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ORIGINAL ARTICLE

Renal tubular acidosis and associated factors in patients with primary Sjögren's syndrome: a registry-based study

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Abstract

Objectives To investigate the clinical features and factors associated with primary Sjögren's syndrome (pSS)–associated renal tubular acidosis (RTA).

Method This case–control study was based on a multicenter pSS registry established by the Chinese Rheumatism Data Center. Patients with pSS, including those with RTA and those without renal involvement, between May 2016 and March 2020 were included in the analysis. Demographic, clinical, and laboratory data were also collected. Univariate and multivariate logistic regression analyses were used to identify factors that were associated with pSS-RTA.

Results This study included 257 pSS patients with RTA and 4222 patients without renal involvement. Significantly younger age at disease onset (40.1 ± 14.1 vs. 46.2 ± 13.1 years, $P < 0.001$), longer diagnosis interval (15.0 interquartile range [IQR] [1.0, 48.0] vs. 6.0 IQR [0, 34.0] months, $P < 0.001$), higher EULAR Sjögren's syndrome disease activity index (9 IQR [5, 15] vs. 3 IQR [0, 8], $P < 0.001$), and a higher prevalence of decreased estimated glomerular filtration rate (25.0% vs. 6.6%, $P < 0.001$) were observed in pSS patients with RTA than in those without renal involvement. Factors that were independently associated with pSS-RTA included age at disease onset ≤ 35 years (odds ratio [OR] 3.00, 95% confidence interval [CI] 2.27–3.97), thyroid disorders (OR 1.49, 95% CI 1.04–2.14), subjective dry mouth (OR 3.29, 95% CI 1.71–6.35), arthritis (OR 1.57, 95% CI 1.10–2.25), anti-SSB antibody positivity (OR 1.80, 95% CI 1.33–2.45), anemia (OR 1.67, 95% CI 1.26–2.21), elevated alkaline phosphatase level (OR 2.14, 95% CI 1.26–3.65), decreased albumin level (OR 1.61, 95% CI 1.00–2.60), and elevated erythrocyte sedimentation rate (OR 1.78, 95% CI 1.16–2.73).

Conclusions Delayed diagnosis and decreased kidney function are common in pSS patients with RTA. pSS should be considered in patients with RTA, and early recognition and treatment may be useful in slowing the deterioration of renal function in patients with pSS-RTA.

Key Points

- *pSS patients with RTA have earlier disease onset and higher disease activity than pSS patients without RTA, but the diagnosis was frequently delayed.*
- *Decreased kidney function are common in pSS patients with RTA.*
- *Sjögren's syndrome should be considered in young female patients with unexplained RTA, whereas RTA should be screened in pSS patients with early disease onset and elevated ALP level.*

Keywords Delayed diagnosis · Glomerulonephritis · Kidney diseases · Renal tubular acidosis · Sjögren's syndrome

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands. The clinical manifestations of pSS are heterogeneous, extending from eye or mouth dryness to systemic

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diseases, such as renal involvement and interstitial lung disease (ILD). Extraglandular involvement is associated with poor quality of life and results in increased mortality in patients with pSS [1, 2].

Renal involvement is an extraglandular manifestation of pSS and includes two distinct subtypes with different pathophysiological mechanisms: tubulointerstitial nephritis (TIN) caused by lymphocytic infiltration of the kidney interstitium and glomerulonephritis (GN) caused by secondary immune complex-mediated processes [3]. Renal tubular acidosis (RTA) is a special complication of pSS renal involvement with typical manifestations such as metabolic acidosis, urolithiasis, bone disease, muscle weakness caused by hypokalemia, and even respiratory arrest and cardiac arrest [4, 5]. Previous studies suggested that the deficiencies of vacuolar H^+-ATPase and anion exchanger 1 in α-intercalated cells and antibodies to carbonic anhydrase II were associated with the development of pSS-RTA [3].

The identification of risk factors associated with pSS-RTA is an essential step in its early recognition and treatment to prevent adverse events, such as fracture, life-threatening muscle paralysis, and chronic kidney disease. Previous studies have shown that multiple factors are associated with pSS-RTA, including anti-SSA and anti-SSB antibodies, younger age, earlier disease onset, longer disease duration, and hypergammaglobulinemia [5–8]. However, most of the current knowledge of pSS-RTA come from patient-specific case studies with small sample sizes and single-center designs. The largest recent studies focusing on pSS-RTA reported 95 patients with pSS-RTA in China [5], 29 in India [7], and 17 in Europe [9]. Registry studies based on a large number of patients and a multicenter design can provide an opportunity to gain a better understanding of pSS-RTA.

In this nationwide multicenter registry study, we aimed to investigate the clinical and laboratory characteristics of Chinese patients with pSS-RTA. Furthermore, we compared the characteristics of patients with pSS-RTA with those of patients without renal involvement, and identified factors associated with pSS-RTA. This is the first registry-based study on pSS-RTA with the largest sample size that could provide reliable answers to the clinical features and associated factors of pSS-RTA.

Material and methods

Patients and study design

This nationwide pSS registry was established by the Chinese Rheumatism Data Center and aimed at collecting data on the clinical characteristics, treatment, and long-term outcomes of pSS in China [10, 11]. The present study included patients from 221 high-ranking rheumatology centers between May 2016 and March 2020. The study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital, which was the primary research center (JS-2038). Written informed consent was obtained from all patients prior to enrollment.

Patients were enrolled if they fulfilled the 2002 American-European Consensus Group (AECG) [12] or the 2016 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for Sjögren's syndrome [13]. Patients with other connective tissue diseases, such as systemic lupus erythematosus, systemic sclerosis, rheumatoid arthritis, and polymyositis/dermatomyositis, were excluded.

In this case–control study, the case group included pSS patients with RTA at enrollment. The control group included patients without renal involvement at enrollment, which was defined as (1) no past medical history of RTA and GN at enrollment, and (2) renal domain of EULAR Sjögren's syndrome disease activity index (ESSDAI) scored as no activity at enrollment. RTA was defined based on ≥ 1 of the following criteria: (1) hyperchloremic metabolic acidosis with a normal anion gap and a urine pH > 5.5 with a positive urine anion gap, and (2) abnormal ammonium chloride loading test [14]. Patients with other known causes of RTA, such as hereditary diseases, drugs, or hypercalciuria, were excluded. GN was defined based on ≥ 1 of the following criteria: (1) proteinuria > 0.5 g/day for > 3 months; (2) active urine sediment (≥ 3 red blood cells per high-power field or red blood casts); (3) renal histology compatible with GN and no evidence of other causes [15].

Data collection

The detailed protocol was described in the previous study [16]. Briefly, patients were interviewed and examined by rheumatologists according to a uniform predefined protocol at enrollment. The information collected at enrollment consisted of demographic characteristics (age at enrollment, age at disease onset, age at diagnosis, and sex), clinical manifestations (including subjective dry eye, subjective dry mouth, parotid enlargement, and extraglandular involvement), comorbidities (including coronary artery disease [CAD], stroke, thyroid disorders, and fragility fractures), laboratory data, and disease activity evaluation. Disease duration was defined as the time from disease onset to enrolment. The diagnostic interval was defined as the time from disease onset to the diagnosis of pSS. Thyroid disorders included hyperthyroidism, hypothyroidism, and thyroiditis. Fragility fracture was defined as a fracture occurring from a fall from a standing height or less. Routine laboratory tests included complete blood count,

urinalysis, and liver and renal function tests (alkaline phosphatase [ALP], albumin, and serum creatinine). Renal function was evaluated with the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Immunologic markers consisted of anti-SSA, anti-SSB, antinuclear antibodies (ANA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin G (IgG), IgA, and IgM; complement 3 (C3); and C4. Information on extraglandular manifestations, including purpura, arthritis, myositis, ILD, pulmonary hypertension, autoimmune hepatitis, peripheral neuropathy, leukopenia, thrombocytopenia, and autoimmune hemolytic anemia, was collected. Disease activity was assessed using the ESSDAI [17] and EULAR Sjögren's syndrome patient-reported index (ESSPRI) [18]. Disease damage was assessed using the Sjögren syndrome disease damage index (SSDDI) [19]. Treatments (glucocorticoids and immunosuppressive agents) were collected in the pSS-RTA group.

Statistical analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as the means with standard deviation or medians with interquartile range (IQR), where deemed appropriate. The Kolmogorov–Smirnov test was used to determine normality. Differences in baseline variables were compared using Fisher's exact test or the chi-squared test for categorical data, the unpaired *t*-test for normally distributed continuous data, and the Mann–Whitney test for non-normally distributed continuous data. Univariate logistic regression analyses were performed to assess the unadjusted association between pSS-RTA and clinical parameters. Multivariate logistic regression analyses were used to identify independent factors associated with pSS-RTA. The variables entering the multivariate model were clinically relevant and statistically significant in the univariate analyses ($P<0.05$). Potential multicollinearity was assessed using the variance inflation factor values and tolerance. Multicollinearity was not detected. The results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). A subanalysis was performed with age- and sex-matched controls (1:3) randomly selected from the original control group. All significance tests were two-tailed, and the level of significance was set at $P<0.05$. All statistical analyses were conducted using SPSS (version 22.0; IBM SPSS Inc., Armonk, NY, USA).

Results

Among the 4930 patients in the registry, 117 patients who lacked data confirming the diagnosis of pSS and 334 patients with renal involvement other than RTA were excluded. A total of 4479 patients with pSS, including 257 with RTA and 4222 without renal involvement, were enrolled in this study.

Demographic characteristics and comorbidities

The study included 4288 (95.7%) female and 191 (4.3%) male participants, with a mean age at entry of 50.9 ± 13.2 years, mean age at disease onset of 45.8 ± 13.3 years, and median disease duration of 3.0 (IQR 1.0–6.1) years. Demographic characteristics are shown in Table 1. Among patients with pSS-RTA, disease onset younger than 35 years old was reported in 109 (42.4%) patients. Patients in the pSS-RTA group were more likely to be female (98.4% vs. 95.6%, $P=0.027$), younger at disease onset (40.1 ± 14.1 vs. 46.2 ± 13.1, $P<0.001$), and younger at enrollment (46.7 ± 14.1 vs. 51.1 ± 13.1, $P<0.001$) compared to those in the control group. Furthermore, longer disease duration (4.0 years [IQR 1.6–9.7] vs. 3.0 years [IQR 1.0–6.0], $P<0.001$) and diagnosis interval (15.0 months [IQR 1.0–48.0] vs. 6.0 months [IQR 0–34.0], $P<0.001$) were observed in the pSS-RTA group than in the control group. Patients with pSS-RTA showed a higher prevalence of fragility fracture (3.5% vs. 1.5%, $P=0.021$) and thyroid disorders (16.7% vs. 11.7%, $P=0.017$) than those in the control group. Among patients with pSS-RTA, 20 (7.8%) received glucocorticoids alone, 57 (22.2%) received immunosuppressive agents alone, and 156 (60.7%) received glucocorticoids in combination with immunosuppressive agents (Table S1).

Clinical manifestations

Subjective dry mouth, subjective dry eye, and parotid enlargement were observed in 246 (95.7%), 199 (77.4%), and 57 (22.2%) patients with RTA, respectively (Table 2). The prevalence of subjective dry mouth (95.7% vs. 90.0%, $P=0.002$) and parotid enlargement (22.2% vs. 17.0%, $P=0.034$) was significantly higher in the pSS-RTA group than in the control group. The most common extraglandular manifestations in patients with pSS-RTA were arthritis (17.9%), ILD (11.7%), and leukopenia (8.9%). Arthritis was more prevalent in the pSS-RTA group than in the control group (17.9% vs. 10.6%, $P<0.001$).

Disease activity and damage

The median ESSDAI was significantly higher in the pSS-RTA group than in the control group (9 [IQR 5–15] vs. 3 [IQR 0–8], $P<0.001$). Furthermore, 76/251 (30.3%) patients with pSS-RTA were scored as having high disease activity (ESSDAI ≥ 14) (Table 2). In the renal domain, 132/251 (52.6%), 32/251 (12.7%), and 13/251 (5.2%) patients with

Table 1 Demographic characteristics and comorbidities of patients in the pSS-RTA group and in the control group

	pSS-RTA ($n=257$)	Control ($n=4222$)	P
Demographic characteristics			
Female, *n* (%)	253 (98.4)	4035 (95.6)	0.027*
Age at enrollment, mean ± SD, years	46.7 ± 14.1	51.1 ± 13.1	< 0.001*
Age at disease onset, mean ± SD, years	40.1 ± 14.1	46.2 ± 13.1	< 0.001*
Age at disease onset ≤ 35 years old	109 (42.4)	925 (21.9)	< 0.001*
Age at diagnosis, mean ± SD, years	43.4 ± 14.4	48.5 ± 13.1	< 0.001*
[a]Disease duration, median (IQR), years	4.0 (1.6, 9.7)	3.0 (1.0, 6.0)	< 0.001*
[b]Diagnosis interval, median (IQR), months	15.0 (1.0, 48.0)	6.0 (0, 34.0)	< 0.001*
Comorbidities			
CAD, *n* (%)	5 (1.9)	99 (2.3)	0.680
Stroke, *n* (%)	5 (1.9)	60 (1.4)	0.495
Fragility fracture, *n* (%)	9 (3.5)	63 (1.5)	0.021*
Malignancy, *n* (%)	3 (1.2)	73 (1.7)	0.498
Thyroid disorders, *n* (%)	43 (16.7)	495/4219 (11.7)	0.017*
Hypothyroidism, *n* (%)	24/43 (55.8)	264/487 (54.2)	
Hyperthyroidism, *n* (%)	4/43 (9.3)	63/487 (12.9)	
Thyroiditis, *n* (%)	15/43 (34.9)	160/487 (32.9)	

CAD coronary artery disease, *RTA* renal tubular acidosis

[a]Disease duration: time from disease onset to enrollment

[b]Diagnosis interval: time from disease onset to diagnosis of pSS

*Statistically significant ($P<0.05$)

pSS-RTA had low, moderate, and high disease activity, respectively. Disease activity scores in the biological, hematological, constitutional, and lymphadenopathy domains were significantly higher in the pSS-RTA group than in the control group (Fig. 1). The median SSDDI was significantly higher among patients with pSS-RTA than among those in the control group (3 [IQR 2–4] vs. 1 [IQR 1–2], $P<0.001$), while ESSPRI did not differ significantly.

Laboratory characteristics

The immunological profile of pSS-RTA included positive ANA in 233/250 (93.2%), positive anti-SSA antibody in 230/252 (91.3%), positive anti-SSB antibody in 163/247 (66.0%), positive anti-Ro-52 antibody in 191/239 (79.9%), elevated ESR in 115/148 (77.7%), elevated CRP in 18/129 (14.0%), hypergammaglobulinemia in 173/244 (70.9%), and hypocomplementemia in 39/131 (29.8%) (Table 3). A higher prevalence of positive ANA (93.2% vs. 89.2%, $P=0.047$), positive anti-SSA antibody (91.3% vs. 84.1%, $P=0.002$), positive anti-SSB antibody (66.0% vs. 47.6%, $P<0.001$), positive anti-Ro-52 antibody (79.9% vs. 67.4%, $P<0.001$), elevated ESR (77.7% vs. 55.4%, $P<0.001$), and hyperglobulinemia (70.9% vs. 53.6%, $P=0.036$) was detected in patients with pSS-RTA.

With regard to renal examination, proteinuria was more common in the pSS-RTA group (24.6% vs. 6.7%, $P<0.001$) than in the control group. The median serum creatinine level was 73.5 IQR (56.6–99.2) μmol/L in the pSS-RTA group, which was significantly higher than that in the control group ($P<0.001$). The median eGFR was 82.8 IQR (58.4–106.3) mL/min/1.73 m^2 in the pSS-RTA group, which was significantly lower than that in the control group ($P<0.001$). The prevalence of decreased eGFR (≤ 60 mL/min/1.73 m^2) was significantly higher in the pSS-RTA group than in the control group (25.0% vs. 6.6%, $P<0.001$). Anemia, elevated ALP, and decreased albumin were also more prevalent in the pSS-RTA group than in the control group.

Associated factors of pSS-RTA

In univariate analysis, factors associated with pSS-RTA included female, age at disease onset ≤ 35 years, fragility fracture, thyroid disorders, subjective dry mouth, parotid enlargement, arthritis, ANA positivity, anti-SSA positivity, anti-SSB positivity, anti-Ro-52 positivity, anemia, elevated ALP, decreased albumin, elevated ESR, hyperglobulinemia, and hypocomplementemia (Table 4). Multivariate analysis indicated that age at disease onset ≤ 35 years (OR 3.00, 95% CI 2.27–3.97), thyroid disorders (OR 1.49, 95% CI 1.04–2.14), subjective dry mouth (OR 3.29, 95% CI 1.71–6.35), arthritis (OR 1.57, 95% CI 1.10–2.25), anti-SSB antibody positivity (OR 1.80, 95% CI 1.33–2.45), anemia (OR 1.67, 95% CI 1.26–2.21), elevated ALP (OR 2.14, 95% CI 1.26–3.65), decreased albumin (OR 1.61, 95% CI 1.00–2.60), and elevated ESR (OR 1.78, 95% CI 1.16–2.73) were independently associated with pSS-RTA.

Table 2 Comparison of clinical characteristics in patients in the pSS-RTA group and in the control group

	pSS-RTA ($n=257$)	Control ($n=4222$)	P
Disease symptoms			
Subjective dry mouth, *n* (%)	246 (95.7)	3798 (90.0)	0.002*
Subjective dry eye, *n* (%)	199 (77.4)	3306 (78.3)	0.742
Parotid enlargement, *n* (%)	57 (22.2)	719 (17.0)	0.034*
Extraglandular manifestations			
Purpura, *n* (%)	13 (5.1)	122 (2.9)	0.058
Arthritis, *n* (%)	46 (17.9)	446 (10.6)	< 0.001*
Myositis, *n* (%)	4 (1.6)	50 (1.2)	0.550
ILD, *n* (%)	30 (11.7)	550 (13.0)	0.632
Pulmonary hypertension, *n* (%)	2 (0.8)	116 (2.7)	0.067
Autoimmune hepatitis, *n* (%)	1 (0.4)	41 (1.0)	0.515
Leukopenia, *n* (%)	23 (8.9)	334 (7.9)	0.552
Thrombocytopenia, *n* (%)	13 (5.1)	214 (5.1)	1.000
AIHA, *n* (%)	3 (1.2)	40 (0.9)	0.735
Peripheral neuropathy, *n* (%)	9 (3.5)	155 (3.7)	1.000
Disease activity and damage			
ESSDAI, median (IQR)	9 (5, 15)	3 (0, 8)	< 0.001*
0, *n* (%)	24/251 (9.6)	1322 (31.3)	< 0.001*
1–4, *n* (%)	25/251 (10.0)	1139 (27.0)	
5–13, *n* (%)	126/251 (50.2)	1286 (30.5)	
≥ 14, *n* (%)	76/251 (30.3)	475 (11.3)	
SSDDI, median (IQR)	3 (2, 4)	1 (1, 2)	< 0.001*
ESSPRI, median (IQR)	3.5 (2.3, 5.0)	3.6 (2.0, 5.1)	0.827

AIHA autoimmune hemolytic anemia, *ESSDAI* EULAR Sjögren's syndrome disease activity index, *ESSPRI* EULAR Sjögren's syndrome patient-reported index, *ILD* interstitial lung disease, *SSDDI* Sjögren's syndrome disease damage index, *RTA* renal tubular acidosis

*Statistically significant ($P<0.05$)

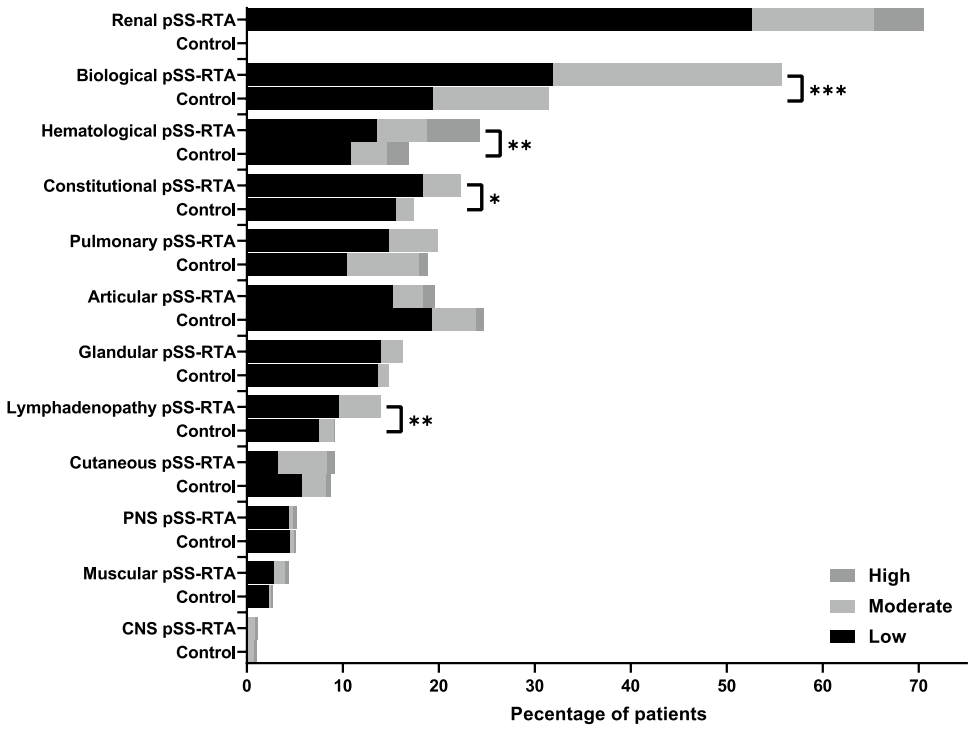

Fig. 1 Percentage of patients scored as active in each ESSDAI domain. *$P<0.05$; **$P<0.01$; ***$P<0.001$

Table 3 Comparison of laboratory data in patients in the pSS-RTA group and in the control group

	pSS-RTA ($n=257$)	Control ($n=4222$)	P
Autoantibodies			
ANA positivity, *n* (%)	233/250 (93.2)	3511/3935 (89.2)	0.047*
Anti-SSA positivity, *n* (%)	230/252 (91.3)	3352/3985 (84.1)	0.002*
Anti-SSB positivity, *n* (%)	163/247 (66.0)	1879/3949 (47.6)	< 0.001*
Anti-Ro-52 positivity, *n* (%)	191/239 (79.9)	2409/3575 (67.4)	< 0.001*
Renal examinations			
Proteinuria, *n* (%)	46/187 (24.6)	160/2385 (6.7)	< 0.001*
SCr, median (IQR), μmol/L	73.5 (56.6, 99.2)	59.0 (51.0, 69.5)	< 0.001*
eGFR, median (IQR), mL/min/1.73 m^2	82.8 (58.4, 106.3)	99.7 (85.4, 109.8)	< 0.001*
Decreased eGFR, *n* (%)	30/120 (25.0)	100/1508 (6.6)	< 0.001*
Laboratory tests			
Anemia, *n* (%)	130/249 (52.2)	1354/4212 (32.1)	< 0.001*
Elevated ALP, *n* (%)	23/112 (20.5)	142/1428 (9.9)	< 0.001*
Decreased ALB, *n* (%)	32/124 (25.8)	219/1530 (14.3)	0.001*
Elevated ESR, *n* (%)	115/148 (77.7)	1219/2201 (55.4)	< 0.001*
Elevated CRP, *n* (%)	18/129 (14.0)	259/1933 (13.4)	0.858
Hypergammaglobulinemia, *n* (%)	173/244 (70.9)	2220/4140 (53.6)	< 0.001*
Hypocomplementemia, *n* (%)	39/131 (29.8)	412/1884 (21.9)	0.036*

ALB albumin, *ALP* alkaline phosphatase, *ANA* antinuclear antibodies, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ESR* erythrocyte sedimentation rate, *RTA* renal tubular acidosis, *SCr* serum creatinine

Low eGFR: eGFR ≤ 60 mL/min/1.73 m^2; anemia: hemoglobin level < 120 g/L; high ALP: ALP ≥ 135 U/L; high ESR level: ESR > 50 mm/h; high CRP: CRP > 10 mg/L; hypergammaglobulinemia: IgG > 16.6 g/L, IgA > 4.0 g/L, or IgM > 2.6 g/L; hypocomplementemia: C3 < 0.73 g/L or C4 < 0.1 g/L

*Statistically significant ($P < 0.05$)

Table 4 Univariate and multivariate logistic regression analyses for factors associated with pSS-RTA

	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Female	2.93 (1.08—7.96)	0.035*	2.17 (0.78—6.02)	0.138
Age at disease onset ≤ 35 years old	2.63 (2.03—3.40)	< 0.001*	3.00 (2.27—3.97)	< 0.001*
Fragility fracture	2.40 (1.18—4.87)	0.016*	1.79 (0.81—3.92)	0.149
Thyroid disorders	1.51 (1.08—2.13)	0.017*	1.49 (1.04—2.14)	0.028*
Subjective dry mouth	2.50 (1.35—4.61)	0.003*	3.29 (1.71—6.35)	< 0.001*
Parotid enlargement	1.39 (1.02—1.88)	0.035*	1.16 (0.84—1.60)	0.372
Arthritis	1.85 (1.32—2.58)	< 0.001*	1.57 (1.10—2.25)	0.014*
ANA positivity	1.66 (1.00—2.74)	0.049*	0.98 (0.57—1.69)	0.942
Anti-SSA positivity	1.97 (1.26—3.08)	0.003*	0.91 (0.54—1.54)	0.727
Anti-SSB positivity	2.14 (1.63—2.80)	< 0.001*	1.80 (1.33—2.45)	< 0.001*
Anti-Ro-52 positivity	1.93 (1.39—2.66)	< 0.001*	1.39 (0.97—1.99)	0.075
Anemia	2.31 (1.78—2.98)	< 0.001*	1.67 (1.26—2.21)	< 0.001*
Elevated ALP	2.34 (1.43—3.82)	0.001*	2.14 (1.26—3.65)	0.005*
Decreased ALB	2.08 (1.36—3.19)	0.001*	1.61 (1.00—2.60)	0.048*
Elevated ESR	2.81 (1.89—4.17)	< 0.001*	1.78 (1.16—2.73)	0.009*
Hypergammaglobulinemia	2.11 (1.59—2.80)	< 0.001*	1.33 (0.98—1.81)	0.068
Hypocomplementemia	1.51 (1.03—2.24)	0.037*	1.00 (0.65—1.52)	0.991

ALB albumin, *ALP* alkaline phosphatase, *ANA* antinuclear antibodies, *ESR* erythrocyte sedimentation rate

*Statistically significant ($P < 0.05$)

A subanalysis with age- and sex-matched controls (1:3) was performed to reduce the exaggeration of tendency with large sample size (Tables S2 and S3). In multivariate analysis, independently associated factor of pSS-RTA included disease onset ≤ 35 years (OR 1.84, 95% CI 1.34–2.51), subjective dry mouth (OR 3.02, 95% CI 1.50–6.06), arthritis (OR 1.84, 95% CI 1.21–2.80), anemia (OR 1.55, 95% CI 1.13–2.13), elevated ALP (OR 2.62, 95% CI 1.34–5.13), and decreased ALB (OR 2.18, 95% CI 1.20–3.94).

Subgroup analysis between pSS-RTA patients with and without GN

To investigate the characteristics of pSS-RTA patients with GN, we divided patients with pSS-RTA into two groups: the pSS-RTA with GN group ($n = 13$) and the pSS-RTA-only group ($n = 244$) (Table S4). Patients in the pSS-RTA with GN group had a significantly higher median serum creatinine (162.9 μmol/L [IQR 96.3–212.0] vs. 70.3 μmol/L [IQR 56–94.7], $P = 0.003$) and lower median eGFR (34.0 mL/min/1.73 m^2 [IQR 25–59.3] vs. 87.6 mL/min/1.73 m^2 [IQR 64.2–106.7], $P = 0.002$) than those in the pSS-RTA-only group. A decreased eGFR was observed in 5/7 (71.4%) patients in the pSS-RTA with GN group. Proteinuria trended to be more common in the pSS-RTA with GN group (41.7% vs. 23.4%, $P = 0.172$) than in the pSS-RTA-only group. The median ESSDAI was significantly higher in the pSS-RTA with GN group than in the pSS-RTA-only group (16 [IQR 12–20] vs. 8.5 [IQR 5–14.8], $P = 0.009$). Moderate and high disease activity was observed in 4 (30.8%) and 9 (69.2%) patients in the pSS-RTA with GN group, respectively.

Discussion

To our knowledge, this study is the largest multicenter study on pSS-RTA and provides a better understanding of the clinical and laboratory characteristics of pSS-RTA. Our findings underline the importance of early recognition and treatment of RTA in patients with pSS to slow the deterioration of renal function.

The prevalence of RTA in patients with pSS remains unclear. In an international registry, the prevalence of RTA among patients with pSS was reported to be 0.5% [20]. However, studies using acidification loading tests have shown that approximately 11.3–73.1% of patients with pSS had RTA [5–7, 9, 21]. This variation may be attributed to the different definitions of RTA. Indeed, RTA is frequent in patients with pSS.

Our data showed that early disease onset is an independent factor associated with pSS-RTA. pSS is relatively more common in middle-aged females, while early disease onset is associated with active systemic disease including renal involvement [22]. Jain et al. reported a relatively young age at disease onset of 29.3 ± 10 years among pSS patients with RTA in India [7]. Therefore, attention should be paid to renal involvement in young patients with pSS.

A delayed diagnosis of pSS is common in patients with pSS-RTA. Our data suggested that the diagnosis interval of pSS was significantly longer in patients with pSS-RTA. Some patients with incomplete RTA remain undiagnosed because of subtle symptoms. In addition, symptomatic patients may first visit the nephrology or endocrinology departments, which accounts for the delayed diagnosis of pSS. In young women with RTA, autoimmune diseases should be carefully screened.

Our study demonstrated that positive anti-SSB antibody was an independent factor associated with pSS-RTA. In previous epidemiological studies, the presence of anti-SSB antibody was considered a marker of active disease with more extraglandular involvement and higher B cell activation [23, 24]. The association between anti-SSB antibody and pSS renal involvement has been reported [25, 26]. In a study that reviewed biopsy-proven cases of pSS renal disease, anti-SSA and anti-SSB antibodies were more prevalent among pSS patients with TIN than among those with GN, and were associated with poor renal prognosis [27]. Several studies have investigated the role of anti-SSB antibody in pSS-RTA. Both et al. reported that the prevalence of positive anti-SSB antibody was the highest among pSS patients with complete distal RTA (dRTA) (100%), followed by those with incomplete dRTA (79%), and those without dRTA (45%) [9]. Takemoto et al. found a higher anti-SSB antibody titer among patients with pSS-RTA than among those without, as well as a positive correlation between anti-SSB antibody levels and anti-carbonic anhydrase II antibody levels, which indicates that anti-SSB antibody may participate in the pathogenesis of pSS-RTA [28].

ESR and CRP levels are widely used as non-specific inflammatory markers in clinical practice. We found a significantly higher frequency of elevated ESR among patients with pSS-RTA than among those in the control group, while no significant difference was observed in CRP levels. After adjusting for hypergammaglobulinemia, a common cause of discordance between ESR and CRP, the positive association between elevated ESR and pSS-RTA remained. Therefore, an elevated ESR may be associated with an active inflammatory status in patients with pSS-RTA. Moreover, we observed a higher prevalence of hypergammaglobulinemia among patients with pSS-RTA, supporting the association between B cell hyperactivity and renal involvement in previous studies [5, 6]. One study suggested that persistent hypergammaglobulinemia was associated with solid organ damage and IgG level could be used to monitor disease activity [29].

The association between sicca syndrome and RTA remains controversial. Jain et al. reported less frequent dry eye and similar dry mouth in patients with pSS-RTA than in those without pSS-RTA [7]. A meta-analysis showed that pSS renal involvement had no significant correlation with dry eye (OR 0.60, 95% CI 0.34–1.06) [30]. RTA and exocrine glandular involvement share common pathogenic mechanisms and histological features [15]. Some targets of pSS-RTA, such as carbonic anhydrase II and H^+-ATPase, are expressed in both salivary glands and renal intercalated cells [31]. Another possible explanation is that patients with tubular dysfunction could present with nephrogenic diabetes insipidus, resulting in polydipsia, which may be reported as dry mouth by patients.

Articular manifestations are common in patients with pSS [32]. Two studies reported that the prevalence of arthralgia or arthritis was lower among pSS patients with RTA than among those without [7, 33], whereas data from a Spanish registry suggested that both arthritis and arthralgia were similar between pSS patients with and without renal involvement [26]. In contrast, Fauchais et al. observed a significantly higher frequency of renal involvement among pSS patients with articular manifestation (defined as arthralgia and/or non-erosive arthritis) than those without [34]. In this study, arthritis was found to be independently associated with pSS-RTA. Further research using a clear definition of articular involvement is required.

Thyroid disorders, particularly autoimmune thyroiditis, often co-occur with pSS. To the best of our knowledge, our study is the first to report a statistically independent association between pSS-RTA and thyroid disorders. A previous case series described five patients with autoimmune thyroid disease and RTA [35]. Three patients had sicca syndrome and ILD, indicating an association between both diseases. This co-existence should be noted in clinical practice because both patients with hyperthyroidism and those with RTA could present with muscle weakness or quadriparesis caused by hypokalemia, and pSS should be considered a differential diagnosis.

Bone disease is a typical manifestation of RTA, which may present with fracture, pseudofracture, or bone pain with elevated serum ALP level [36]. In our study, the prevalence of fragility fracture was significantly higher in the patients with pSS-RTA. Elevated ALP was independently associated with pSS-RTA. Our data support a positive association between impaired bone health and pSS-RTA, as observed in patients with idiopathic RTA [37]. However, Both et al. suggested that pSS patients with RTA ($n = 15$) had no significant difference in bone mineral density (BMD) compared to those without RTA ($n = 39$) after adjusting demographic variables [38]. Nevertheless, routine BMD assessment is recommended for patients with pSS-RTA to evaluate fracture risk and treatment response.

Although pSS-RTA is considered to be benign, increasing evidence shows that CKD can occur in these patients [27, 39]. Our study showed that the eGFR of patients with pSS-RTA was significantly lower than that of patients without pSS-RTA, and approximately 25% of patients with pSS-RTA had decreased renal function. Anemia and decreased albumin level, the complications of CKD, were also more prevalent among patients with pSS-RTA. Local inflammation in the kidney caused by autoantibodies and activated lymphocyte infiltration contributes to renal interstitial fibrosis and tubular atrophy, ultimately resulting in chronic kidney disease. However, slowly progressive TIN does not usually draw clinical attention and eventually leads to CKD. In a follow-up study, chronic renal failure developed in half of patients with pSS-TIN [39]. The high proportion of CKD in patients with pSS-RTA emphasizes the need for early treatment.

GN is an uncommon subtype of pSS renal involvement caused by a secondary immune complex-mediated process. pSS-GN is associated with lymphoma development and higher mortality [39]. The differences in clinical features between TIN and GN have been described in previous studies, but the co-existence of RTA and GN is rare and has not been well summarized [15, 39]. We found that approximately 5% of patients with pSS-RTA had simultaneous GN. Compared to patients with pSS-RTA only, pSS patients with both RTA and GN had worse renal function and higher disease activity. These findings suggest that more aggressive treatment should be considered for these patients.

There is few evidence for treatment of pSS extraglandular involvement. For patients with pSS-RTA, oral supplementation such as bicarbonate and potassium citrate can be used to reverse the acidosis to reduce the risk of nephrolithiasis and bone disease. As reported by Jasiek et al., renal biopsy is recommended for patients with pSS-RTA to determine the types and activity of renal involvement [27]. The use of immunosuppressants should be decided based on the renal biopsy findings.

Our study had several limitations. First, pSS-RTA was not the primary objective of the registry. Hence, data on pSS-RTA, such as RTA-related symptoms, subtypes of RTA, biomarkers of tubular function, and kidney biopsy, were not systematically collected. Some laboratory results such as anti-thyroglobulin antibodies, anti-neutrophil cytoplasm antibodies, and rheumatoid factor level were lacking in this study. Second, we could not draw conclusions on the causal relationship between pSS-RTA and its associated factors because of the case–control nature of this study. Prospective studies including patients with newly diagnosed pSS are necessary to figure out the risk factors and biomarkers for the development of pSS-RTA. Besides, prospective studies to follow up patients with pSS-RTA are needed to

further evaluate the effects of the factors on the prognosis of pSS-RTA.

In conclusion, based on multicenter registry data, patients with pSS-RTA had earlier disease onset but delayed diagnosis. Decreased renal function is common, particularly in patients with concomitant pSS-GN. Therefore, patients with pSS, particularly young women, should be routinely screened for RTA. Early diagnosis and treatment are necessary for pSS-RTA.

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Author contribution MTL, LYZ, JLZ, DX, YZ, and XFZ contributed to the conception and design of the study. LQ, LYZ, QL, JL, PTY, XDK, XWD, MJZ, XML, YFW, and JX contributed to data collection. YYZ and YHW participated in statistical analysis and interpretation. YYZ drafted the manuscript. MTL and DX revised the manuscript critically. DX, MTL, YZ, and XFZ supervised the study. All authors read and approved the final manuscript.

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Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliancewith ethical standards

Ethics approval and consent to participate Written informed consent was obtained from all patients at enrollment. Ethics approval for the registry was obtained from the Medical Ethics Committee of Peking Union Medical College Hospital (JS-2038).

Disclosures None.

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