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Association between atherosclerosis and primary Sjogren's syndrome: A cross-sectional study

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Abstract

Background and Aims: Atherosclerosis (AS) risk increases in patients with systemic autoimmune diseases. The association and mechanism between primary Sjogren's syndrome (pSS) and AS haven't been explained for now. We did this cross-sectional study to clarify the prevalence and risk factors of AS in patients with pSS, and to further explore how immune cells and inflammatory cytokines work in the process.

Methods: Patients with pSS were enrolled. General information, AS events, immune cells, inflammatory cytokines, and related clinical data were recorded. Prevalence of AS events was calculated. Correlation analysis between immune factors and AS quantitative parameters were conducted by SPSS v20.0.

Results: A total of 155 pSS patients were included with a median Framingham 10-year risk of 7%. Sixty-four AS events were recorded, with a prevalence of 41.3%. Carotid intima-media thickness was positively correlated to immunoglobulin (Ig) A ($r = 0.245$, $p = 0.030$) and negatively correlated to IgM ($r = -0.227$, $p = 0.045$). Left ankle-brachial pulse wave velocity (baPWV) was positively correlated to the course of disease ($r = 0.352$, $p = 0.004$), B cells ($r = 0.410$, $p = 0.001$), and T helper (Th) cells ($r = 0.284$, $p = 0.029$), while negatively correlated to IgM ($r = -0.257$, $p = 0.042$). Right baPWV was positively correlated to the course of pSS ($r = 0.319$, $p = 0.010$), B cells ($r = 0.453$, $p < 0.001$), Th cells ($r = 0.302$, $p = 0.020$), and C-reactive protein (CRP) ($r = 0.286$, $p = 0.042$). Use of hydroxychloroquine, cyclophosphamide, and glucocorticoids had no impact on AS events.

Conclusion: The prevalence of AS in patients with pSS is reported to be 41.3%. Several risk factors have been associated with AS in these patients, including the duration of the disease, levels of Th cells, B lymphocytes, and CRP. Interestingly, IgM appears to have a protective effect against AS. It is worth noting that traditional therapy for pSS does not seem to have any effect in preventing AS events.

KEYWORDS
atherosclerosis, inflammation, primary Sjogren's syndrome

Shuang Liu, Xingjun Li, and Qian Yang contributed equally to this work.

1 | BACKGROUND AND AIMS

Atherosclerosis (AS) is a common pathologic condition, which could involve large and medium arteries, such as coronary arteries, cerebral arteries, carotid arteries, and so on. Mainstream views deemed both fat and inflammation as the crucial points in the onset and progression of AS. Fat deposition, "foam cells," smooth muscle cells, and fibroblasts together form the atherosclerotic plaque. Plaque formation results in the stenosis of artery lumen. Rupture of atherosclerotic plaque associates with acute cardiac/cerebral events.[1,2]

Primary Sjogren's syndrome (pSS) is a systemic autoimmune disease featured by dry mouth and dry eye, in which multiple organs, especially the lung and nervous system can be affected. Existing epidemiological data have shown that the incidence of cardiovascular diseases in patients with systemic autoimmune diseases has increased significantly, however previous studies mainly focused on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[3–6] There were few data on pSS, but similar trends could be seen.[7] Multiple immune factors, including lymphocytes, cytokines, immunoglobulin (Ig), and autoimmune antibodies might play roles in the process leading to AS in these patients (Figure 1). Still, lacking enough data and evidence, the exact mechanisms remain unknown and deeper research are required. We did this cross-sectional study to clarify the prevalence and risk factors of AS in patients with pSS, and to further explore how immune cells and inflammatory cytokines work in the process.

Keypoints

- **What is already known about this subject?**
  Atherosclerosis (AS) could be caused and accelerated by inflammation of arteries' wall. Previous studies have proved patients with autoimmune diseases have enhanced systemic inflammatory reaction and are at high risks of cardiovascular diseases, but the exact immune mechanisms are still unknown.
- **What does this study add?**
  Our research proved the association between primary Sjogren's syndrome (SS) and AS. The results of this study showed multiple inflammatory cells and factors participated in the process, including B/T lymphocytes and different immunoglobulins. These findings discovered potential immune mechanisms from the autoimmune condition to the AS events.
- **How might this impact on clinical practice?**
  Test of lymphocytes and serum natural immunoglobulins in patients with primary SS could be used in the clinical practice as AS risk predictor, which will help to improve clinical strategies. Deep discovering of potential immune mechanisms might provide novel targets for drug development.

2 | METHODS

From year 2018 to 2021, the study included a total of 155 pSS patients who were admitted to the Department of Rheumatology and Immunology, First Affiliated Hospital of Kunming Medical University. All subjects were enrolled according to the following inclusion and exclusion criteria. Inclusion criteria: (1) Age ≥18 years; (2) Fulfill the 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's Syndrome; (3) Agree to participate in this study. Exclusion criteria: (1) Complicated with other systemic autoimmune diseases (SLE, RA, systemic sclerosis, etc.); (2) Cannot cooperate with blood tests or other necessary examinations.

General population characteristics (gender, age, height, and weight), clinical information of pSS (course of disease, recurrence, and medications), and traditional AS risk factors (hypertension,

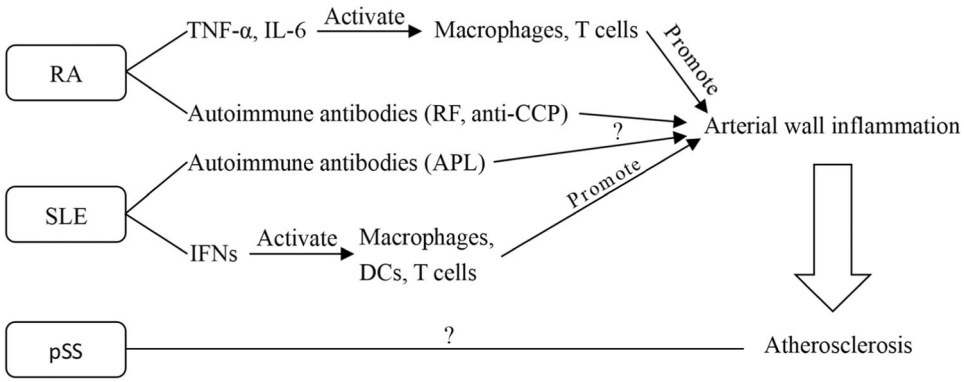

FIGURE 1 Possible association between autoimmune diseases and atherosclerosis. APL, antiphospholipid; CCP, cyclic citrullinated peptide; DC, dendritic cell; IFN, interferon; IL, interleukin; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

abnormal blood glucose and lipids, smoking) were recorded. All enrolled patients accepted blood tests including blood routine, blood biochemistry, autoantibody profile, immune proteins, light chains, thyroid function, C-reactive protein (CRP), erythrocyte sedimentation rate, B-cell activating factor (BAFF), and interleukin (IL).

Framingham risk scores were calculated based on the seven traditional AS risk factors including age, gender, total cholesterol, high density lipoprotein cholesterol, blood pressure, history of diabetes, and smoking habits. Ten-year risk of atherosclerotic cardiovascular diseases in percentage was calculated and classified as low risk (<10%), intermediate risk (10%–20%), and high risk (>20%).

Single cell suspensions were obtained from peripheral blood for the sorting of CD3+T cells, CD3+CD4+ T cells, CD3+CD8+ T cells, CD19+ B cells, and CD16+CD56+ NK cells. Single cell suspensions were resuspended with 500 μL of 10% FBS 1640 medium, and added to cell staining buffer (420201; BioLegend) and incubated with various combinations of fluorochrome-coupled antibodies. Briefly, a cell stimulation cocktail (560798; BD Pharmingen) was used to activate lymphocytes for 6 h according to the manufacturer's protocol. After washing the cells with 0.5% BSA-PBS, 1 × permeabilization buffer (88-8824-00; eBioscience) was added to resuspend the precipitate. CD3 (MA1-80640; eBioscience), CD3 + CD4 (MA5-17392; eBioscience), CD3 + CD8 (MA1-10304; eBioscience), CD19 (MA1-12050; eBioscience), and CD16 (MA1-19563; eBioscience) + CD56 (MA1-21343; eBioscience) antibodies were incubated for 30 min at room temperature in the dark. After washing and resuspension of cells using 0.5% BSA-PBS, cells were sorted on a Novocyte Advanteon Flow Cytometer Systems (Agilent Technologies), and the percentage of positive cells was analyzed using NovoExpress (Agilent Technologies).

Count of T lymphocytes with CD3+, T helper (Th) cells with CD3+CD4+, suppressor T cells with CD3+CD8+, B lymphocytes with CD19+, and NK cells with CD16+CD56+ was calculated by multiplying the percentage by the corresponding total number of cells from the blood routine.

Ultrasound was used to measure carotid intima-media thickness (IMT) and detect related manifestations of AS. Ankle-brachial pulse wave velocity (baPWV) and Ankle Brachial Index were detected by automated detector. Other imaging examinations were arranged if necessary.

AS events were recorded with definitions as follow. Terms of main events: Acute coronary syndrome, including unstable angina, acute non-ST elevation myocardial infarction, and acute ST elevation myocardial infarction; stable coronary heart disease, with or without ischemic symptoms, confirmed by coronary angiography or enhanced computed tomography (CT) showing main branches of coronary artery stenosis ≥50%; myocardial ischemia confirmed by electrocardiography, myocardial radionuclide, or PET; ischemic stroke; peripheral artery stenosis ≥50% confirmed by imaging examinations. Terms of minor events: Main branches of the coronary arteries have plaque or stenosis less than 50% confirmed by coronary angiography or enhanced CT; other medium to large arteries (aorta, carotid artery, intracranial arteries, upper and lower limbs arteries, and fundus arteries) have atherosclerotic changes (rough vascular intima; plaque formation; increased blood flow resistance; stiff blood vessel wall) with stenosis <50% confirmed by vascular ultrasound, angiography, CT, or fundus examination; small intracranial ischemic foci or lacunar infarction detected by CT or MRI.

Based on previous studies, it has been found that patients with pSS have a higher risk of cardiovascular diseases compared to healthy individuals. The odds ratio for this risk ranges from 1.05 to 5.67 across various subgroups.[7] The prevalence of carotid AS in Chinese people was reported as 36.2% in 2018.[8] Therefore, we hypothesized that the prevalence of total AS events in pSS patients might be as high as 50.0%. To calculate the sample size, we used PASS v15 and conducted tests for one proportion with a two-sided alternative hypothesis. The power and α were set at 0.90 and 0.05, respectively. The calculated sample size was 132, and we ultimately enrolled 155 cases, which exceeded our expectations.

SPSS v20.0 was used for statistical analysis. The normality test of continuous variables was done by the Shapiro–Wilk test. Normally distributed continuous variables were described by mean and standard deviation; non-normally distributed continuous variables were described by median and interquartile range (IQR); categorical variables were described by count and percentage. Correlation analysis between continuous variables of normal distribution was done by the Pearson's correlation test, while that of non-normal distribution was done by the Spearman's correlation test. The independent sample *t*-test was used for the comparison of the mean between two-category variables. The Mann–Whitney *U* test was used for the comparison of non-normally distributed continuous data between two-category variables. The χ^2 test was used in crosstab analysis to determine the influencing factors of AS events. All the above analyses were considered statistically significant with $p < 0.05$.

This study was approved by the ethics committee of Kunming Medical University. We confirm that informed consent was obtained from each enrolled patient.

3 | RESULTS

General information, clinical characteristics of pSS, and traditional risk factors were shown in Table 1. Age, height, weight, and body mass index were continuous data with normal distribution; the course of disease and 10-year risk in percentage were data with non-normal distribution. The rest were classified data.

Among the 155 patients, a total of 64 people had AS events; 8 of them had both main and minor events. In this pSS population, the prevalence of total AS events was as high as 41.3%, and the prevalence of main cardiovascular and cerebrovascular events was 5.2%.

Correlation analysis showed that IMT was significantly positively correlated with IgA ($r = 0.245$, $p = 0.030$), and significantly negatively correlated with IgM ($r = -0.227$, $p = 0.045$); left baPWV was significantly positively correlated with the course of disease

TABLE 1 General information of the pSS patients.

Variables	Value
Popular characteristics	
Gender (male/female), n1/n2	7/148
Age (years)	57.2 ± 11.7
Height (cm)	157.5 ± 6.7
Weight (kg)	54.7 ± 10.0
BMI $(kg/m)^2$	21.99 ± 3.21
Clinical characteristics of pSS	
Course of disease (months), median and IQR	60 (12–108)
Labratory tests	
SSA-52KD positive, *n* (%)	90 (58.1)
SSA-60KD positive, *n* (%)	105 (67.7)
SSB positive, *n* (%)	50 (32.3)
ESSDAI score, median and IQR	9 (5, 12)
Medication	
Use of glucocorticoids, *n* (%)	83 (53.5)
Use of cyclophosphamide, *n* (%)	11 (7.1)
Use of hydroxychloroquine, *n* (%)	99 (63.9)
Traditional AS risk factors	
Hypertension, *n* (%)	28 (18.1)
Abnormal blood glucose, *n* (%)	18 (11.6)
Hyperlipidemia, *n* (%)	35 (22.6)
Smoke, *n* (%)	4 (2.6)
Laboratory tests	
Total cholesterol (mmol/L)	4.22 ± 1.02
Low density lipoprotein cholesterol (LDL-C) (mmol/L)	2.57 ± 0.85
High density lipoprotein cholesterol (HDL-C) (mmol/L)	1.24 ± 0.43
Triglycerides (mmol/L)	1.50 ± 0.85
Serum creatinine (μmol/L)	69.34 ± 17.33
AS risk evaluated by FRS	
Ten-year risk in percentage (%), median and IQR	7 (4–11)
Classification	
Low risk, *n* (%)	106 (68.4)
Intermediate risk, *n* (%)	41 (26.4)
High risk, *n* (%)	8 (5.2)

Abbreviations: AS, atherosclerosis; BMI, body mass index; FRS, Framingham risk scores; pSS, primary Sjogren's syndrome.

($r = 0.352$, $p = 0.004$), Th cells ($r = 0.284$, $p = 0.029$), B lymphocytes ($r = 0.410$, $p = 0.001$), and significantly negatively correlated with IgM ($r = -0.257$, $p = 0.042$); right baPWV was significantly positively correlated with the course of disease ($r = 0.319$, $p = 0.010$), CRP ($r = 0.286$, $p = 0.042$), Th cells ($r = 0.302$, $p = 0.020$), and B lymphocytes ($r = 0.453$, $p < 0.001$). Relationship between serum IgM and AS parameters was shown in Figure 2.

The independent sample *t*-test and Mann–Whitney *U* test showed the impact of medications on the immune system. Use of cyclophosphamide and hydroxychloroquine had no impact on B and T lymphocytes. Nevertheless, glucocorticoids could significantly reduce the counts of T and B lymphocytes (mean value of T lymphocytes: 914.5 ± 472.9 vs. 1126.2 ± 462.9 μL^{-1}, $p = 0.032$; mean value of B lymphocytes: 171.2 ± 97.9 vs. 239.7 ± 141.9 μL^{-1}, $p = 0.008$) and significantly reduce the BAFF value (median and IQR: 2.05 [0.30–4.80] vs. 10.90 [2.80–21.00], ng/mL, $p = 0.004$), as shown in Figure 3. However, the χ^2 test showed all the three drugs couldn't reduce the risk of AS events. Duration on each medication was showed with median and IQR, measured by months (Table 2).

4 | DISCUSSION

A cohort study in 2015 showed that compared with healthy controls, the incidence of cerebrovascular events (2.5% vs. 1.4%, $p = 0.005$) and myocardial infarction (1.0% vs. 0.4%, $p = 0.002$) in pSS patients were significantly increased compared to age-matched healthy controls.[7] Sabio team reported that the PWV of female patients with pSS was significantly increased ($p = 0.030$).[9] The study by Atzeni team reached a similar conclusion. Compared with healthy controls, in patients with pSS, not only PWV significantly increased, but also coronary flow reserve significantly reduced.[10] In our study, the prevalence of AS was as high as 41.3%, and the rate of major cardiovascular and cerebrovascular events was 5.2%. Considering our main events included both cardiovascular and cerebrovascular diseases, it is reasonable that the prevalence is higher than the former study. According to the *Report on Cardiovascular Diseases in China 2018*, the total prevalence of carotid AS in Chinese people older than 40 years was 36.2%.[8] Even take traditional risk factors into account, the prevalence of AS in pSS patients is indeed higher than the general population. In addition, the course of disease was positively correlated to the baPWV. Combining the aforementioned studies and our results, pSS does increase the risk of AS. The longer the course of disease is, the higher the AS risk and severity will be. Therefore, to better prevent AS events, pSS must be paid enough attention to. It's a key autoimmune risk factor.

The thickening of IMT is an early manifestation of AS. It has been observed that functional damage to the arterial wall occurs in the early stage of pSS, and damage to the vascular endothelial and smooth muscle cells can get worse as the disease progresses. PWV is a quantitative indicator of AS. The increase of baPWV has been demonstrated to represent the weakening of vascular elasticity and relate to the severity of AS. In our study, IMT was positively correlated to IgA and negatively correlated to IgM; baPWV was positively correlated to CRP, Th cells, B lymphocytes, and negatively correlated to IgM. These results suggest that the count and functional changes of immune cells in pSS patients influence the

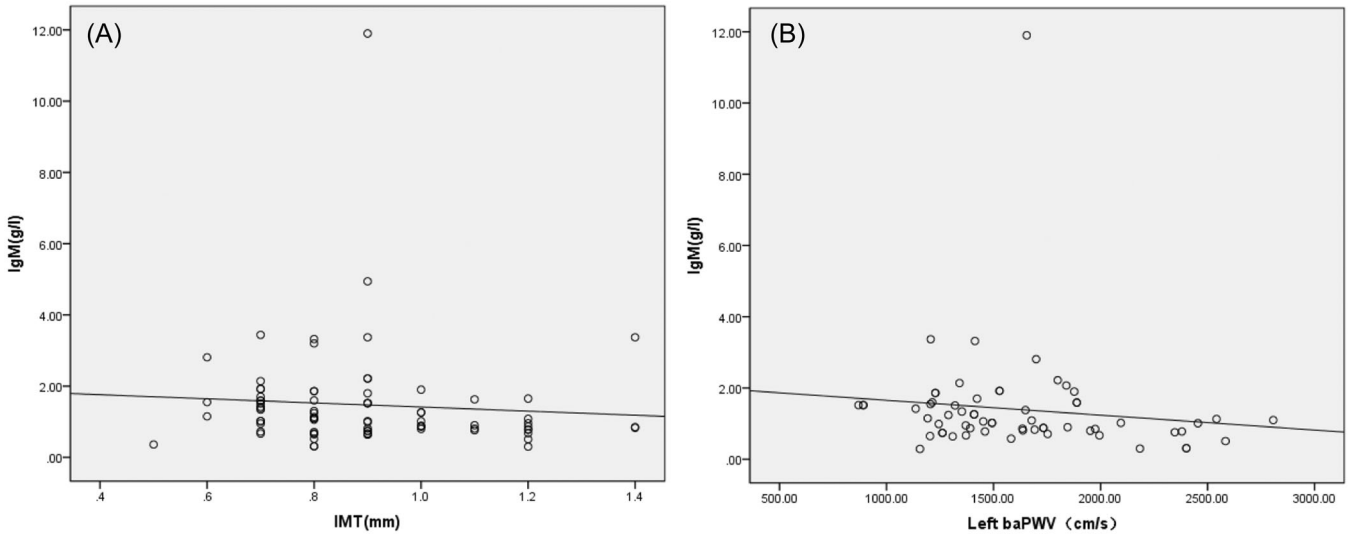

FIGURE 2 (A) Serum IgM was negatively correlated with IMT ($r = -0.227$, $p = 0.045$). (B) Serum IgM was negatively correlated with left baPWV ($r = -0.257$, $p = 0.042$). baPWV, ankle-brachial pulse wave velocity; IgM, immunoglobulin M; IMT, carotid intima-media thickness.

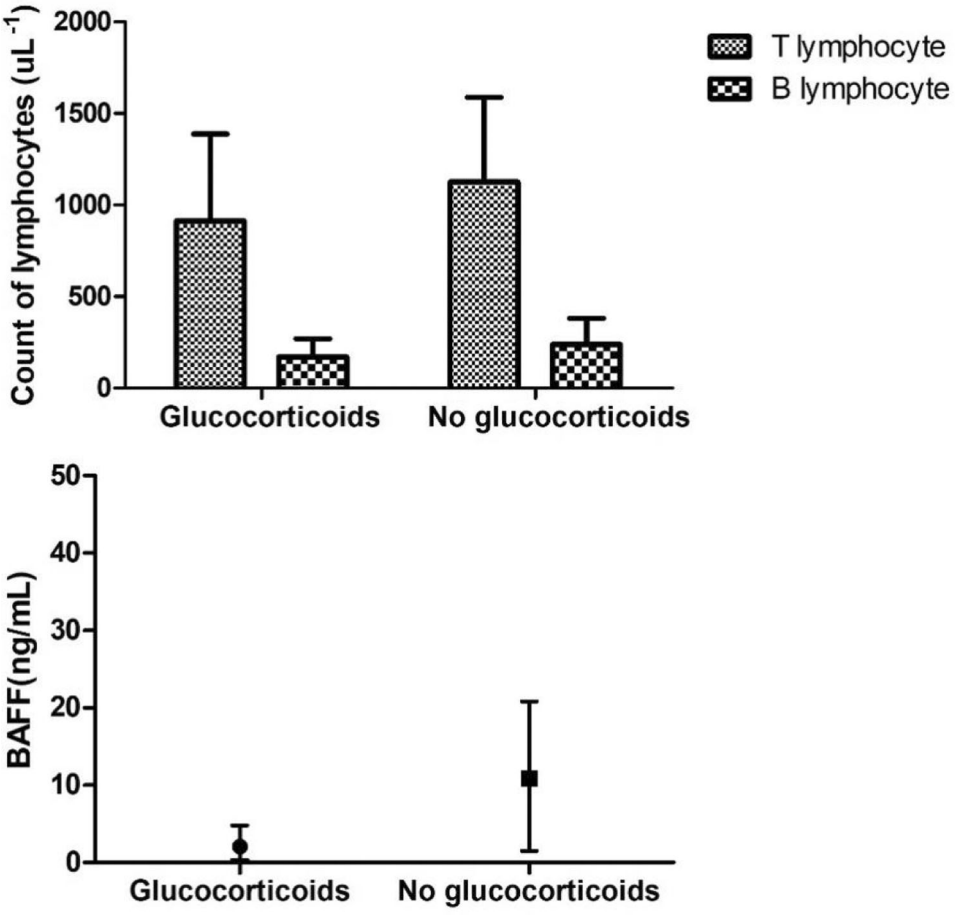

FIGURE 3 Glucocorticoids could significantly reduce the counts of T and B lymphocytes (mean value of T lymphocytes: 914.5 ± 472.9 vs. 1126.2 ± 462.9 μL^{-1}, $p = 0.032$; mean value of B lymphocytes: 171.2 ± 97.9 vs. 239.7 ± 141.9 μL^{-1}, $p = 0.008$) and significantly reduce the BAFF value (median and IQR: 2.05 [0.3–4.8] versus 10.90 [2.80–21.00] ng/mL, $p = 0.004$). BAFF, B-cell activating factor.

TABLE 2 Impact of medications on AS events.

Variables	Duration on each medication (months)	OR (95% CI)	*p*
Use of glucocorticoids	12 (3–60)	1.08 (0.57–2.05)	0.81
Use of cyclophosphamide	1 (0.1–1)	0.51 (0.13–2.00)	0.51
Use of hydroxychloroquine	21 (6–60)	1.01 (0.52–1.97)	0.97

Abbreviation: AS, atherosclerosis.

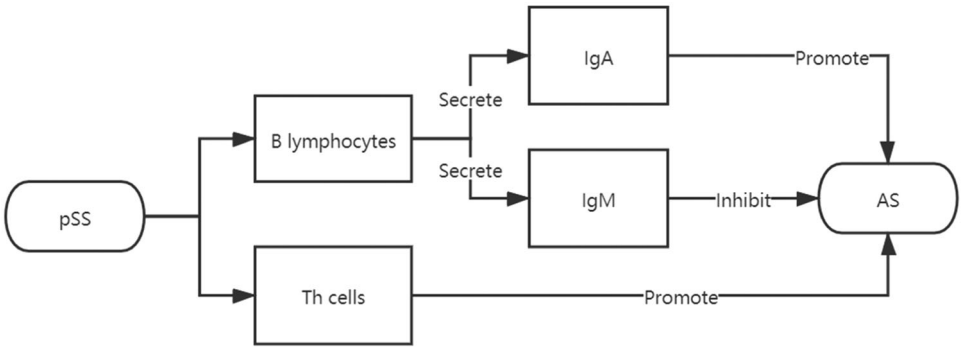

FIGURE 4 Possible immune mechanisms between pSS and AS. AS, Atherosclerosis; pSS, primary Sjogren's syndrome.

occurrence and development of AS, and the possible mechanism is summarized in Figure 4.

The mechanism derived from our research mainly considers that in pSS patients, a series of immune inflammatory reactions mediated by B lymphocytes and Th cells are the key factors that cause the occurrence and development of AS. The amount of B lymphocytes and secreted immunoglobulins are related to AS. Abnormal proliferation of B lymphocytes might be a powerful factor in promoting arterial inflammation. According to previous studies, IgM specified to malondialdehyde-modified LDL had an inverse association with carotid AS.[11] Natural IgM antibodies produced by B1 cells might protect against AS.[12] However, why IgA and IgM have opposite effects is not clear, which needs further exploration. The promotion effects of Th cells might be attributed to the abnormal proliferation and the excessive secretion of proinflammatory factors such as TNF-α and IL-2/6. These factors further provoke inflammation of the vessel walls and damage to the endothelia. With a pity, due to the small sample size, we did not find a significant correlation between TNF-α, IL-2/6, and AS in this study. These issues need to be explored in the future.

For the treatment of pSS, currently common medications consist of glucocorticoids, hydroxychloroquine, and cyclophosphamide. Glucocorticoids has been proved to have strong immunosuppressive effects, and our research found that glucocorticoids could significantly reduce the count of T/B lymphocytes and BAFF value in pSS patients. Cyclophosphamide and hydroxychloroquine did not show similar results. However, all these three drugs had no significant effects, either positive or negative, on the occurrence and development of AS in pSS patients. As far as glucocorticoid is concerned, although it has strong effects on the immune system and can inhibit the inflammatory response mediated by T and B lymphocytes, it also has side effects such as increasing blood pressure and dysfunction of blood glucose and lipid metabolism. Ultimately, its positive and negative effects couldn't make the goal of preventing AS in pSS patients. As we know, lymphocytes, related immunoglobulins and inflammatory cytokines all play roles in the occurrence and development of AS. If drugs with a relatively single effect could be accessed, such as various biological agents (BAFF receptor monoclonal antibodies, CD20 monoclonal antibody, etc.), it might help to achieve the purpose of prevention AS in the pSS population. Actually, for now these biological agents have no indications for pSS, and their effects are not really "single," so the final outcomes are not satisfactory. In the further in-depth research, searching for "single effect" drugs on immune system will be meaningful to prevent and treat AS in patients with autoimmune diseases.

5 | CONCLUSION

The prevalence of AS in patients with pSS is reported to be 41.3%. Several risk factors have been associated with AS in these patients, including the duration of the disease, levels of Th cells, B lymphocytes, and CRP. Interestingly, IgM appears to have a protective effect against AS. It is worth noting that traditional therapy for pSS does not seem to have any effect in preventing AS events.

AUTHOR CONTRIBUTIONS

Shuang Liu: Data curation; formal analysis; funding acquisition; investigation; methodology; writing—original draft. **Xingjun Li**: Data

curation; methodology. **Qian Yang**: Data curation; methodology. **Nan Wang**: Data curation. **Jian Xu**: Conceptualization; supervision. **Luqiong Li**: Methodology. **Yulong Guo**: Conceptualization; formal analysis; methodology; project administration; writing—original draft; writing—review and editing. All authors have read and approved the final version of the manuscript. All authors agree to publish.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Yulong Guo had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author Yulong Guo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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