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Analysis of risk factors and development of a nomogram prediction model for renal tubular acidosis in primary Sjogren syndrome patients

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Abstract

Objective To investigate the risk factors of renal tubular acidosis (RTA) in patients with primary Sjögren's syndrome (pSS) and create a personalized nomogram for predicting pSS-RTA patients.

Method Data from 99 pSS patients who underwent inpatient treatment at our hospital from January 2012 to January 2024 were retrospectively collected and analyzed. Bootstrap resampling technique, single-factor, and multi-factor logistic regression analyses were used to explore the risk factors for pSS-RTA. A nomogram was developed based on the results of the multivariate logistic model. The model was evaluated through receiver operating characteristic curve, C-index, calibration curve, and decision curve analysis. In addition, we graded the severity of pSS-RTA patients and used univariate analysis to assess the relationship between pSS-RTA severity and risk factors.

Results A multivariate logistic regression analysis revealed that concurrent thyroid disease, long symptom duration, subjective dry mouth, and positive RF were independent risk factors for pSS-RTA patients. Based on them, a personalized nomogram predictive model was established. With a p-value of 0.657 from the Hosmer-Lemeshow test, the model demonstrated a good fit. The AUC values in the training and validation groups were 0.912 and 0.896, indicating a strong discriminative power of the nomogram. The calibration curves for the training and validation groups closely followed the diagonal line with a slope of 1, confirming the model's reliable predictive ability. Furthermore, the decision curve analysis showed that the nomogram model had a net benefit in predicting pSS-RTA, emphasizing its clinical value.This study did not find an association between the severity of pSS-RTA and risk factors.

Discussion We developed a nomogram to predict RTA occurrence in pSS patients, and it is believed to provide a foundation for early identification and intervention for high-risk pSS patients.

Key message

- Having thyroid disease, experiencing prolonged symptoms, reporting subjective dry mouth, and testing positive for rheumatoid factor (RF) were independent risk factors for pSS-RTA patients.
- According to the nomogram, the probability of pSS-RTA patients can be identified.
- Multi-centre studies and the inclusion of more quantitative indicators may lead to better predictive models.

Keywords Primary Sjögren's syndrome, Renal tubular acidosis, Nomogram, Risk factors

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Introduction

Sjogren's syndrome (SS) is a progressive systemic autoimmune disease that develops slowly, being one of the most common autoimmune diseases with an estimated prevalence of around 0.1-4.8%. Due to its slow progression, the rate of diagnosis is low. This disease can occur either independently (primary Sjogren's syndrome, pSS) or in conjunction with other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis (DM), or systemic sclerosis (SSc)(secondary Sjogren's syndrome, sSS). The primary affected demographic includes middle-aged women, with a gender ratio of 1:9, making it a significant public health issue. The hallmark feature of the syndrome is the infiltration of lymphocytes in the exocrine glands, including the salivary and tear glands, leading to dysfunction of these glands and causing symptoms such as dry mouth and dry eyes [1–3]. Apart from affecting the exocrine glands, Sjogren's syndrome can also impact various organs and systems in the body, including the kidneys, lungs, thyroid, heart, blood system, nervous system, and digestive system, resulting in corresponding symptoms [4].

A large retrospective study in China [5] found a higher prevalence of kidney involvement in Chinese pSS patients compared to other countries, at 33.5%. Renal manifestations related to pSS range from mild electrolyte abnormalities to complete distal renal tubular acidosis (cRTA), interstitial nephritis (IN), and glomerulonephritis (GN) [6], with glomerular diseases are not uncommon in the cohort of pSS patients with kidney involvement. Renal biopsies were carried out on patients with positive urine analysis, and the results indicated that 83.3% of them had various types of glomerular lesions, such as minimal-change nephropathy, IgA nephropathy, mesangial proliferative glomerulonephritis, focal segmental glomerulosclerosis, diffuse proliferative glomerulone-phritis and membranous nephropathy [7]. However, the causes and mechanisms of pSS-related glomerular diseases remain unknown. Researches suggest that the deposit of circulating immune complexes might be related to it, and even cryoglobulinemia may be involved as well, along with late sequelae and a poor prognosis [8, 9]. In SS, the most prevalent kidney disease is tubulointerstitial nephritis, which typically presents as renal tubular acidosis (RTA) [7]. In recent years, an increasing number of clinicians have observed a higher incidence of RTA in pSS patients, sometimes occurring even before the onset of pSS. They highlighted in case reports [10–12]that many pSS patients presenting symptoms related to hypokalemia due to RTA seek treatment in other departments, posing challenges for the early diagnosis and management of Sjogren's syndrome. Without prompt treatment, this might even endanger the patients' lives. Hence, early identification of pSS-RTA holds substantial clinical value in improving patient prognosis, such as preventing fractures, life-threatening muscle paralysis, and chronic kidney disease.

The etiology and pathogenesis of pSS-RTA remain unclear. Pertovaara [13] and others detected autoantibodies against carbonic anhydrase in the serum of Sjogren's syndrome patients, which seemed to be connected with RTA. Animal studies [14] have also shown that inducing anti-carbonic anhydrase in mice can lead to the development of pSS-RTA. However, it is not yet clear whether these autoantibodies result from or cause renal damage. Studies suggest a relationship between α-intercalated cell vesicle H+-ATPase and anion exchanger I deficiency and pSS-RTA [6]. RTA and exocrine gland involvement share common pathogenic mechanisms and histological characteristics [15]. Some targets in pSS-RTA, such as carbonic anhydrase II and H+-ATPase, are expressed in salivary glands and kidney intercalated cells [6]. Current clinical analyses of pSS-RTA risk factors are limited and not without controversy. Jain et al. [16] reported a lower incidence of dry eyes in pSS-RTA patients compared to those without RTA, with a similar rate of dry mouth occurrence. Conversely, a meta-analysis showed no significant correlation between renal involvement in pSS and anti-SSA antibodies, rheumatoid factor, dry eye syndrome, or labial salivary gland biopsy [17]. Synthesizing previous studies [16, 18–20], it is revealed that several factors are associated with pSS-RTA, including a younger age of onset, longer disease duration, subjective dry mouth, arthritis, EULAR disease activity index, decreased glomerular filtration rate, thyroid disease, anemia, elevated alkaline phosphatase levels, decreased albumin levels, increased erythrocyte sedimentation rate, anti-SSA and anti-SSB antibodies, and high gamma globulin levels. However, these studies are mostly based on small samples and are not specific to pSS-RTA, underscoring the need for further clarification on the relationship between demographic characteristics, laboratory indicators, clinical features of pSS patients, and RTA risk.

In clinical practice, physicians often require tools to aid in the identification of pSS-RTA. In recent years, the use of online tools for prognosis and risk prediction of diseases has become popular among clinicians and patients, with the nomogram widely used as a predictive method for various types of cancers [21–24]. Predictive models serve as valuable tools to guide clinical practitioners in considering the uniqueness of individual pSS patients and making appropriate treatment decisions. Therefore, we conducted a systematic review of the medical records of pSS patients over the years to explore the clinical and laboratory features of pSS patients with and without RTA, aiming to identify risk factors for pSS-RTA and establish a risk prediction model based on demographic,

clinical features, and laboratory indicators. Our study results will offer guidance for clinical practice.

Materials and methods

Patients

We conducted a retrospective analysis of data from 99 patients with pSS who received inpatient treatment at the Affiliated Hospital of Xuzhou Medical University from January 2012 to January 2024. Patients were categorized into two groups: pSS-RTA group (37 cases) and pSS group (62 cases) based on the presence of renal tubular acidosis (RTA). RTA was defined by the following criteria ≥ 1: (1) metabolic acidosis with high chloride levels, normal anion gap, urine pH > 5.5, and positive urine anion gap; (2) abnormal results on the ammonium chloride loading test [25]. Inclusion criteria were: (1) age ≥ 18 years; (2) patients meeting the 2002 American-European Consensus Group (AECG) [26] or the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for primary Sjögren's syndrome [27]; (3) initial visit and treatment without medication interference. Exclusion criteria were: (1) age < 18 years; (2) patients with irreversible kidney damage, end-stage renal disease, kidney malformations, or other known causes of RTA such as genetic disorders, drug-related RTA, or hypercalcemia; (3) patients with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, or other autoimmune diseases; (4) patients with cancer; (5) pregnant or lactating women; (6) patients with significant missing clinical data. The severity of pSS-RTA was graded according to(one of the blood biochemical indicators and clinical symptoms is sufficient): 1. Blood biochemical indexes: (1) mild to moderate: bicarbonate ion concentration 18-10mmol/L, blood potassium 2.5-3.5mmol/L. (2) Severe: bicarbonate ion concentration < 10mmol/L, blood potassium < 2.5mmol/L. 2. Clinical symptoms: (1) Mild to moderate: only mild fatigue, loss of appetite and other non-specific symptoms, or obvious fatigue, muscle aches, polyuria, polydipsia and other symptoms. (2) Severe: there are serious complications such as arrhythmia, dyspnea, disturbance of consciousness and even coma. (This study was a retrospective study with a long span of years, so there were many missing values in blood gas analysis data, so blood PH was not used.) This study was approved by the Ethics Committee of Xuzhou Medical University Affiliated Hospital.

Data collection

Collecting the demographic characteristics of patients involves gender, age, body mass index (BMI), and disease duration; clinical symptoms include Initial symptoms, subjective dry eyes, subjective dry mouth, tooth loss, fever, and joint pain; concurrent conditions encompass thyroid disease, diabetes, hypertension, and infections; laboratory parameters comprise white blood cell count, red blood cell count, hemoglobin, platelet count, erythrocyte sedimentation rate, C-reactive protein, alkaline phosphatase, IgG, IgA, IgM, complement C3, complement C4, ANA, RF, SSA antibodies, RO52 antibodies, SSB antibodies, urea, creatinine, GFR, K^+, Na^+, Cl^-, $HCO3^-$ and urine PH.The glomerular estimate filtartion(GFR) was calculated using CKD-EPI formula: female GFR mL/min= ((140-age) * weight kg*1.04)/ creatinine umol/L; Male GFR mL/min= ((140- age) * weight kg*1.23)/ creatinine umol/L. The initial symptoms refer to the symptoms occurring at the very beginning of the disease; duration of symptoms is measured from symptom onset to initial diagnosis; thyroid disease encompasses hyperthyroidism, hypothyroidism, and thyroiditis.

Data processing and statistical analysis

Normally distributed data are presented as mean ± standard deviation (mean ± SD) for comparison using independent sample t-tests. Non-normally distributed data are described using the median and quartiles 25% and 75% [M (Q1, Q3)], with comparisons done through the Mann-Whitney U test. Categorical data are displayed as percentages (%), compared using the χ^2 test or Fisher's exact test. Variables with a p-value < 0.05 in the univariate analysis are considered statistically significant. Exclude variables with a proportion of missing values and outliers exceeding 5%. Split the data into a training group ($n = 80$) and a validation group ($n = 19$) at an 8:2 ratio through random assignment. Multicollinearity is assessed using variance inflation factor and tolerance, showing no issues detected. Given the small sample size, bootstrapping is implemented in univariate analysis by resampling the data 1000 times to mitigate errors due to the limited sample size. Identified significant factors from the univariate analysis are further examined in a multivariable logistic regression to construct a nomogram based on the multivariable logistic model results. The model's discriminatory ability in the training set is evaluated using receiver operating characteristic (ROC) curves and the C-index. Calibration curves are introduced for validation of predictive performance, and decision curve analysis (DCA) is employed to assess the new model's clinical utility. In addition, to further analyze the relationship between the severity of pSS-RTA and risk factors, we divided pSS-RTA patients ($n = 37$) into mild to moderate ($n = 20$) and severe ($n = 17$) according to potassium ion, bicarbonate level and clinical symptoms. A single factor analysis was performed to evaluate the relationship between the severity of pSS-RTA and risk factors. Statistical analysis is performed utilizing SPSS (version 22.0) and R software (version 4.3). A significance level of $P < 0.05$ is deemed statistically significant.

Results

Baseline demographic and clinical features

In this study, 80 patients were included in the training group (7 males, 73 females; with an average age of 44.95±14.54 years and average BMI of 21.83±2.65; median illness duration of 3 months), while the validation group consisted of 19 patients (1 male, 19 females; average age 48.65±14.62 years, average BMI 22.06±3.16; median illness duration of 4 months). Among the 99 patients, 12 had concurrent infections(Specific types of infection are shown in Figure S1), 6 had a history of hypertension, 3 had a history of diabetes, and 31 had thyroid diseases. The training group's baseline data encompassed demographic characteristics, clinical symptoms and relevant laboratory tests as detailed in Table 1. Comparability between the training and validation groups was confirmed with no statistically significant differences observed in the baseline clinical data, as presented in Table S1.

Nomogram development

Significant baseline data were subjected to a univariate logistic analysis, highlighting BMI, thyroid diseases, duration of symptoms, subjective dry mouth, platelet count, alkaline phosphatase, RF, and SSB antibodies as statistically meaningful risk factors (Table 2) (As the purpose of this study was to explore the risk factors of pSS patients with RTA, data related to renal function including urea, creatinine, GFR, K^+, Na^+, Cl^-, $HCO3^-$ and urine PH were not included). To address selection bias due to the high prevalence of thrombocytopenia in hospitalized pSS patients, platelet count was excluded. Subsequently, a multivariate logistic analysis was conducted to further evaluate the significant risk factors identified in the univariate analysis. The findings confirmed the statistical significance of thyroid diseases, symptom duration, subjective dry mouth, and RF in the multivariable logistic regression. Leveraging the regression coefficients from the multivariate logistic analysis, an individualized nomogram prediction model for pSS-RTA was formulated (Fig. 1). The nomogram assigns scores to each risk factor, and the cumulative score corresponds to the predicted risk of pSS patients developing RTA.

Nomogram validation

The effectiveness and calibration of the predictive model were assessed through the area under the receiver operating characteristic curve (AUC) and calibration plots. Receiver operating characteristic curves (ROC) were constructed, and the AUC values were computed for both the training and validation datasets. The Hosmer-Lemeshow test resulted in a p-value of 0.657, indicating a good model fit. The AUC values for predicting combined RTA risk in the training and validation groups were 0.912 and 0.896, respectively (Fig. 2), highlighting the nomogram's strong discriminative capacity. The calibration curves for the training and validation groups (solid lines in Fig. 3) closely followed the ideal prediction line with a slope of 1 (dashed diagonal line), indicating the model's reliable predictive performance. Moreover, decision curve analysis demonstrated a positive net benefit in predicting RTA risk in pSS patients using the Nomogram model, underlining its clinical relevance in RTA risk prediction (Fig. 4).

Initial symptoms

We statistically analyzed the initial symptoms of 37 pSS-RTA patients and found that: 14 cases (37.8%) of the initial symptoms for limbs powerless, 12 patients (32.4%) of the initial symptoms of dry mouth and/or dry eyes, 7 patients (18.9%), the initial symptoms of the digestive tract include anorexia or fatigue and nauseaI. In addition, 4 patients (2.7%, 2.7%, 2.7%, 2.7%) had fever, arthrodynia, edema, and thrombocytopenia as their initial symptoms (Fig. 5).

Association between the severity of the pSS-RTA and the risk factors

We classified pSS-RTA patients ($n=37$) into mild to moderate ($n=20$) and severe ($n=17$) based on blood biochemical results and clinical symptoms. Univariate analysis was used to assess the relationship between the severity of pSS-RTA and risk factors. However, the baseline analysis results (Table S2) suggest that only the differences in symptomduration and arthrodynia are statistically significant, and no correlation was found in subsequent univariate logistic regression (not shown).

Discussion

In primary Sjögren's syndrome (pSS) patients, the kidneys are commonly affected. Chronic and acute tubulointerstitial nephritis are the most common manifestations, often leading to renal tubular acidosis (RTA) clinically, similar to exocrine glands, due to lymphocyte infiltration around the kidney tubules [28]. However, pSS-RTA typically starts insidiously, presenting few noticeable symptoms apart from electrolyte imbalances, elevated creatinine, and proteinuria. Nevertheless, the complications of fractures, life-threatening muscle paralysis, and chronic kidney disease are significant [6], underscoring the importance of early identification of pSS-RTA patients for timely intervention, improved prognosis, and enhanced quality of life.

Prior studies have examined potential risk factors in pSS-RTA patients, encompassing demographics, clinical features, and laboratory parameters [16–20]. Nevertheless, there has been a lack of studies specifically tackling pSS-RTA and developing a model that integrates multiple laboratory findings into clinical decision-making. In this

Table 1 Baseline clinical features between pSS group and pSS-RTA group

Variables	pSS group($n=50$)	pSS-RTA group($n=30$)	*p*
Age(year)	46.06 ± 14.89	43.1 ± 13.98	0.374
Sex			0.706
Female	45 (90)	28 (93)	
Man	5 (10)	2 (7)	
BMI(kg/m2)	22.46 ± 2.61	20.79 ± 2.41	0.005
Infection			0.164
No	46 (92)	24 (80)	
Yes	4 (8)	6 (20)	
Hypertension			0.645
No	46 (92)	29 (97)	
Yes	4 (8)	1 (3)	
Diabetes			0.553
No	49 (98)	28 (93)	
Yes	1 (2)	2 (7)	
Thyroid dysfunction			0.028
No	41 (82)	17 (57)	
Yes	9 (18)	13 (43)	
Symptom duration(month)	2 (0.45, 12)	6 (0.55, 84)	0.244
Dry mouth			< 0.001
No	34 (68)	7 (23)	
Yes	16 (32)	23 (77)	
Dry eyes			0.246
No	36 (72)	17 (57)	
Yes	14 (28)	13 (43)	
Rampant tooth			0.073
No	47 (94)	24 (80)	
Yes	3 (6)	6 (20)	
Fever			0.722
No	45 (90)	26 (87)	
Yes	5 (10)	4 (13)	
Arthrodynia			1
No	40 (80)	24 (80)	
Yes	10 (20)	6 (20)	
WBC(1*109)	5.45 (3.6, 7.3)	5.7 (4.12, 7.55)	0.444
RBC(1*1012)	3.91 ± 0.69	3.98 ± 0.72	0.688
Hb(g/L)	118.5 (108, 131.5)	116 (106, 127.75)	0.474
PLT(1*109)	182.56 ± 101.12	233.5 ± 103.83	0.036
ESR(mm/L)	48.82 (23, 54.95)	48.82 (42.2, 52.5)	0.34
CRP(mg/L)	5.28 (2.06, 16.62)	6.54 (2.21, 15.66)	0.834
Alkaline phosphatase(U/L)	74 (61.75, 89.5)	100.5 (72.75, 140.75)	0.003
IgG(g/L)	18.85 (14.25, 20.57)	20.17 (17.58, 26.4)	0.096
IgA(g/L)	3.02 (2.29, 3.54)	3.02 (2.65, 4.26)	0.108
IgM(g/L)	1.64 (1, 1.83)	1.29 (1.05, 1.64)	0.105
C3(g/L)	0.92 ± 0.19	0.92 ± 0.22	0.981
C4(g/L)	0.2 (0.17, 0.24)	0.2 (0.17, 0.22)	0.495
RF			<0.001
-	21 (42)	1 (3)	
+	29 (58)	29 (97)	
ANA			0.375
-	0 (0)	1 (3)	
+	50 (100)	29 (97)	
Anti-SSA			1
-	1 (2)	0 (0)	

Table 1 (continued)

Variables	pSS group($n=50$)	pSS-RTA group($n=30$)	*p*
+	49 (98)	30 (100)	
Anti-RO52			0.041
-	7 (14)	0 (0)	
+	43 (86)	30 (100)	
Anti-SSB			0.003
-	32 (64)	8 (27)	
+	18 (36)	22 (73)	
Urea(mmol/L)	4.44 (3.6, 5.29)	4.28 (3.63, 5.53)	0.889
Creatinine(umol/L)	53.5 (49, 63.75)	72 (56, 84)	< 0.001
GFR(mL/min)	105.92 ± 37.36	78.93 ± 28.47	< 0.001
K(mmol/L)	3.89 (3.65, 4.18)	2.58 (2.05, 3.01)	< 0.001
Na(mmol/L)	140.85 (139.22, 142.07)	141.3 (138.35, 143.6)	0.612
Cl(mmol/L)	103.25 (101.25, 105.68)	110.9 (104.93, 112.73)	< 0.001
HCO3(mmol/L)	22.8 (21.6, 25.08)	17.75 (14.85, 20.7)	< 0.001
Urine PH			0.002
PH ≤ 6	15 (19)	15 (30)	0 (0)
PH<6	65 (81)	35 (70)	30(100)

The variables mentioned were all collected at baseline

Table 2 Univariate and multivariate logistic regression of development set

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
BMI(kg/m2)	0.752	0.607–0.932	0.009			
Thyroid dysfunction	3.484	1.255–9.668	0.017	9.982	1.8-55.369	0.008
Symptom duration(month)	1.017	1.003–1.03	0.013	1.017	1.001–1.034	0.04
Dry mouth	6.982	2.483–19.633	0.000	17.843	3.464–91.903	0.001
PLT(1*109)	1.005	1-1.01	0.039			
Alkaline phosphatase(U/L)	1.008	1-1.015	0.051			
RF	21	2.647-166.599	0.004	25.208	2.412–263.47	0.007
Anti-SSB	4.889	1.809–13.211	0.002			

study, we constructed a prediction model for pSS-RTA using both univariate and multivariate logistic regression analyses, visually represented as a graph to aid in assessing the risk of RTA in pSS patients. This research determined the independent risk factors of pSS-RTA. Subsequently, we devised and validated a straightforward model to predict RTA in pSS patients. Our study outcomes may help clinicians recognize these risk factors to facilitate early detection, diagnosis, and treatment of pSS-RTA patients, thus enhancing their prognosis and quality of life.

Our group of pSS-RTA patients has an average age of 41 years, which is approximately 10 years younger than European pSS patients with kidney involvement (average age 52 years), and similar to previously reported Indian (average age 40.19 years) and Chinese cohorts (average age 40.1 years) [29–31]. This confirms that kidney involvement in Asian populations with pSS tends to occur at a younger age compared to Western countries.

This research discovered that although it was insignificant in the multivariate logistic regression analysis, in the univariate analysis, the BMI (20.79 ± 2.41) of the pSS-RTA patient group was notably lower than that of the pSS patient group (22.46 ± 2.61). Currently, worldwide, there are relatively few studies on the occurrence rate of weight loss and malnutrition among pSS-RTA patients. We think it is associated with the following three aspects: (1) Metabolic disorders: Renal tubular acidosis can influence the acid-base balance and electrolyte metabolism within the body, causing metabolic disorders. This might affect the absorption and utilization of nutrients, and thus impact BMI. (2) Damaged renal function: Abnormal renal tubular function can affect the reabsorption of nutrients by the kidneys, leading to an increased loss of nutrients like proteins and carbohydrates, making it challenging for patients to maintain normal weight and nutritional status. (3) Reduced appetite: As patients with combined RTA are related to hypokalemia, when it involves the gastrointestinal tract, symptoms such as loss of appetite, nausea, and vomiting might emerge, resulting in insufficient or lost nutritional intake, thereby influencing BMI. Naturally, regardless of whether it is combined with RTA or not, nutritional support plays a vital role in the treatment and rehabilitation process of patients. It

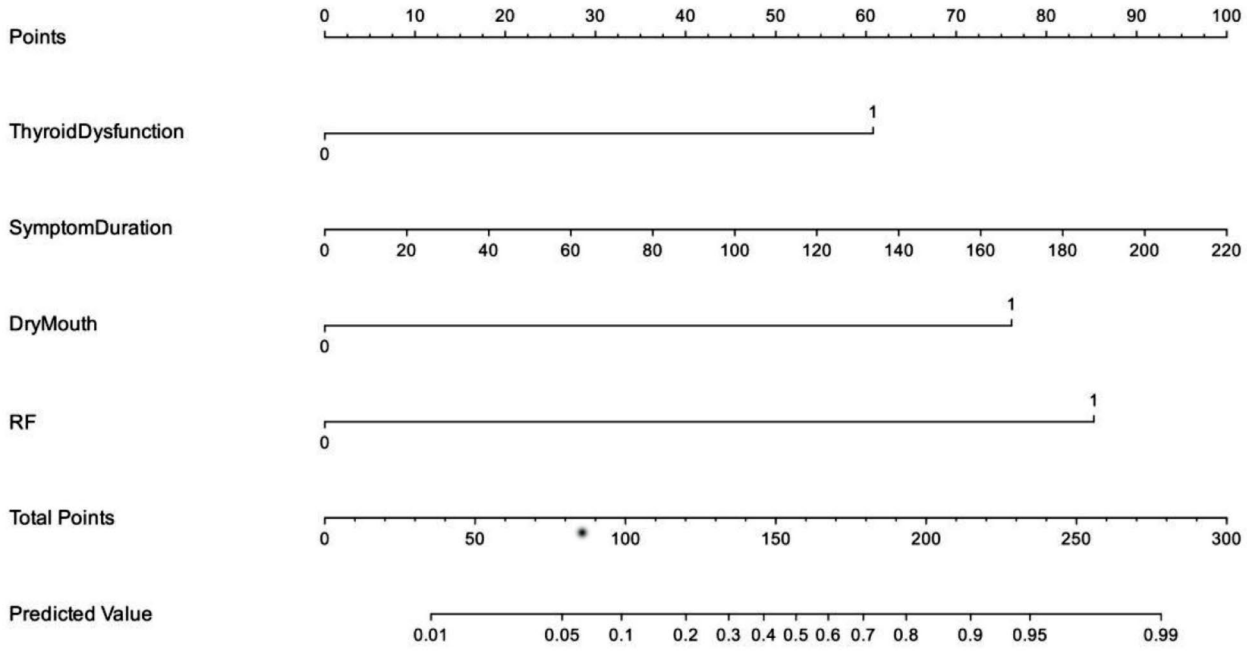

Fig. 1 Nomogram for predicting the probability of pSS-RTA patients

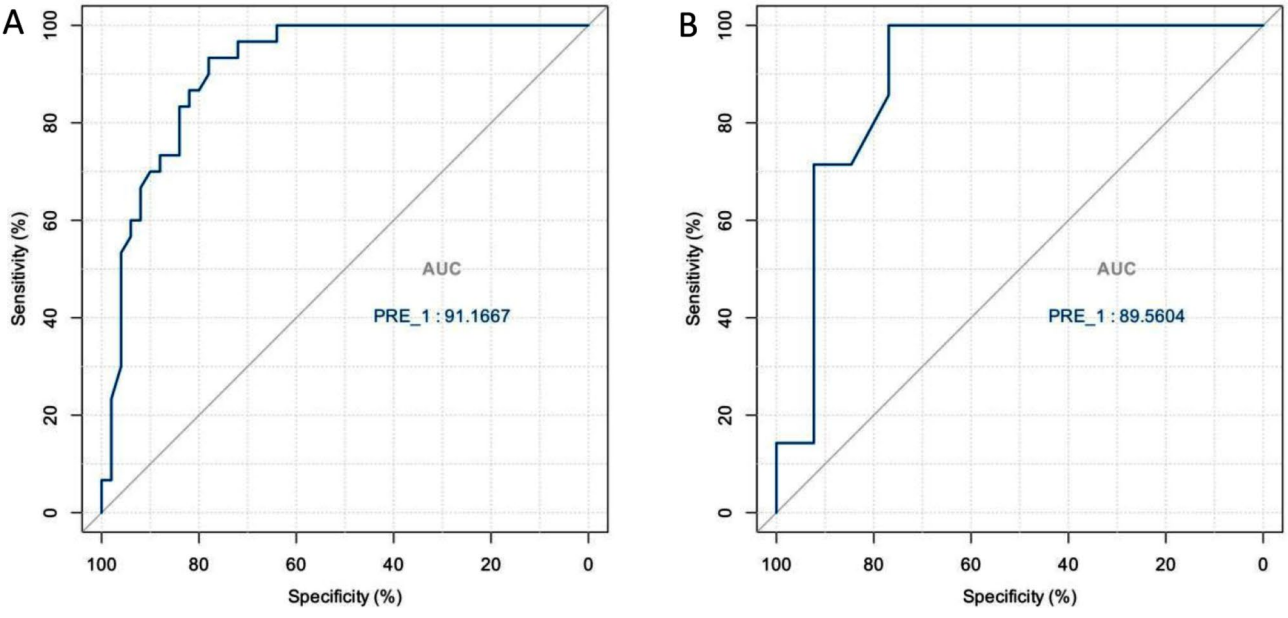

Fig. 2 Receiver operating characteristic curves (ROC) of the development set and validation set. (**A**) Development set. (**B**) Validation set (AUC = 0.912 vs. 0.896)

assists in maintaining the normal physiological functions of the body, strengthening the immune function, improving nutritional status and physical fitness, promoting tissue repair and regeneration, and optimizing therapeutic outcomes. Therefore, early and appropriate nutritional support is an important step in the treatment process of pSS and pSS-RTA patients.

The link between thyroid disease and systemic autoimmune diseases is well-known. Among 5 patients with both thyroid disease and renal tubular acidosis, 3 also had Sjögren's syndrome, indicating a possible connection among these conditions, although the exact mechanism remains unclear [32]. A multicenter study involving 4479 pSS patients found that thyroid disease (OR 1.49, 95%

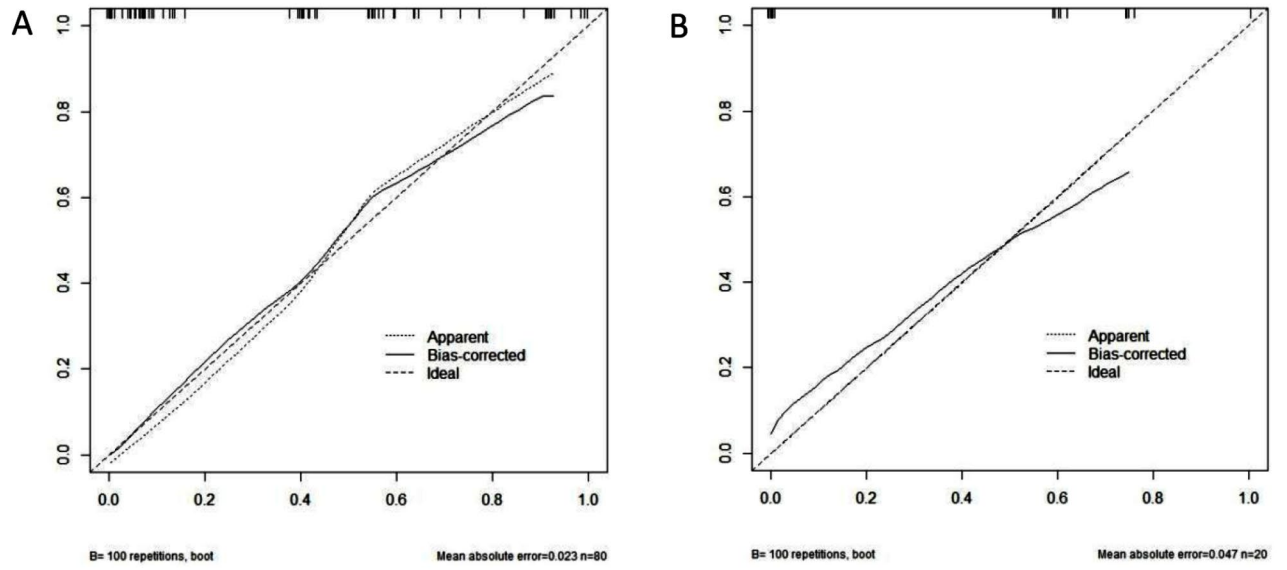

Fig. 3 Calibration plots of the development set and validation set. (**A**) Development set. (**B**) Validation set

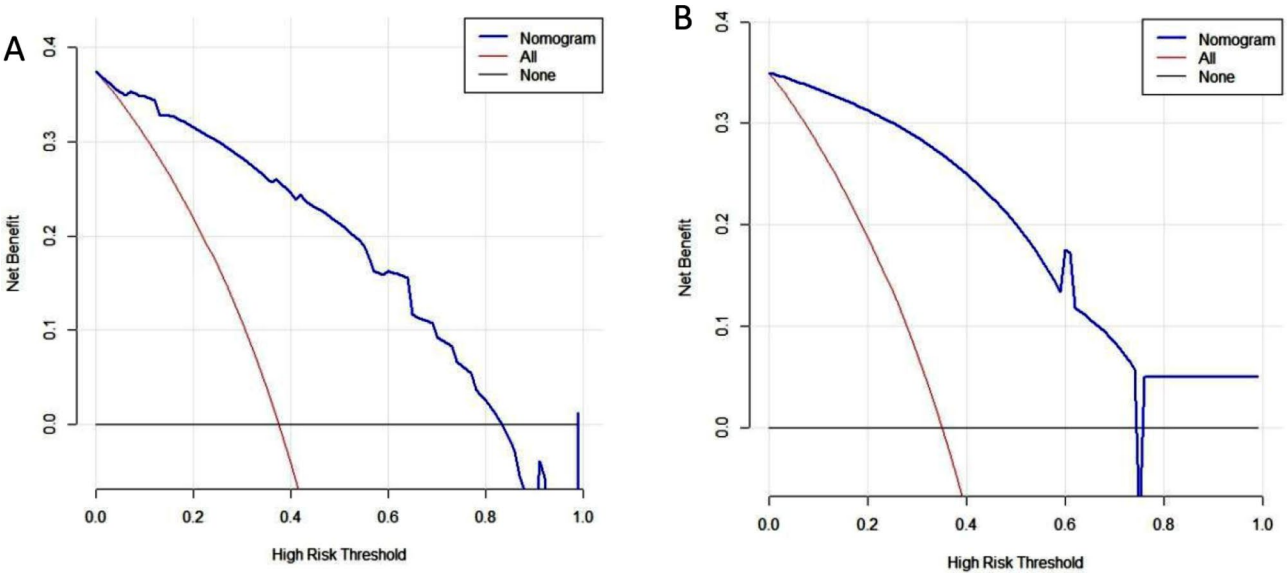

Fig. 4 Decision curve analysis for the development set and validation set. (**A**) Development set. (**B**) Validation set

CI 1.04–2.14) is an independent risk factor for pSS-RTA [31]. Our study also supports the association between thyroid disease and pSS-RTA, emphasizing the importance of screening young women with thyroid disease for autoimmune conditions, especially pSS. Similarly, diagnosed pSS patients should be screened for thyroid disease to enable early detection and intervention.

Our findings suggest that pSS-RTA patients experience symptoms for a longer duration than pSS patients, highlighting a diagnostic delay possibly due to some RTA patients being undiagnosed due to mild symptoms. Additionally, symptoms related to low potassium levels may lead patients to seek care in specialties such as nephrology, gastroenterology, or endocrinology, contributing to delays in pSS diagnosis. Therefore, thorough autoimmune disease screening, particularly for pSS, is recommended for young women with RTA.

There is debate regarding whether there are differences in dry mouth symptoms between pSS patients with and without RTA. Jain et al. reported a lower occurrence of dry eyes in pSS-RTA patients compared to those without RTA, while the difference in dry mouth occurrence was not statistically significant [16]. In our study, dry mouth was more prevalent in pSS-RTA patients than in those

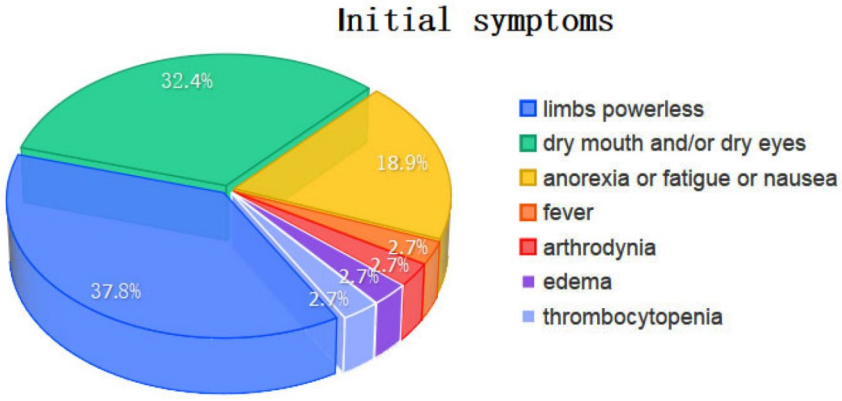

Fig. 5 Pie chart of first symptoms in pSS-RTA patients

without RTA, while the occurrence of dry eyes was similar. One possible explanation is that RTA and exocrine gland involvement share common pathogenic mechanisms and histological characteristics. Certain targets of pSS-RTA, such as carbonic anhydrase II and H±ATPase, are expressed in both salivary glands and renal intercalated cells [6]. Another explanation could be that patients with renal tubular dysfunction may develop nephrogenic diabetes insipidus, leading to polydipsia and subjective dry mouth symptoms.

We also discovered a positive correlation between RF positivity and the risk of pSS patients developing RTA. This is the first report indicating a link between RF positivity and pSS-RTA. RF, one of the autoantibodies associated with pSS, is an immunoglobulin with varying isotypes and affinities first discovered over 80 years ago, although its mechanisms and pathophysiology are not fully understood [33]. RF is commonly found in patients with RA, connective tissue diseases, and various infections, and occasionally in healthy individuals. Studies have shown RF positivity in 75–95% of pSS patients [34]. Recent research has revealed RF positivity as an independent predictor of lymphoma in pSS patients, underscoring its critical role in lymphoma development [35, 36]. There is evidence suggesting that RF positivity is associated with more severe and prolonged disease in RA patients [37]. These findings collectively demonstrate the significant role of RF in the occurrence, development, and prediction of autoimmune diseases. While more research has focused on RF in the RA field, there is a need for further exploration of RF in the context of pSS to identify new therapeutic targets and predict the evolution of pSS-related complications more accurately.

The statistics of the initial symptoms revealed that apart from presenting as limb weakness (37.8%) and dry mouth or dry eyes (32.4%) symptoms, 18.9% of pSS-RTA patients might have digestive tract symptoms including anorexia or fatigue or nausea as the initial manifestations. When these patients have digestive tract symptoms, they most frequently visit the gastroenterology department. If digestive doctors fail to rule out the disease of pSS-RTA, it is highly likely to cause missed diagnosis or misdiagnosis, resulting in serious consequences. Additionally, a small number of patients present fever, arthrodynia, edema, and thrombocytopenia as their first symptoms. These symptoms also need to alert clinicians, and screening for autoimmune diseases, especially pSS, should be conducted as much as possible for early detection and early intervention to enhance the survival quality of patients.

The severity of pSS-RTA patients was classified, and the relationship between the severity and risk factors was investigated and analyzed. Nevertheless, the results of this study did not reveal a correlation between the two for the time being. We suppose that this might be because this research was a single-center one and the sample size was relatively small. Subsequently, it is necessary to increase the sample size and carry out related research through multi-center cooperation to provide a solid theoretical foundation for the early identification of pSS-RTA patients with severe conditions.

This study has limitations, including a relatively small number of eligible patients due to strict inclusion criteria, the retrospective nature of the study introducing potential biases, and single-center data limiting generalizability. Moreover, the lack of time-series data in the predictive model hinders accurate risk assessment for pSS patients developing RTA. Future plans involve expanding the sample size in collaboration with multiple hospitals to establish a Nomogram with additional clinical predictors and time-series data.

Conclusions

In conclusion, our Nomogram for predicting the likelihood of pSS patients developing RTA exhibits good discrimination, calibration, and clinical benefits. Utilizing this Nomogram can guide early identification of high-risk patients and prompt intervention for better outcomes.

Abbreviations

SS	Sjogren's syndrome
RTA	renal tubular acidosis
RA	rheumatoid arthritis
SLE	systemic lupus erythematosus
DM	dermatomyositis
SSc	systemic sclerosis
IN	interstitial nephritis
GN	glomerulonephritis
AECG	American-European Consensus Group
ACR	American College of Rheumatology
EULAR	European League Against Rheumatism
BMI	body mass index
GFR	glomerular estimate filtartion
ROC	receiver operating characteristic
DCA	decision curve analysis

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

Author contributions
Yanzhen Zeng participated in the study design and analysis and wrote the manuscript. Runzhi Liu and Shuyi Li participated in study design and manuscript revision. Jingwen Wei and Fei Luo wrote the main manuscript tables and figures.Yongkang Chen and Dongmei Zhou participated in manuscript revision.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written informed consent for all data was obtained from patients during their hospitalization, and the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University approved the study (XYFY2024-KL202-01).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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