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. 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. 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. Furthermore, Brito-Zeron and colleagues also found that the mortality of patients with pSS was significantly higher than that of the control group. 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. 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. Several cohort studies have shown that levels of elevated SUA were closely associated with the risk of hypertension in the general population. In patients with CTD, there were few studies focusing on the association between SUA and hypertension, 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. However, unlike SLE and RA, pSS is characterized by relatively low-grade systemic inflammation levels, 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. 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: 2019-5-20).

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. Treatment measures included the use of glucocorticoids, anti-rheumatic drugs, non-steroidal anti-inflammatory (NSAIDs) drugs. Laboratory data included SUA, hemoglobin, white leucocyte 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-RNP 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,
or May 2020. Hypertension was described as SBP $\geq 140$ mmHg and/or DBP $\geq 90$ mmHg, or current use of anti-HT drugs.\textsuperscript{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.\textsuperscript{16} Diabetes mellitus was defined as fasting glucose $\geq 7.0$ mmol/L, or typical diabetic symptoms with random glucose $\geq 11.1$ mmol/L, or being on hypoglycemic drugs.\textsuperscript{17} Renal insufficiency was defined as a glomerular filtration rate (GFR), 60 ml/min/1.73 m\textsuperscript{2}, 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.\textsuperscript{18,19}

2.4 Statistical analysis

Statistical analyses were performed on R 3.5. The data of normal distribution were expressed as mean $\pm$ 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. $p \leq 0.05$ 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 ($P = 0.01$), DBP ($P = 0.01$), SUA levels ($P = 0.01$), ESR levels ($P = 0.01$), leukocyte count ($P = 0.01$), neutrophils count ($P = 0.01$), creatinine ($P = 0.01$), urea ($P = 0.01$), and fasting glucose levels ($P = 0.05$) 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   |
| Xerophthalmia (n, %)                   | 17 (9.10%)                   | 40 (24.00%)                | .41   |
| Rash (n, %)                            | 15 (7.60%)                   | 18 (10.80%)                | .59   |
| Erythema nodosum (n, %)                | 1 (0.50%)                    | 2 (1.20%)                  | .75   |
| Reynolds’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

| Variable                              | Without HT (mean ± SD) | With HT (mean ± SD) | P     |
|----------------------------------------|------------------------|---------------------|-------|
| 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 (0.83, 1.50)      | 1.28 (0.82, 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 (0.54%)              | 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 (10⁹/L)              | 1.151 (95%CI: 1.001–1.323) | .049    | .819 (95%CI: .626–1.073)    | .148    |
| Neutrophils (10⁹/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 1.005, 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.
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. 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. 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. Furthermore, in another systematic review, elevated SUA level in hypertension patients was significantly associated with all-cause mortality and major adverse cardiovascular events. 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. In addition, gout, a disease closely related to hyperuricemia, is thought to be somewhat less common in RA than in the general population. 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. Other studies also indicated that SUA levels were closely related to arteriosclerosis, pulmonary hypertension, and cardiovascular events in patients with CTD. 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,
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.

ACKNOWLEDGMENTS
We would like to thank Dr. Peiying Gao for her helpful assistance during the preparation of this manuscript. This work was supported by Sichuan Administration of Traditional Chinese Medicine [2020JC0010], Chengdu Health Commission Medical Research Project [2021206], Project of Sichuan Science and Technology Department [19YYJC0580].

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.

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