risk nomogram.[28] Harrell's C-index was measured to quantify the discrimination of the cardiovascular risk model. Bootstrapping validation (1000 bootstrap resamples) was used to

obtain a relatively calibrated C-index of the model.[29] Decision curve analysis was performed to assess the clinical applicability of the cardiovascular risk model through the quantification of the net benefits (the value of the proportion of true-positive patients minus the proportion of false-positive patients, weighing the relative harm of non-intervention against the negative effects of unnecessary intervention) at different threshold probabilities in the pSS cohort.[30,31]

Results

Characteristics of patients

In this study, 392 patients with pSS were diagnosed and followed at Tongji Hospital, School of Medicine, Tongji University from 2010 to 2022. However, 1 patient was excluded due to the subsequent development of systemic lupus erythematosus, 12 patients were excluded due to lack of follow-up cardiovascular event records, 30 patients were excluded due to missing records of critical data, such as blood pressure, and 349 patients were eventually included (Supplemental Figure S2).

Finally, there were 31 males and 318 females included, aged between 16 and 87 years. According to whether they had cardiovascular events after diagnosis, 63 patients were divided into the CVD group, whereas 286 patients were divided into the non-CVD group. The characteristics of all study patients (CVD group and non-CVD group) are shown in Table 1 and Supplemental Figure S1.

The proportion of men in the CVD group was higher than that in the non-CVD group (17.5% *versus* 7%, $p=0.016$). Also, the occurrence of dry mouth and dental caries in the CVD group was also higher than that in the non-CVD group (93.7% *versus* 78.7%, $p=0.01$; 74.6% *versus* 53.5%, $p=0.003$). Compared with the non-CVD group, the CVD group also had a higher probability of diabetes and high systolic blood pressure (p-values were both less than 0.001). There was a higher prevalence of joint pain as an initial symptom, oral ulcers, and normal TSH levels in the CVD group than in the non-CVD group (marginal statistical significance). No statistical significance was observed for other characteristics between the two groups.

In addition, the proportion of RP in the CVD group was lower than that in the non-CVD group ($p=0.011$). Considering the unusual difference in the incidence of RP between the CVD group and non-CVD group, we divided pSS patients into the RP group and non-RP group, and the results are shown in Supplemental Table S1. The average age of diagnosis and age of disease onset of the RP group were lower than that of the non-RP group (54.2 ± 12.8 *versus* 58.5 ± 13, $p=0.031$; 44.3 ± 14.1 *versus* 50 ± 13.9, $p=0.009$). The RP group showed lower incidences of hypertension, high systolic blood pressure, and CVD than the non-RP group (p-values were 0.034, 0.001, and 0.004, respectively).

Feature selection

Based on 349 patients in the cohort, 71 sociodemographic and clinical characteristics were reduced to 10 potential predictors with nonzero coefficients (about a 7:1 ratio) *via* the LASSO regression model (Figure 1). These features included sex, initial joint pain, dry mouth, oral ulcers, dental caries, RP, fatigue, diabetes, elevated TSH, and systolic blood pressure.

Identification of significant risk factors for CVD

The logistic regression model incorporating sex, initial joint pain, dry mouth, oral ulcers, dental caries, RP, fatigue, diabetes, elevated TSH, and systolic blood pressure was built and presented as the nomogram (Table 2). Males were more likely to develop CVD than females (OR: 3.764, 95% CI: 1.354–12.548, $p=0.012$). Patients with joint pain as an initial symptom (OR: 3.365, 95% CI: 1.282–8.709, $p=0.012$), dry mouth (OR: 4.264, 95% CI: 1.463–15.997, $p=0.015$), dental caries (OR: 3.173, 95% CI: 1.558–6.852, $p=0.002$), fatigue (OR: 2.405, 95% CI: 1.098–5.197, $p=0.026$), diabetes (OR: 3.528, 95% CI: 1.458–8.471, $p=0.005$), and elevated systolic blood pressure (OR: 4.149, 95% CI: 2.18–8.016, $p<0.001$) showed a higher prevalence of CVD than those without initial joint pain, dry mouth, dental caries, fatigue, diabetes, or elevated systolic blood pressure. Patients with RP seem

Table 1. Clinical characteristics of patients with primary Sjögren's syndrome.

Characteristics	*n* (%)		*p*
	Non-CVD (*n* = 286)	CVD (*n* = 63)	
Sex			
Female	266 (93)	52 (82.5)	0.016*
Male	20 (7.0)	11 (17.5)	
Joint pain at first	25 (8.7)	11 (17.5)	0.067
Dry mouth	225 (78.7)	59 (93.7)	0.01*
Oral ulcer	65 (22.7)	22 (34.9)	0.062
Dental caries	153 (53.5)	47 (74.6)	0.003**
Raynaud's phenomenon	54 (18.9)	3 (4.8)	0.011*
Fatigue	47 (16.4)	16 (25.4)	0.135
Elevated TSH	38 (13.3)	4 (6.3)	0.187
Diabetes	21 (7.3)	14 (22.2)	<0.001***
Systolic blood pressure	59 (20.6)	34 (54)	<0.001***

CVD, cardiovascular disease; TSH, thyroid-stimulating hormone.
Data are expressed as count (percent). The *p*-value was calculated by the chi-square test.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

unlikely to develop CVD (OR: 0.238, 95% CI: 0.053–0.748, $p = 0.028$).

Establishment of the cardiovascular risk nomogram

To facilitate clinical evaluation, a nomogram based on 10 important risk factors was built and shown as an image (Figure 2). The nomogram model had satisfactory prediction accuracy (consistency index was 0.824; 95% CI: 0.712–0.936). The points of each risk factor ranged from 0 to 100 with total points between 0 and 600.

Assessment of the cardiovascular risk nomogram

The area under the ROC curve of the cardiovascular risk nomogram was 0.824 (Figure 3(a)), which demonstrated a good prediction capability. The calibration curves of the nomogram used to predict cardiovascular risk in patients with pSS showed good consistency (Figure 3(b)). The C-index verified by bootstrapping is 0.8, suggesting that the model had good discrimination.

The decision curve showed that the use of the cardiovascular risk nomogram to predict cardiovascular risk added more benefit than the scheme when the threshold probability of a patient and a clinician was more than 3% and less than 68%, respectively (Figure 3(c)). The net benefit in the cardiovascular risk nomogram was comparable with several overlaps within this range.

Discussion

The purpose of our retrospective study was to identify potential risk factors for cardiovascular events in Chinese patients with pSS. The main finding of this study was to identify 10 risk factors associated with cardiovascular risk. In addition to the traditional risk factors for cardiovascular events, we also found that cardiovascular events may be closely related to multiple characteristic symptoms of SS, such as dental caries, which may help us better

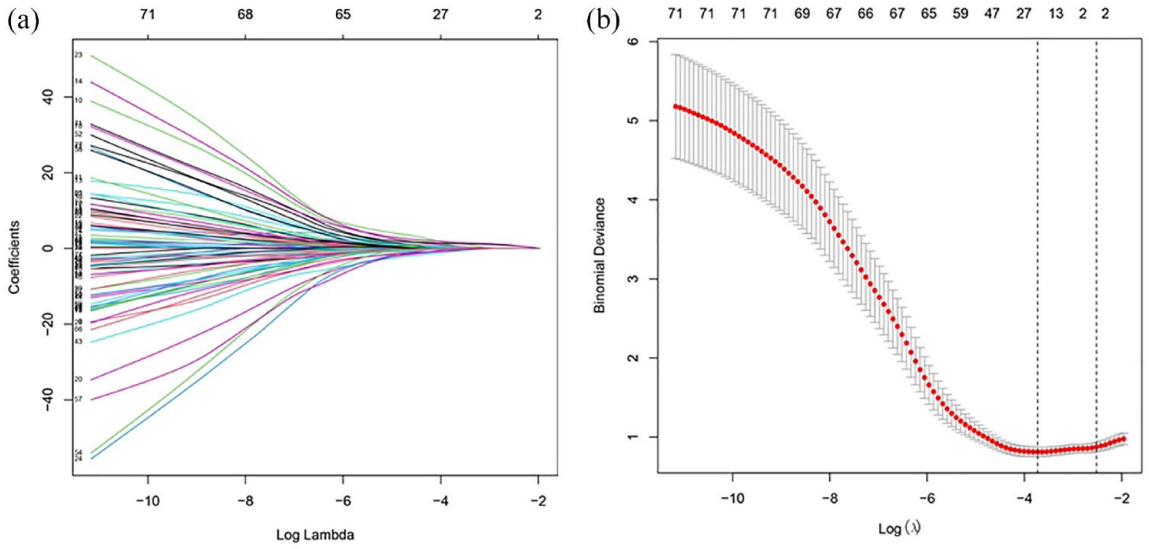

Figure 1. Demographic and clinical feature selection using the LASSO binary logistic regression model. (a) Optimal parameter (lambda) selection in the LASSO model used fivefold cross-validation *via* minimum criteria. The partial likelihood deviance (binomial deviance) curve was plotted *versus* log (lambda). Dotted vertical lines were drawn at the optimal values using the minimum criteria and the 1 SE of the minimum criteria (the 1-SE criteria). (b) LASSO coefficient profiles of the 77 features. A coefficient profile plot was produced against the log (lambda) sequence. A vertical line was drawn at the value selected using fivefold cross-validation, where optimal lambda resulted in five features with nonzero coefficients.
LASSO, least absolute shrinkage and selection operator; SE, standard error.

Table 2. Prediction factors for cardiovascular risk in patients with primary Sjögren's syndrome.

Intercept and variable	Prediction model		*p*
	β	OR (95% CI)	
Intercept	−4.681	0.009 (0.002–0.032)	<0.001***
Sex	1.326	3.764 (1.44–9.736)	0.006**
Joint pain at first	1.213	3.365 (1.282–8.709)	0.012*
Dry mouth	1.45	4.264 (1.463–15.997)	0.015*
Oral ulcer	0.508	1.663 (0.818–3.347)	0.155
Dental caries	1.155	3.173 (1.558–6.852)	0.002**
Raynaud's phenomenon	−1.436	0.238 (0.053–0.748)	0.028*
Fatigue	0.878	2.405 (1.098–5.197)	0.026*
Elevated TSH	−0.365	0.694 (0.172–2.165)	0.564
Diabetes	1.261	3.528 (1.458–8.471)	0.005**
Systolic blood pressure	1.423	4.149 (2.18–8.016)	<0.001***

CI, confidence interval; TSH, thyroid-stimulating hormone.
β is the regression coefficient.
*$p<0.05$; **$p<0.01$; ***$p<0.001$.

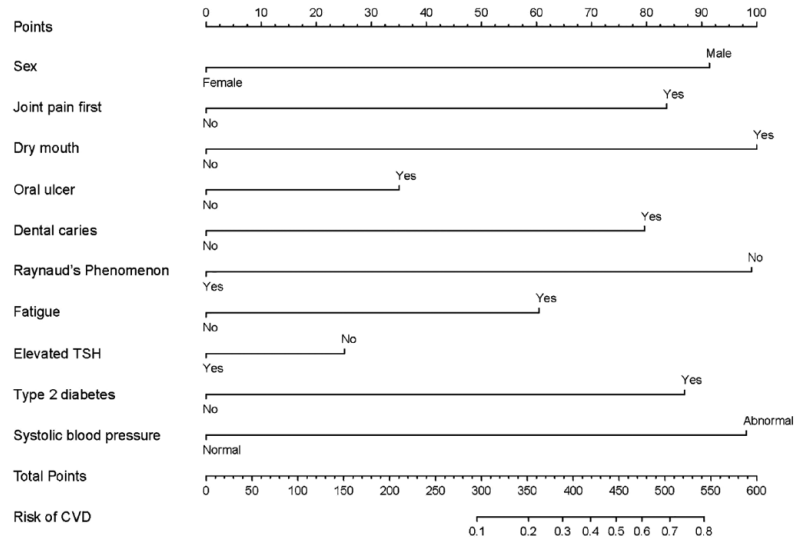

Figure 2. Developed cardiovascular risk nomogram. The cardiovascular risk nomogram was developed in the cohort, with the sex, initial joint pain, dry mouth, oral ulcer, dental caries, Raynaud's phenomenon, fatigue, diabetes, elevated TSH, and systolic blood pressure incorporated.
TSH, thyroid-stimulating hormone.

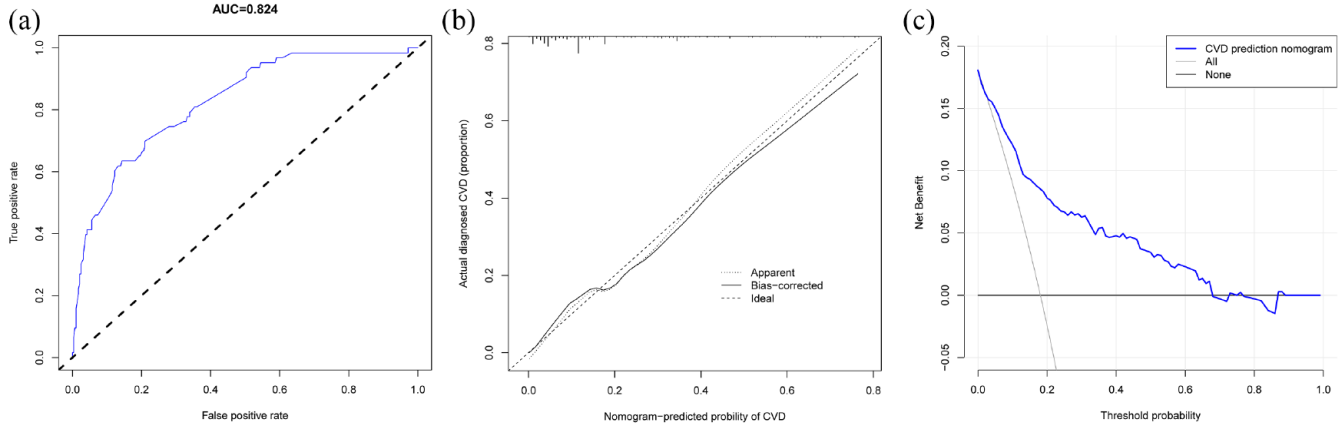

Figure 3. (a) ROC curves of the cardiovascular risk nomogram prediction in the cohort. The area under the curve was 0.824 (95% confidence interval: 0.712–0.936). (b) Calibration curves of the cardiovascular risk nomogram prediction in the cohort. The x-axis represents the predicted cardiovascular risk. The y-axis represents the actual diagnosed CVD. The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction. (c) Decision curve analysis for the cardiovascular risk nomogram. The y-axis measures the net benefit. The dotted line represents the cardiovascular risk nomogram. The thin solid line represents the assumption that all patients have CVDs. The thin thick solid line represents the assumption that no patients have CVDs. The decision curve showed that if the threshold probability of a patient and a doctor is $>3\%$ and $<68\%$, respectively, using this cardiovascular risk nomogram in the current study to predict cardiovascular risk adds more benefit than the intervention-all-patients scheme or the intervention-none scheme.

assess the cardiovascular risk of patients with pSS. As far as we know, this is the first observational study to find that a dry mouth might be a characteristic of cardiovascular risk in pSS.

Currently, nomograms have been widely used clinically for their user-friendly interface, higher accuracy, easier-to-understand prognosis, and better guidance for clinical decision-making.[32]

However, there is no cardiovascular risk nomogram for patients with pSS. Our study developed the first nomogram to predict cardiovascular risk in patients with pSS.

The prediction tool, including 10 easily available variables for cardiovascular risk in patients with pSS, was developed and validated. Incorporating risk factors of sociodemographic and clinical features into a nomogram will enable an accurate and personalized prediction of cardiovascular risk in patients with pSS. The high C-index of the internal validation showed good identification and calibration capabilities.[33] The relatively large sample size of our cohort made it possible to apply it widely and accurately.

About 18% of the patients with pSS in our cohort developed CVD, which seems to be a high level. In the risk factor analysis, sex, initial joint pain, dry mouth, oral ulcers, dental caries, RP, fatigue, diabetes, elevated TSH, and systolic blood pressure were associated with cardiovascular risk in patients with pSS. In the nomogram, male, joint pain as an initial symptom, dry mouth, oral ulcer, dental caries, non-RP, fatigue, diabetes, normal TSH, and elevated systolic blood pressure might be key independent risk factors for cardiovascular events in patients with pSS.

Similar to the general population, men are more likely to develop CVD in patients with pSS, which may be related to the cardiovascular protection of estrogen in female patients.[32] In addition, it may also be related to the differentially expressed antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and NADPH oxidase) in different genders and the higher compound dietary antioxidant index in women.[32] Given that the majority of our patients were women, there could be other factors contributing to the higher incidence of CVD in patients with pSS, such as age and hyperlipidemia.

Dry mouth and its associated oral ulcers and dental caries (Supplemental Table S2) are closely related to chronic oral inflammation, which may be associated with increased atherosclerosis and cardiovascular events.[34] A meta-analysis of 10 studies found that the CVD risk of patients with chronic root canal infection was 1.38 times higher than those without root canal infection.[35] Periodontitis, a risk factor for systemic inflammation and subsequent CVD, may also be a major reason for the increase in cardiovascular events in patients with pSS compared with the normal population. Therefore, the triad of dry mouth, dental caries, and oral ulcers may be important markers of cardiovascular events in patients with pSS. Salivary gland damage caused by lymphocyte infiltration results in a dry mouth in patients with pSS. The reduction of bacteriostatic substances caused by the reduction of saliva secretion and the increase in food residues create an environment conducive to bacterial reproduction, resulting in persistent periodontitis. Chronic inflammation is associated with oral ulcers and can also lead to dental caries. At the same time, persistent chronic oral inflammation may be related to atherosclerosis by affecting inflammatory cells and inflammatory factors in the blood, and then increasing the incidence of CVD. To reduce the incidence of cardiovascular events, it seems particularly important to maintain oral hygiene and reduce oral inflammation in patients with pSS using artificial saliva and mouthwash.

Although harmlessness in Caucasian populations and with no correlation in African populations,[36] RP seems to be a protective factor for cardiovascular events in our studies, which might be due to ethnic differences. Patients with RP developed and were diagnosed with pSS at an earlier age, which might be the reason for a lower incidence of hypertension and associated CVD (Supplemental Table S1). The low incidence of CVD may also be related to a greater emphasis on health management in patients with RP, which is also reflected in the earlier onset and diagnosis of symptoms. In addition, non-smoking among patients with RP in our population may also explain a lower risk of cardiovascular events. Considering that this is the first time a relationship has been found between RP and CVD in a Chinese population, it needs to be validated in a larger population.

Fatigue is a common symptom in patients with pSS. Patients with symptoms of fatigue are more likely to develop CVD, which may be because the risk factors and CVD itself can cause fatigue.[37] To determine whether fatigue can promote CVD by affecting the chronic inflammatory state *in vivo*, further research is needed. Although the causes of fatigue are multifactorial, sleep improvement and exercise have a significant effect on alleviating fatigue, which may improve the life quality of patients and reduce the incidence of CVD.

Patients with diabetes mellitus type 2 (T2DM) alone are more likely to develop CVD than those without diabetes, which might be associated with changes in microvascular function and structure.[38] Early blood glucose control can improve microvascular function in patients with T2DM and CVD, but may not improve the incidence of CVD events. In addition, some diabetes drugs, such as rosiglitazone, can increase the rate of CV events. Nevertheless, the blood glucose control of diabetes patients who also have pSS is still very important. In addition to blood glucose, lipids are usually considered a risk factor for cardiovascular events, but our study found no significant correlation, which may be closely related to the widespread use of lipid-lowering drugs, such as statins, in patients with dyslipidemia.

As with existing studies in other populations, high systolic blood pressure was strongly associated with the risk of CVD in our study.[39] In our cohort, diastolic blood pressure did not appear to be associated with the incidence of cardiovascular events in patients with pSS. Elevated systolic blood pressure may be associated with increased stroke volume or aortic stiffness, reflecting hypertension in multiple organs, such as the brain, heart, and kidney, which may lead to poor outcomes. Diastolic blood pressure is related to arterial resistance, heart rate, and arterial compliance, which leads to less increase in the vascular load. Therefore, it is necessary to take measures to control blood pressure, especially systolic blood pressure, to reduce cardiovascular risk.

The pSS patients with early interventions showed better outcomes than those without interventions, demonstrating the importance of cardiovascular risk prediction tools. However, there are still no prediction tools for cardiovascular risk in patients with pSS. We built an effective prediction tool for cardiovascular risk in patients with pSS to help clinicians identify patients at a high risk of cardiovascular events early. In addition, early interventions, including blood pressure control, medication adjustment, and lifestyle improvement, will benefit patients with high cardiovascular risk at the start of their treatment.

Thus, an accurate prognostic assessment will lead clinicians to focus on the cardiovascular risk of patients and timely interventions with a high likelihood of a favorable net benefit. Predicting cardiovascular risk in patients with pSS is not easy, and appropriate measurements and multiple interventions might be important.

Limitations

Although our research had several advantages, it also had some limitations. First, our study could not represent all patients with pSS. Our study had a low representation of male patients with pSS because the proportion of men was too low, which was determined by the gender distribution of patients with pSS. Patients without sufficient data were excluded, which might result in bias. In addition, our patients were mainly from eastern China, which was not a good representation of other pSS populations. Second, although we have tried to include possible influencing factors, it is still inevitable that several potential factors affecting cardiovascular risk were not included. Third, although we have conducted internal verification, the robustness of our nomogram was not verified in other cohorts, and its applicability in other pSS populations in other regions and countries is uncertain, which requires external evaluation in wider pSS populations.

Conclusion

Sex, joint pain as an initial symptom, dry mouth, oral ulcers, dental caries, RP, fatigue, diabetes, elevated TSH, and systolic blood pressure were closely related to the CVD incidence rate. This study built a relatively accurate nomogram to help clinicians access the risk of CVD in patients with pSS at the beginning of treatment according to these 10 risk factors. After a risk assessment for CVD, clinicians and patients can select more interventions, such as improvements in lifestyle and medical treatment. External validation in other pSS cohorts is required to assess whether this nomogram is useful for individual interventions in reducing cardiovascular risk and improving outcomes for patients with pSS.

Declarations

Ethics approval and consent to participate

This study involved human participants and was approved by the Medical Ethical Committee of Tongji Hospital, School of Medicine, Tongji University (Approval No. K-W-2023-001), and

complied with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part. Consent was verbally obtained directly from the patients.

Consent for publication

Consent for publication was verbally obtained directly from the patients.

Author contributions

Jincheng Pu: Conceptualization; Methodology; Software; Writing – original draft.

Jiamin Song: Conceptualization; Methodology; Resources; Writing – original draft.

Shengnan Pan: Data curation; Formal analysis; Writing – original draft.

Shuqi Zhuang: Formal analysis; Validation; Writing – original draft.

Ronglin Gao: Conceptualization; Visualization; Writing – original draft.

Yuanyuan Liang: Investigation; Software; Writing – original draft.

Zhenzhen Wu: Formal analysis; Software; Writing – original draft.

Yanqing Wang: Investigation; Software; Writing – original draft.

Youwei Zhang: Investigation; Software; Writing – original draft.

Fang Han: Formal analysis; Resources; Writing – original draft.

Lufei Yang: Formal analysis; Software; Writing – original draft.

Huihong Wu: Methodology; Writing – original draft.

Jianping Tang: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Xuan Wang: Conceptualization; Funding acquisition; Supervision; Writing – review & editing.

Acknowledgements

The authors thank all the members of the Department of Rheumatology and Immunology, Tongji Hospital, School of Medicine, Tongji University for their fruitful discussion and contributions.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by the National Natural Science Foundation of China (Grant Nos 81671598, 81801601, and 82070102), the Natural Science Foundation of Shanghai (Grant No. 20ZR1451400), the Science and Technology Commission of Shanghai (Grant No. 20Y11911600), the Shanghai Sailing Program (Grant No. 17YF1417200), Shanghai Wu Mengchao Medical Foundation (Grant No. JJHXM-2019011), Clinical research program of Tongji Hospital Tongji University (Grant Nos ITJZD1909, ITJQN2001), and the Program of Shanghai Academic Research Leaders (Grant No. 22XD1422700).

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data are available on reasonable request.

ORCID iDs

Jincheng Pu https://orcid.org/0000-0001-9242-3067

Jiamin Song https://orcid.org/0000-0001-9815-8508

Shengnan Pan https://orcid.org/0000-0002-4520-0239

Shuqi Zhuang https://orcid.org/0000-0002-3506-0631

Ronglin Gao https://orcid.org/0000-0002-4507-480X

Yuanyuan Liang https://orcid.org/0000-0003-0360-286X

Zhenzhen Wu https://orcid.org/0000-0003-4384-3473

Yanqing Wang https://orcid.org/0000-0002-9946-159X

Youwei Zhang https://orcid.org/0000-0001-5765-7618

Fang Han https://orcid.org/0000-0001-5584-8971

Lufei Yang https://orcid.org/0000-0002-6756-7293

Huihong Wu https://orcid.org/0000-0002-2842-4812

Jianping Tang https://orcid.org/0000-0003-4629-7631

Xuan Wang https://orcid.org/0000-0002-6588-2951

Supplemental material

Supplemental material for this article is available online.

References

1. Brito-Zerón P, Baldini C, Bootsma H, *et al.* Sjögren syndrome. *Nat Rev Dis Primers* 2016; 2: 16047.
2. Mavragani CP and Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. *Autoimmun Rev* 2010; 9: A305–A310.
3. Yong WC, Sanguankeo A and Upala S. Association between primary Sjögren's syndrome, cardiovascular and cerebrovascular disease: a systematic review and meta-analysis. *Clin Exp Rheumatol* 2018; 36(Suppl. 112): 190–197.
4. Hinorani AD, Cross J, Kharbanda RK, *et al.* Acute systemic inflammation impairs endothelium-dependent dilatation in humans. *Circulation* 2000; 102: 994–999.
5. Scofield RH. Vasculitis in Sjögren's syndrome. *Curr Rheumatol Rep* 2011; 13: 4828.
6. Atzeni F, Sarzi-Puttini P, Signorello MC, *et al.* New parameters for identifying subclinical atherosclerosis in patients with primary Sjögren's syndrome: a pilot study. *Clin Exp Rheumatol* 2014; 32: 361–368.
7. Sezis Demirci M, Karabulut G, Gungor O, *et al.* Is there an increased arterial stiffness in patients with primary Sjögren's syndrome? *Intern Med* 2016; 55: 455–459.
8. Sabio JM, Sánchez-Berná I, Martinez-Bordonado J, *et al.* Prevalence of and factors associated with increased arterial stiffness in patients with primary Sjögren's syndrome. *Arthritis Care Res* 2015; 67: 554–562.
9. Klocke R, Cockcroft JR, Taylor GJ, *et al.* Arterial stiffness and central blood pressure, as determined by pulse wave analysis, in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 414–418.
10. Juarez M, Toms TE, de Pablo P, *et al.* Cardiovascular risk factors in women with primary Sjögren's syndrome: United Kingdom primary Sjögren's syndrome registry results. *Arthritis Care Res* 2014; 66: 757–764.
11. Bartoloni E, Baldini C, Schillaci G, *et al.* Cardiovascular disease risk burden in primary Sjögren's syndrome: results of a population-based multicentre cohort study. *J Intern Med* 2015; 278: 185–192.
12. Wu XF, Huang JY, Chiou JY, *et al.* Increased risk of coronary heart disease among patients with primary Sjögren's syndrome: a nationwide population-based cohort study. *Sci Rep* 2018; 8: 2209.
13. Bartoloni E, Alunno A, Valentini V, *et al.* The prevalence and relevance of traditional cardiovascular risk factors in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2018; 36(Suppl. 112): 113–120.
14. Rempenault C, Combe B, Barnetche T, *et al.* Metabolic and cardiovascular benefits of hydroxychloroquine in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2018; 77: 98–103.
15. Sumpter MD, Tatro LS, Stoecker WV, *et al.* Evidence for risk of cardiomyopathy with hydroxychloroquine. *Lupus* 2012; 21: 1594–1596.
16. Yogasundaram H, Putko BN, Tien J, *et al.* Hydroxychloroquine-induced cardiomyopathy: case report, pathophysiology, diagnosis, and treatment. *Can J Cardiol* 2014; 30: 1706–1715.
17. Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, *et al.* Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. *Rheumatology* 2013; 52: 68–75.
18. Davis JM III, Maradit Kremers H, Crowson CS, *et al.* Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2007; 56: 820–830.
19. Souverein PC, Berard A, Van Staa TP, *et al.* Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population-based case-control study. *Heart* 2004; 90: 859–865.
20. Salles G, Barrett M, Foà R, *et al.* Rituximab in B–cell hematologic malignancies: a review of 20 years of clinical experience. *Adv Ther* 2017; 34: 2232–2273.

21. Shiboski CH, Shiboski SC, Seror R, *et al.* 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017; 69: 35–45.

22. Sauerbrei W, Royston P and Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. *Stat Med* 2007; 26: 5512–5528.

23. Friedman J, Hastie T and Tibshirani R. Regularization paths for generalized linear models via coordinate descent. *J Stat Softw* 2010; 33: 1–22.

24. Kidd AC, McGettrick M, Tsim S, *et al.* Survival prediction in mesothelioma using a scalable LASSO regression model: instructions for use and initial performance using clinical predictors. *BMJ Open Respir Res* 2018; 5: e000240.

25. Xing J, Min L, Zhu S, *et al.* Factors associated with gastric adenocarcinoma and dysplasia in patients with chronic gastritis: a population-based study. *Chin J Cancer Res* 2017; 29: 341–350.

26. Balachandran VP, Gonen M, Smith JJ, *et al.* Nomograms in oncology: more than meets the eye. *Lancet Oncol* 2015; 16: e173–e180.

27. Iasonos A, Schrag D, Raj GV, *et al.* How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* 2008; 26: 1364–1370.

28. Kramer AA and Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: the Hosmer–Lemeshow test revisited. *Crit Care Med* 2007; 35: 2052–2056.

29. Pencina MJ and D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004; 23: 2109–2123.

30. Vickers AJ, Cronin AM, Elkin EB, *et al.* Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* 2008; 8: 53.

31. Huang YQ, Liang CH, He L, *et al.* Development and validation of a radiomics nomogram for preoperative prediction of lymph node metastasis in colorectal cancer. *J Clin Oncol* 2016; 34: 2157–2164.

32. Arosio B, Corbi G, Davinelli S, *et al.* Sex differences in cardiovascular diseases: a matter of estrogens, ceramides, and sphingosine 1-phosphate. *Int J Mol Sci* 2022; 23: 4009.

33. Zhang Y, Li M, Zhang L, *et al.* Association between comorbidities and extraglandular manifestations in primary Sjögren's syndrome: a multicenter cross-sectional study. *Clin Rheumatol* 2020; 39: 2677–2688.

34. Cotti E, Dessì C, Piras A, *et al.* Can a chronic dental infection be considered a cause of cardiovascular disease? A review of the literature. *Int J Cardiol* 2011; 148: 4–10.

35. Koletsi D, Iliadi A, Tzanetakis GN, *et al.* Cardiovascular disease and chronic endodontic infection: Is there an association? A systematic review and meta-analysis. *Int J Environ Res Public Health* 2021; 18: 9111.

36. Nietert PJ, Shaftman SR, Silver RM, *et al.* Raynaud phenomenon and mortality: 20+ years of follow–up of the Charleston Heart Study cohort. *Clin Epidemiol* 2015; 7: 161–168.

37. Qiao Y, Martinez-Amezcua P, Wanigatunga AA, *et al.* Association between cardiovascular risk and perceived fatigability in mid–to–late life. *J Am Heart Assoc* 2019; 8: e013049.

38. Collaboration Emerging Risk Factors Sarwar N, Gao P, *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375: 2215–2222.

39. Wan EYF, Fung WT, Schooling CM, *et al.* Blood pressure and risk of cardiovascular disease in UK Biobank: a Mendelian Randomization Study. *Hypertension* 2021; 77: 367–375.