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Relationship between serum uric acid and hypertension in patients with primary Sjögren's syndrome: A retrospective cohort study

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Abstract

Primary Sjögren's syndrome (pSS) patients with hypertension (pSS-HT) have a significantly increased risk of cardio-cerebrovascular events. Serum uric acid (SUA), a potential inflammatory substance, is considered to be closely related to hypertension in the general population. Our aim is to assess the association between SUA and pSS-HT. This is a retrospective cohort study. The diagnosis of pSS is based on the American European Consensus Classification criteria. Primary outcome was incident hypertension in pSS patients. Cox regression model was used to estimate the hazard ratios (HR) and 95% CI of SUA in pSS-HT. The authors also plotted Kaplan–Meier plots to assess the cumulative risk of first hypertension in patients with hyperuricemia and normal uric acid. In addition, the dose-response curve was also used to discuss the relationship between SUA and pSS-HT. Finally, three hundred and fifty-one pSS patients were enrolled from May 2011 to May 2020, of which 166 cases developed hypertension within a mean follow-up of 3.91 years. Univariate Cox regression demonstrated that SUA was associated with the onset of hypertension in pSS (HR: 1.005 95%CI: 1.002–1.009). After adjusting for the potential risk factors, the relationship remained unchanged (HR: 1.003, 95%CI: 1.001–1.005). Kaplan-Meier survival analysis showed a statistically significant difference of hypertension risk between hyperuricemia patients and normal uric acid patients ($P = .026$). There was also a significant dose-effect relationship between SUA and hypertension in pSS in dose-response model. In this study, the authors find that SUA may be closely associated with the development of hypertension in pSS, which is also confirmed by our dose-response model. Therefore, SUA could be considered in the management of pSS-HT.

KEYWORDS
cohort study, hypertension, Primary Sjögren's syndrome, serum uric acid

1 | INTRODUCTION

Primary Sjögren's syndrome (pSS) is a systemic connective tissue disease (CTD) affecting the exocrine glands and multiple organs. Its prevalence ranges from .33% to .77% in China.[1] Nevertheless, epidemiological surveys show that the prevalence of pSS is about .43% in Europe, second only to rheumatoid arthritis (RA) and pSS is considered to be the second most common CTD.[2,3] Despite significant progress made in therapies, pSS and its complications place heavy burdens on patients and society. Cardiovascular diseases (CVD) including heart failure and coronary artery disease are the leading cause of death in pSS. Beltai and colleagues demonstrated that pSS patients had a significantly increased risk of coronary artery complications (RR = 1.34, 95%CI: 1.06–1.38) and heart failure (OR = 2.54, 95%CI: 1.30–4.97) compared with the general population.[4] Furthermore, Brito-Zeron and colleagues also found that the mortality of patients with pSS was significantly higher than that of the control group.[5] The traditional cardiovascular risk factors including hypertension often are used to evaluate CVD risk. In fact, hypertension is a major risk factor of CVD, both in the general population and in patients with systemic lupus erythematosus (SLE) or RA. Recently, several studies also showed that pSS-HT patients are more likely to develop subclinical atherosclerosis, asymptomatic cardiovascular damage, and left ventricular dysfunction than pSS patients with normal blood pressure. Furthermore, these patients were prone to atherosclerosis, congestive heart failure, and stroke.[6,7] Therefore, the management of hypertension is an important issue for the prevention of CVD events in pSS.

Serum uric acid (SUA), as an end product of purine metabolism, is considered to be closely related to the occurrence of hypertension.[8] Several cohort studies have shown that levels of elevated SUA were closely associated with the risk of hypertension in the general population.[9] In patients with CTD, there were few studies focusing on the association between SUA and hypertension,[10] and these studies have pointed out a close relationship between the two. But the exact role of SUA on blood pressure modulation in CTD patients was still not well clarified. Recent studies have demonstrated that SUA may promote the increase of blood pressure by mediating inflammatory response, eventually leading to vascular endothelial dysfunction and kidney injury.[8] However, unlike SLE and RA, pSS is characterized by relatively low-grade systemic inflammation levels,[11,12] so the specific relationship between SUA and pSS-HT is not entirely clear.

In the retrospective cohort study, our aim is to determine the independence of the association between SUA and hypertension in pSS patients, and draw a dose-response curve to further confirm their relationships.

2 | METHODS

2.1 | Study design and participants

A retrospective cohort of pSS in patients was studied. Moreover, all pSS patients involved in this study were diagnosed according to the American European Consensus Classification criteria.[13] For example, patients diagnosed with pSS had significant ocular and oral symptoms with histopathological abnormalities or positive autoantibodies. The study cohort was created using the pSS database, which was a subset of the CTD database (CTTD). CTDD consisted of 621 representative pSS participants who met the 2002 international diagnostic criteria. And it was constructed by collecting electronic medical record information in Affiliated Hospital of Southwest Jiaotong University from May 2011 to May 2020. This study has been approved by the Ethics Committee of Affiliated Hospital of Southwest Jiaotong University (Approval number: 2019-S-20).

In this study cohort, pSS patients without a history of hypertension (patients diagnosed as hypertensive by a clinician, taking anti-hypertensive medication, with blood pressure greater than 140/90 mmHg at baseline measurement) were recruited, and they were all older than 18. The investigators followed up the subjects at 6-month intervals for three consecutive days as outpatients during follow-up. Moreover, systolic blood pressure (SBP) and diastolic blood pressure (DBP) readings were made with Korotkoff sounds I and IV using a mercury sphygmomanometer while the subjects were resting. Hypertension was diagnosed if SBP ≥140 mm Hg (1 mmHg = .133 kPa) or DBP ≥90 mmHg or taking antihypertensive medication within 2 weeks of investigation. After excluding CVD, malignant tumor, overlap syndrome, primary aldosteronism, respiratory failure, chronic liver, kidney dysfunction, heart failure, and use of diuretics drugs, 351 pSS patients were enrolled in our cohort (Figure 1). In addition, all subjects were invited to participate in a telephone follow-up survey. The first diagnosis date of hypertension of each patient was defined as the index date. After a mean of 3.19 years of follow-up, 166 cases developed hypertension.

2.2 | Data collection

Baseline demographics, laboratory data, clinical data and treatment measures were included by trained medical students from electronic medical records and final examination by a senior clinician. Demographic data included sex, age, blood pressure, smoking history, diabetes mellitus, pSS duration, and symptoms associated with pSS, including xerophthalmia, xerostomia, recurrent parotid enlargement, rampant dental care, tongue pain, and rashes.[14] Treatment measures included the use of glucocorticoids, anti-rheumatic drugs, nonsteroidal anti-inflammatory (NSAIDs) drugs. Laboratory data included SUA, hemoglobin, white leukocyte count, erythrocyte sedimentation rate (ESR), albumin, total protein, cystatin C, apolipoproteins A, apolipoproteins B, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine, fasting glucose, anti-nuclear antibody, anti SSA antibody, anti SSB antibody, anti-dsDNA, U1-nRNP antibodies, anti-Sm antibody, anti-Jo-1 antibody, anti-Rib-P, anti-Ro52.

2.3 | Clinical outcome and definition

Primary outcome was incident hypertension in pSS patients. All patients were followed from the index date to incident hypertension,

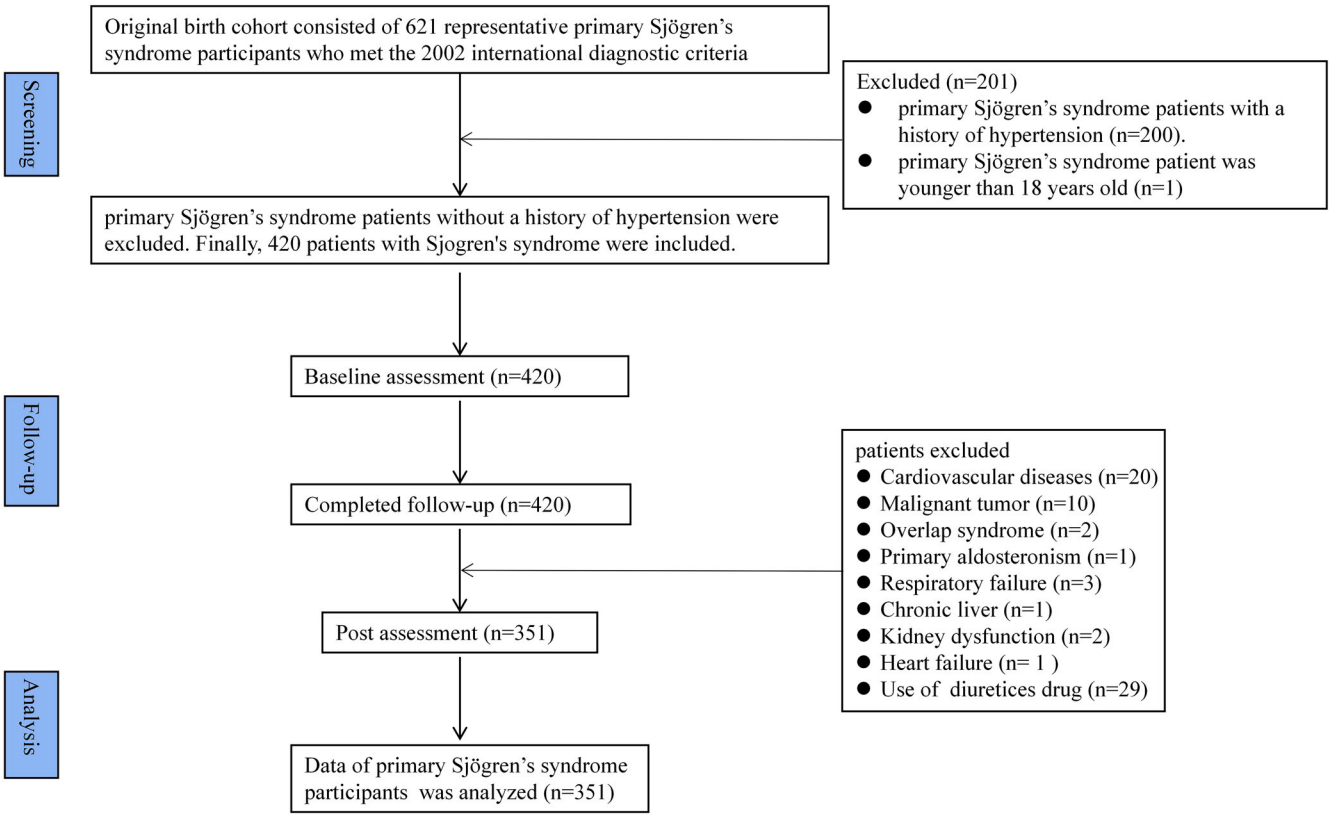

FIGURE 1 Flow diagram of the study population

or May 2020. hypertension was described as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, or current use of anti-HT drugs.[15] Smokers were defined as subjects who smoked at least one cigarette per day for more than 1 year, and those who rarely smoked or quit for more than 1 year were considered as nonsmokers.[16] Diabetes mellitus was defined as fasting glucose ≥ 7.0 mmol/L, or typical diabetic symptoms with random glucose ≥ 11.1 mmol/L, or being on hypoglycemic drugs.[17] Renal insufficiency was defined as a glomerular filtration rate (GFR), 60 ml/min/1.73 m2, liver dysfunction was defined as elevated AST level (>45 IU/L) concomitant with the elevated LDH level (>400 IU/L), and heart failure was defined as the development of left ventricular (LV) ejection fraction < 50% or hospitalization for heart failure.[18,19]

2.4 | Statistical analysis

Statistical analyses were performed on R 3.5. The data of normal distribution were expressed as mean ± standard deviation and tested by One-way ANOVA. The non-normal distribution data were represented by median (interquartile range) and tested by non-parametric test. Categorical data were expressed as a percentage, and the Chi-square test was used to compare the difference between them. Univariate and multivariate Cox regression models were used to estimate the hazard ratios (HRs) and 95% CI of hypertension in pSS. Furthermore, the multivariate Cox regression models adjusted with cardiovascular risk factors, SBP, DBP, CPR, ESR, glucocorticoid, anti-rheumatic drugs, NSAIDs, hemoglobin, and related Antibodies, eGFR, creatinine, were also used to assess the relationship between SUA and pSS-HT. $p \leq .05$ is considered to be statistically significant. In addition, Kaplan-Meier survival analysis was used to assess the effect of hyperuricemia on hypertension risk in pSS.

Furthermore, we also modeled SUA level as a continuous variable using restricted cubic splines (with knots at the 5th, 25th, 75th and 95th percentiles of their sample distributions) to provide a flexible dose-response relationship between SUA and change in blood pressure. The goodness of fit of the model was calculated by using Akaike information criterion (AIC), and its stability was also discussed.

3 | RESULTS

3.1 | Baseline characteristics

Three hundred and fifty-one patients (female 322, male 29, mean age 60.34 ± 14.52 years) were included in our study. 166 pSS patients developed hypertension and the mean follow-up time was 3.91 years (range .1–10 years). Baseline characteristics of these patients were shown in Table 1. Compared with non- hypertension patients, hypertension patients were older, and had higher SBP ($P = .01$), DBP ($P = .01$), SUA levels ($P = .01$), ESR levels ($P = .01$), leukocyte count ($P = .01$), neutrophils count ($P = .01$), creatinine ($P = .01$), urea ($P = .01$), and fasting glucose levels ($P = .05$) at baseline, while these patients had lower

TABLE 1 Baseline data of primary Sjögren's syndrome patients after follow-up

Variables	Patients without HT ($n = 185$)	Patients with HT ($n = 166$)	*P*
Age (years)	53.47 ± 14.159	68.01 ± 10.577	.01
Female (*n*, %)	175 (94.59%)	147 (88.55%)	.04
Smoker (*n*, %)	8 (4.32%)	9 (5.42%)	.62
Follow-up (mean ± SD) (years)	4.56 ± 1.45	5.31 ± 1.93	.66
Xerostomia (*n*, %)	51 (27.50%)	50 (28.30%)	.93
Rampant caries (*n*, %)	13 (7.00%)	12 (7.20%)	1.00
Recurrent parotid enlargement (*n*, %)	3 (1.60%)	3 (1.80%)	.88
Glossalgia (*n*, %)	3 (1.60%)	0 (0%)	.10
Xerophthalmia (*n*, %)	17 (9.10%)	40 (24.00%)	.41
Rash (*n*, %)	15 (7.60%)	18 (10.80%)	.59
Erythema nodosum (*n*, %)	1 (.50%)	2 (1.20%)	.75
Reynold's phenomenon (*n*, %)	3 (1.30%)	5 (3.00%)	.07
Arthralgia (*n*, %)	23 (12.40%)	19 (11.40%)	.79
SBP (mmHg)	114.33 ± 11.99	136.49 ± 20.98	.01
DBP (mmHg)	69.14 ± 8.85	76.78 ± 13.51	.01
Laboratory data			
eGFR	101.68 (89.16, 113.31)	96.55 (85.65, 103.45)	.32
CPR (mg/L)	4.93 (2.48, 18.75)	9.16 (3.14, 25.67)	.11
ESR (mm/H)	43.31 ± 21.00	62.91 ± 25.92	.01
Leukocyte count (10^9/L)	4.57 (3.27, 6.23)	5.47 (4.15, 10.21)	.01
Neutrophils (10^9/L)	3.14 (2.37, 4.49)	6.34 (3.67, 7.91)	.01
Lymphocyte count (10^9/L)	1.21 (.83, 1.50)	1.28 (.82, 2.14)	.46
Hemoglobin (g/L)	115 (99, 128)	118 (105, 129)	.11
Red blood cell count (10^{12}/L)	3.88 (3.42, 4.24)	3.92 (3.49, 4.63)	.23
Creatinine (μmol/L)	53.80 (45.73, 63.03)	64.10 (55.60, 85.80)	.01
Serum uric acid (μmol/L)	303.28 (241.45, 345.15)	392.30 (297.20, 486.49)	.01
Hyperuricemia (*n*, %)	15 (7.18%)	43 (25.14%)	.01
Urea (mmol/L)	4.335 (3.475, 5.385)	5.46 (4.34, 7.30)	.01
Albumin (g/L)	39.43 (33.64, 45.66)	36.90 (33.25, 44.28)	.01
Total protein (g/L)	71.70 (67.25, 76.90)	69.70 (63.75, 81.66)	.58
HDL-C (mean ± SD) (mmol/L)	1.399 ± .422	1.311 ± .506	.11
LDL-C (mmol/L)	2.458 ± .86	2.418 ± 1.175	.21
TC (mmol/L)	4.33 ± 1.26	4.21 ± 1.578	.14
TG (mmol/L)	1.16 (.84, 1.71)	1.17 (.86, 1.8)	.76
Fasting glucose (mmol/L)	5.00 (4.51, 6.01)	5.34 (4.71, 6.66)	.05
Anti-nuclear antibody (*n*, %)	103 (55.68%)	68 (40.96%)	.01
Anti SSA/Ro antibody (*n*, %)	100 (54.05%)	67 (40.36%)	.01
Anti SSB/La antibody (*n*, %)	52 (28.11%)	20 (12.05%)	.01
Anti-dsDNA (*n*, %)	1 (.54%)	5 (3.01%)	.16
U1-nRNP antibodies (*n*, %)	4 (2.15%)	6 (3.61%)	.26
Anti-Sm antibody (*n*, %)	2 (1.08%)	0 (0%)	.11
Anti-Jo-1 antibody (*n*, %)	5 (2.70%)	3 (1.81%)	.32
Anti-Rib-P (*n*, %)	0 (0%)	3 (1.81%)	.11
Anti-Ro52 (*n*, %)	0 (0%)	0 (0%)	1.00

(Continues)

TABLE 1 (Continued)

Variables	Patients without HT ($n = 185$)	Patients with HT ($n = 166$)	*P*
Medication			
Glucocorticoid (*n*, %)	79 (42.70%)	39 (23.49%)	.01
Anti-rheumatic drugs (*n*, %)	35 (17.60%)	16 (9.63%)	.01
NSAIDs drugs (*n*, %)	28 (18.92%)	25 (15.06%)	.94

Abbreviations: CPR, C-reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; GFR: glomerular filtration rate; HDL-C: High-density lipoprotein-cholesterol; HT: hypertension; LDL-C, low-density lipoprotein-cholesterol; NSAIDs drugs: non-steroidal anti-inflammatory drugs; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

TABLE 2 Univariate and multivariable Cox regression model for features of hypertension in primary Sjögren's syndrome

Variables	Univariate Cox regression	*P*	Multivariate Cox regression	*P*
Age (years)	1.048 (95%CI: 1.010–1.085)	.012	1.026 (95%CI: .984–1.070)	.232
Female	6.092 (95%CI: 2.051–18.094)	.001	4.299 (95%CI: .842–21.244)	.08
Systolic blood pressure	.999 (95%CI: .992–1.007)	.999	–	–
Diastolic blood pressure	1.001 (95%CI: 1.001–1.015)	.868	–	–
Leukocyte count (10^9/L)	1.151 (95%CI: 1.001–1.323)	.049	.819 (95%CI: .626–1.073)	.148
Neutrophils (10^9/L)	1.369 (95%CI: 1.207–1.553)	.001	1.404 (95%CI: 1.187–1.661)	.001
ESR (mm/h)	1.017 (95%CI: 1.017–1.012)	.001	1.040 (95%CI: 1.040–1.064)	.001
Creatinine (μmol/L)	.999 (95%CI: .992–1.007)	.887	–	–
Urea (mmol/L)	1.37 (95%CI: .978–1.099)	.228	.956 (95%CI: .840–1.088)	.495
Serum uric acid (μmol/L)	1.005 (95%CI: 1.002–1.009)	.006	1.006 (95%CI: 1.002–1.011)	.007
Fasting glucose (mmol/L)	1.187 (95%CI: .988–1.426)	.068	–	–
Anti-nuclear antibody	.491 (95%CI: .195–1.237)	.131	–	–
Anti SSA/Ro antibody	.546 (95%CI: .217–1.376)	.200	–	–
Anti SSB/La antibody	.516 (95%CI: .154–1.731)	.284	–	–
Glucocorticoid	.483 (95%CI: .192–1.218)	.123	–	–
Anti-rheumatic drugs	.677 (95%CI: .231–1.981)	.477	–	–

Abbreviation: ESR, erythrocyte sedimentation rate.

albumin levels ($P = .01$). Hypertension patients also tended to have lower proportions of positive anti-SSA antibody ($P = .01$), anti-SSB antibody ($P = .01$), and anti-nuclear antibody ($P = .01$) at baseline. In addition, the use of glucocorticoids and anti-rheumatic drugs was less frequent in hypertension patients ($P = .01$).

3.2 | Association between SUA and hypertension in pSS patients

In univariate Cox analysis, we found that SUA was associated with pSS-HT (HR 1.005, 95%CI: 1.002–1.009). Then multivariate Cox regression model was used to assess the relationship between SUA and hypertension. The result showed that SUA level (HR 1.006, 95%CI: 1.002–1.011) was independently associated with hypertension in pSS (Table 2). After adjusting for cardiovascular risk factors, ESR, the use of glucocorticoid, anti-rheumatic drugs, and NSAIDs, the association between SUA and hypertension remained constant (HR: 1.003, 95%CI: 1.001–1.005), suggesting a reliable and stable relationship between them in pSS (Figure 2). In addition, we performed Kaplan-Meier survival analysis on the hyperuricemia patients and normal uric acid patients and found a statistically significant difference in the development of hypertension between the two groups by Kaplan-Meier survival analysis (Log-rank = 4.946, $P = .026$) as shown in Figure 3.

3.3 | Dose-response relationship between SUA and hypertension in pSS

As shown in Figures 4 and 5, dose-response analysis was performed with hypertension and SBP as dependent variable and SUA as independent variable. A J-type association was observed between SUA and hypertension and SBP in pSS. Additionally, we also found a linear relationship between SUA and hypertension (non-linear test $P = .11$), and the dose-response curve indicated that increase of SUA by per standard deviation was related with an increased risk of hypertension (HR .13, 95%CI: .12–.24).

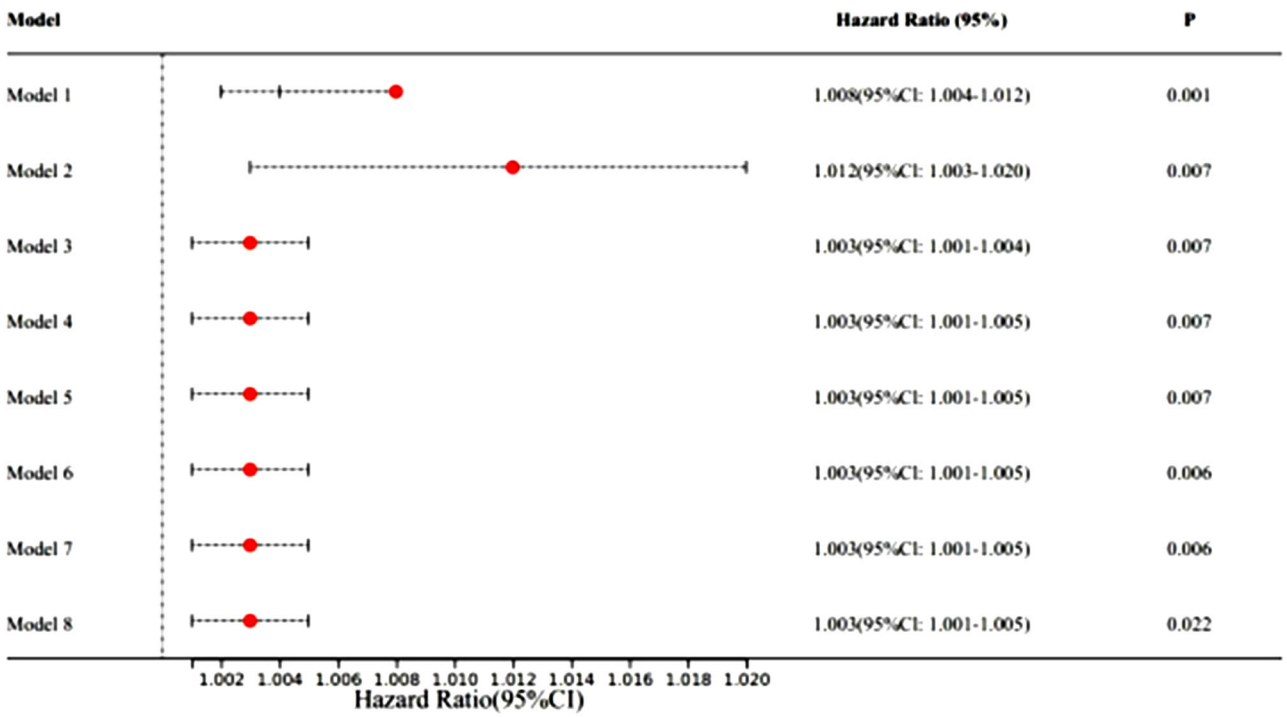

FIGURE 2 Adjusted hazard ratios of hypertension by comorbidities in pSS. Model 1: unadjusted. Model 2: Model 1 plus adjusted for the traditional cardiovascular risk factors (age, sex, systolic blood pressure, diastolic blood pressure, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, triglyceride, total cholesterol, fasting glucose). Model 3: Model 2 plus adjusted for c-reactive protein, erythrocyte sedimentation rate. Model 4: Model 3 plus adjusted for anti-nuclear antibody, anti-SSA/Ro antibody, anti-SSB/La antibody, anti-dsDNA, U1-nRNP antibodies, anti-Sm antibody, anti-Jo-1 antibody, anti-Rib-P, Anti-Ro52. Model 5: Model 4 plus adjusted for glucocorticoid drugs. Model 6: Model 5 plus adjusted for anti-rheumatic drugs. Model 7: Model 6 plus adjusted for non-steroidal anti-inflammatory drugs. Model 8: Model 7 plus adjusted for hemoglobin, eGRF, creatinine

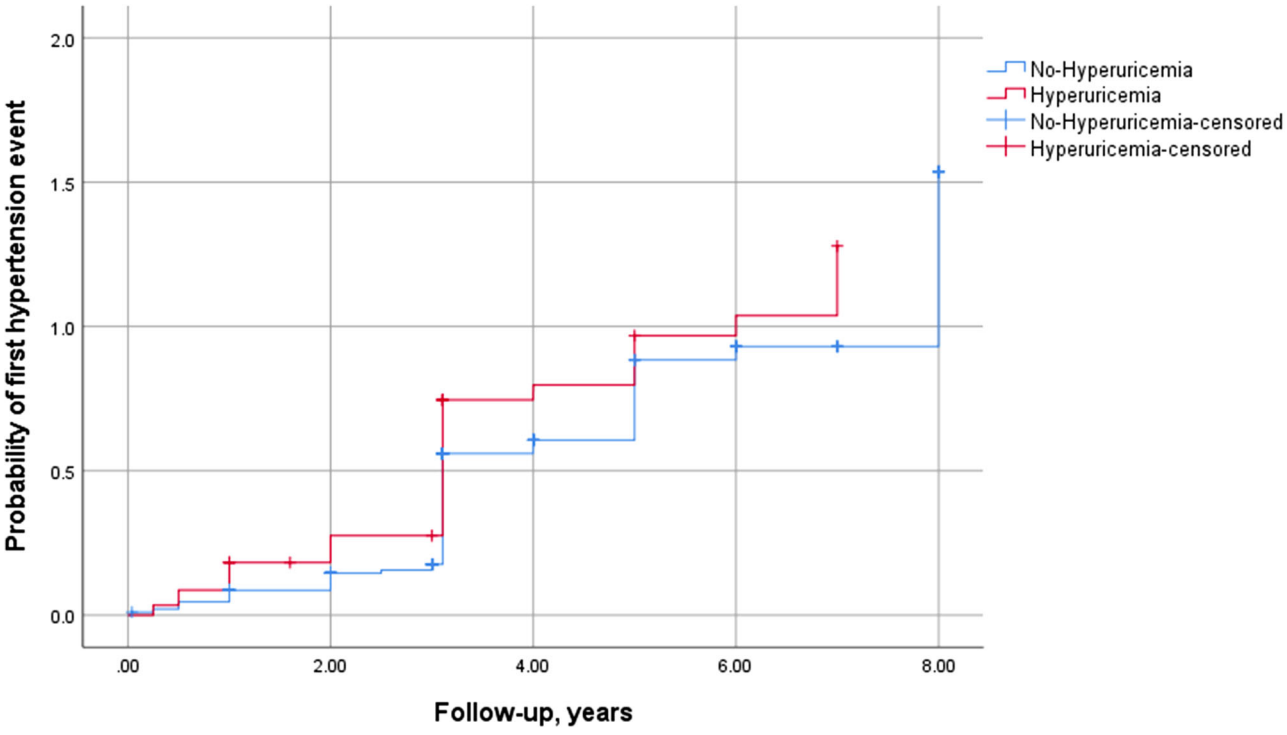

FIGURE 3 Kaplan-Meier estimate of the cumulative incidence of hypertension in patients with hyperuricemia

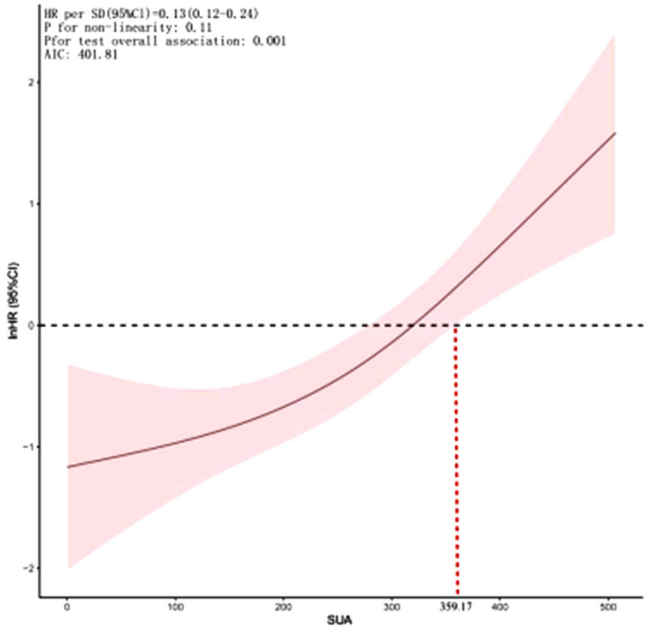

FIGURE 4 The dose-response relationships between serum uric acid and hypertension. RCS, restricted cubic spline; SUA, serum uric acid; SD, standard deviation

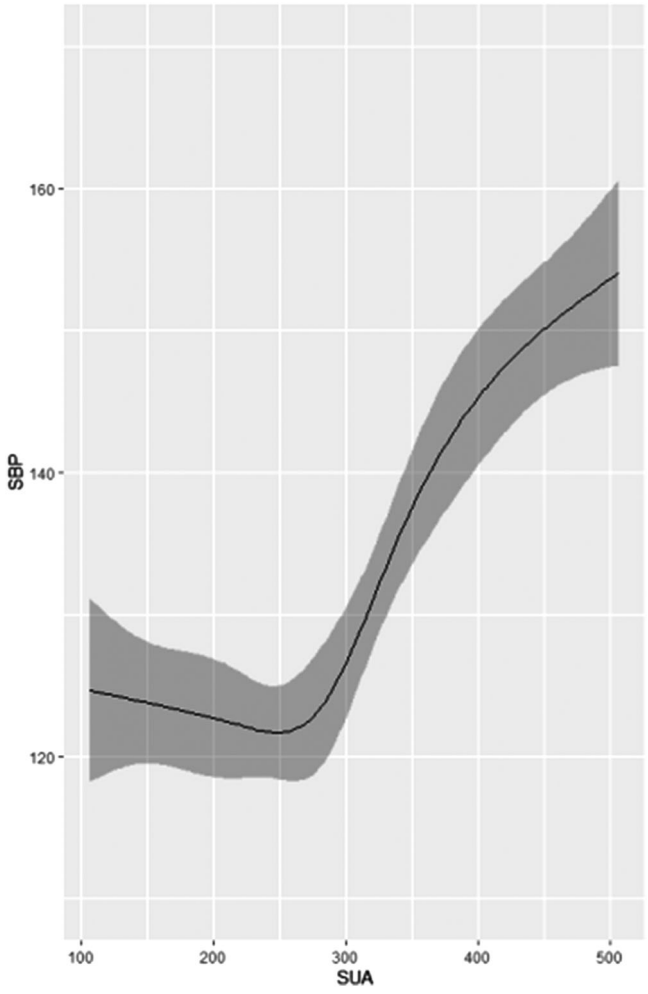

FIGURE 5 The dose-response relationships between serum uric acid and systolic blood pressure

4 | DISCUSSION

In this retrospective cohort, our results indicated that SUA may be positively associated with the onset of pSS-HT. Even after adjusting for potential confounders, the relationship remained constant. In addition, the dose-response curve showed that the increase of SUA per standard deviation was associated with the increase of hypertension risk. These results demonstrated that SUA could take part in the development of pSS-HT, so it should be considered in the management of pSS-HT.

To the best of our knowledge, this is the first study to use a dose-response model to assess the association between SUA and hypertension in pSS patients. The dose-effect model showed a J-shaped relationship between uric acid and the development of hypertension. Moreover, some studies examining the relationship between SUA and CVD in the general population and CTD also showed a J-shaped curve.[20,21] The J-type relationship may reflect a continuum, from decreased plasma antioxidant activity (at very low-SUA levels) to normality and then increasing detrimental vascular effects counteracting antioxidant properties when SUA levels increase. In fact, higher level of SUA appears to be associated with incidental adverse health outcomes. Accumulating studies have shown a strong relationship between the two diseases in the general population.[22,23] For example, in a systematic review including 65 890 hypertension and 321 716 controls, Liu and colleagues found that the pooled RR of the hypertension risk was 1.10 per 1 mg/dl change in the SUA level, suggesting patients with higher level of SUA had a higher risk of hypertension.[22] Furthermore, in another systematic review, elevated SUA level in hypertension patients was significantly associated with all-cause mortality and major adverse cardiovascular events.[23] These results have demonstrated that SUA involved in the incident hypertension and CVD in the general population. However, elevated SUA levels were rarely observed in CTD. For instance, Chen and colleagues reported patients with polymyositis/dermatomyositis had lower concentration of SUA in comparison with healthy people, suggesting an excessive oxidative stress in these patients.[24] In addition, gout, a disease closely related to hyperuricemia, is thought to be somewhat less common in RA than in the general population.[25] Therefore, the association between SUA and CTD is complicated and may involve a multifaceted model that remains only partially elucidated. Indeed, few studies to date have investigated the link between SUA and hypertension in patients with CTD. In an observational study, Panoulas and colleagues reported that SUA levels were closely associated with hypertension in RA, and the association is independent of hypertension risk factors, RA characteristics and relevant drugs.[21] Other studies also indicated that SUA levels were closely related to arteriosclerosis, pulmonary hypertension, and cardiovascular events in patients with CTD.[26,27] Therefore, SUA may also be positively associated with cardiovascular events, even though SUA levels may be relatively low in patients with CTD. Similar to these results, we found that SUA was associated with pSS-HT in our study (HR: 1.010,

95%CI: 1.002–1.018), furthermore, the association was independence of age, sex, blood pressure, HDL-C, LDL-C, triglyceride, TC, fasting glucose, ESR, glucocorticoid, anti-rheumatic drugs, NSAIDs.

In the general population, SUA can cause hypertension by extracellular UA and intracellular UA pathway.[8] The former mainly included urate crystals deposits in urinary lumen and endothelium, which can trigger a pro-inflammatory reaction in vessels.[28] The intracellular UA pathway mainly included the activation of renin-angiotensin system and reduction of endothelial nitric oxide, which can deplete ATP capacity.[29] In fact, a large number of studies have also confirmed the relationship among SUA, renal dysfunction and hypertension. For example, SUA can activate inflammatory and immune pathways, causing abnormal renal vasoconstriction, and exacerbating renal damage, leading to an abnormal increase in blood pressure.[30] Additionally, SUA may also directly induce renal microvascular disease, renal vasoconstriction, and eventually lead to the increase of blood pressure.[31] On the other hand, hypertension can cause decreased renal blood flow, which stimulates urate reabsorption, additionally, hypertension also can cause renal microvascular disease, even local ischaemia, resulting in increased SUA synthesis.[32] In this way, hypertension and SUA formed a vicious circle. However, the detailed mechanism by which SUA induced pSS-HT remained unclear. In addition to the above reasons, pSS is a systemic CTD affecting the exocrine glands and multiple organs. Recent studies have also demonstrated that pSS is strongly associated with a number of cardiovascular risk factors, including metabolic syndrome, abnormal lipid, diabetes, insulin resistance, as well as inflammation.[33] In our study, higher SUA levels were accompanied by a high prevalence of these metabolic abnormalities, which also may further damage vascular endothelial cells and worsen renal function.

Our study also has some limitations. Firstly, it was a retrospective cohort study and there may be various biases. For example, recall bias, selective bias, etc. Therefore, the causal relationship might be less convincing. Secondly, the complex relationship of SUA and pSS-HT, resulting in the study not being validated in other populations, limited the generalizability of the findings to other populations. However, our results suggested that higher SUA levels were associated with incident hypertension in pSS, as they do in the general population, and the relationship remained constant after adjusting for related confounding. These findings confirmed the relationship between SUA and hypertension in pSS. Thirdly, the small sample size included in the study for various reasons may have affected the accuracy of the results. Fourthly, some risk factors including the doses of glucocorticoid, BMI and drinking are not fully documented, which may lead to bias. Fifthly, these patients were followed-up every 6 months, and we do not effectively monitor the 24 h ambulatory blood pressure of patients, this may lead to the deviation of blood pressure in some patients and affect the accuracy of our results. Finally, patients with hypertension still had a significant higher baseline blood pressure values than patients without hypertension, which may influence the results of this study. However, the results remained unchanged after we adjusted for blood pressure values in the multivariate analysis.

In conclusion, we found that SUA levels may be independently associated with hypertension in pSS, whose dose-response relationship also reinforced the plausibility of the result. Therefore, SUA could be considered in the management of pSS-HT.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Study design: Han Wang, Qiang Luo. Study conduct, data collection and data analysis: Qiang Luo, Yiwen Zhang, Li Qin. Data interpretation: Han Wang, Qiang Luo, Li Qin. Drafting manuscript: Han Wang, Qiang Luo, Xiaoqian Yang. All authors participated in the critical editing of the manuscript and approved the final version of manuscript. Qiang Luo takes responsibility for the integrity of the data analysis.

REFERENCES

1. Zhang NZ, Shi CS, Yao QP, et al. Prevalence of primary Sjögren's syndrome in China. *J Rheumatol*. 1995;22(4):659-661.
2. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008;58(1):15-25.
3. Fox RI. Sjögren's syndrome. *Lancet*. 2005;366(9482):321-331.
4. Beltai A, Barnetche T, Daien C, et al. Cardiovascular morbidity and mortality in primary Sjögren's syndrome: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2020;72(1):131-139.
5. Brito-Zerón P, Kostov B, Solans R, et al. Systemic activity and mortality in primary Sjögren syndrome: predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. *Ann Rheum Dis*. 2016;75(2):348-355.
6. Bartoloni E, Alunno A, Gerli R. Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. *Nat Rev Cardiol*. 2018;15(1):33-44.
7. Bartoloni E, Alunno A, Valentini V, et al. Role of inflammatory diseases in hypertension. 2017:353-361.
8. Sanchez-Lozada LG, Rodriguez-Iturbe B, Kelley EE, et al. Uric acid and hypertension: an update with recommendations. *Am J Hypertens*. 2020;33(7):583-594.
9. Kuwabara M, Niwa K, Hisatome I, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases: five-year Japanese cohort study. *Hypertension*. 2017;69(6):1036-1044.
10. Sheikh M, Movassaghi S, Khaledi M, Moghaddassi M. Hyperuricemia in systemic lupus erythematosus: is it associated with the neuropsychiatric manifestations of the disease?. *Rev Bras Reumatol Engl Ed*. 2016;56(6):471-477.
11. Baldini C, Pepe P, Quartuccio L, et al. Primary Sjogren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. *Rheumatology (Oxford)*. 2014;53(5):839-844.
12. Argyropoulou OD, Valentini E, Ferro F, et al. One year in review 2018: Sjögren's syndrome. *Clin Exp Rheumatol*. 2018;36(3):14-26. Suppl 112.

13. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61(6):554-558.
14. Seror R, Bowman SJ, Brito-Zeron P, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. *RMD Open*. 2015;1(1):e000022.
15. Jones NR, McCormack T, Constanti M, McManus RJ. Diagnosis and management of hypertension in adults: NICE guideline update 2019. *Br J Gen Pract*. 2020;70(691):90-91.
16. Bai B, Chen M, Fu L, et al. Quality of life and influencing factors of patients with rheumatoid arthritis in Northeast China. *Health Qual Life Outcomes*. 2020;18(1):119.
17. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013;36 (Suppl 1): S67-S74.
18. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39(2 Suppl 1): S1-S266.
19. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-e327.
20. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?. *Hypertension*. 2003;41(6):1183-1190.
21. Panoulas VF, Douglas KM, Milionis HJ, et al. Serum uric acid is independently associated with hypertension in patients with rheumatoid arthritis. *J Hum Hypertens*. 2008;22(3):177-182.
22. Liu L, Zhang X, Qie R, et al. Dose-response association between serum uric acid levels and incident hypertension: a systematic review and meta-analysis of 17 prospective cohort studies of 32 thousand participants. *Acta Cardiol*. 2021;76(7):748-753.
23. Yang Y, Zhang X, Jin Z, Zhao Q. Association of serum uric acid with mortality and cardiovascular outcomes in patients with hypertension: a meta-analysis. *J Thromb Thrombolysis*. 2021;52(4):1084-1093.
24. Chen Z, Su Z, Pang W, Huang Y, Lin J, Ding Z, et al. Antioxidant status of serum bilirubin and uric acid in patients with polymyositis and dermatomyositis. *Int J Neurosci*. 2017;127:617-623.
25. Merdler-Rabinowicz R, Tiosano S, Comaneshter D, Cohen AD, Amital H. Comorbidity of gout and rheumatoid arthritis in a large population database. *Clin Rheumatol*. 2017;36(3):657-660.
26. Kim KJ, Baek IW, Park YJ, Yoon CH, Kim WU, Cho CS. High levels of uric acid in systemic lupus erythematosus is associated with pulmonary hypertension. *Int J Rheum Dis*. 2015;18(5):524-532.
27. Hannawi S, AlSalmi I, Moller I, Naredo E. Uric acid is independent cardiovascular risk factor, as manifested by increased carotid intima-media thickness in rheumatoid arthritis patients. *Clin Rheumatol*. 2017;36(8):1897-1902.
28. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440(7081):237-241.
29. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16(12):3553-3562.
30. Feig DI, Madero M, Jalal DI, Sanchez-Lozada LG, Johnson RJ. Uric acid and the origins of hypertension. *J Pediatr*. 2013;162(5):896-902.
31. Hwu CM, Lin KH. Uric acid and the development of hypertension. *Med Sci Monit*. 2010;16(10):RA224-RA230.
32. Mocan M, Vesa Ş, Suciu Ş, Blaga SN. Systemic markers of oxidative stress in relation to metabolic syndrome components. *Clujul Med*. 2013;86(3):227-234.
33. Qin L, Zhang Y, Yang X, Luo Q, Wang H. Cardiac involvement in primary Sj ö gren's syndrome. *Rheumatol Int*. 2022;42(2):179-189.

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