Risk of cardiovascular involvement in patients with primary Sjögren's Syndrome: a large-scale cross-sectional cohort study

Cai X[1], Luo J[2], Wei T[2], Qin W[2], Li X[1], Wang X[2]

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ABSTRACT

Objective: To evaluate the presence of cardiovascular involvement and analyze potential risk factors independently associated with cardiovascular disease in primary Sjögren's syndrome (pSS) patients.

Methods: We recruited a cohort of 367 pSS patients and 367 age- and gender-matched controls from the First Affiliated Hospital of Wenzhou Medical University. Demographic, clinical and laboratory data, and overt cardiovascular involvement events were recorded. Potential risk factors associated with cardiovascular involvement were determined by multivariate analyses.

Results: pSS patients had a significantly higher cardiovascular events rate than that of the controls (61.6% versus 29.7%; p<0.01). Compared with pSS patients without cardiovascular involvement, those with cardiovascular events were significantly older; had higher rates of hypertension, diabetes, hypoalbuminemia, and hyperlipemia; were more likely to have extraglandular organ involvement; and had a higher level of C-reactive protein (CRP) (all p<0.05). In the multivariate analysis, age, hypertension, and extraglandular organ involvement were found to be risk factors independently correlated with cardiovascular events in pSS patients.

Conclusions: pSS patients are more vulnerable to cardiovascular diseases (CVDs). In addition to traditional CVD risk factors such as age and hypertension, extraglandular organ involvement was found to be independently associated with cardiovascular involvement in pSS patients, which suggests the need for early detection and prevention measures to improve the prognosis in those patients.

Keywords: Hypertension; Primary Sjögren's syndrome.

1. Department of Cardiology, The First Affiliated Hospital of Soochow University, Suzhou
2. Department of Rheumatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease that is mainly characterized by a combination of dry eye (keratoconjunctivitis sicca) and dry mouth (xerostomia) symptoms[1-3]. In addition, a variety of extraglandular disease manifestations can occur that may affect a range of tissues involving most organ systems[4]. The incidence has been documented to be 3–11 cases per 100 000 persons; the prevalence rate is between 0.01% and 0.72%[5,6], according to the 2002 American-European Consensus Group (AECG) criteria[7], with female predominance (approximately 14:1)[8].

It is now clear that chronic inflammatory/autoimmune rheumatic diseases (such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA)) are characterized by an acceleration of atherosclerosis, which is considered a significant predictor of cardiovascular events[9,10]. As a slowly progressing inflammatory disease, pSS shares several clinical and pathophysiologic characteristics with SLE and RA, and atherosclerotic damage is also found in patients with pSS[11-13]. Moreover, cardiovascular diseases (CVDs) have been found to be one of the leading causes of death in pSS patients[14,15].

Many pathogenic mechanisms underlying the increased risk of vascular complications, especially the high prevalence of atherosclerosis in autoimmune patients, are likely due to the pathophysiology of connective tissue diseases (CTD) , including systemic or localized inflammation and autoimmune processes[16]. As a major contributor to atherosclerosis, inflammation can affect blood mononuclear cells, vascular cell adhesion molecule 1, proinflammatory cytokines, and matrix metalloproteinases[17,18]. The existence of an inflammatory component of atherosclerosis is supported by the presence of elevated levels of inflammatory markers, such as C-reactive protein, in patients with atherosclerosis. In addition to inflammation, prolonged steroid therapy and postmenopausal status might also

increase the risk of atherosclerosis in these patients with CTD[19, 20].

In their early phases, CVDs are typically asymptomatic and occur at much younger ages in patients with autoimmune disease than in those without autoimmune disease[21,22]. Therefore, a regular assessment of cardiovascular risk factors has been recommended in patients presenting with pSS[23]. Previous studies investigated whether pSS patients may be more likely than non-pSS patients to suffer cardiovascular and metabolic abnormalities, such as subclinical atherosclerosis[12]; however, few studies have evaluated the relationship between CVD risk and glandular or extraglandular manifestations in pSS patients. Thus, we conducted a study to analyze factors that may be associated with cardiovascular events in a cohort of pSS patients.

METHODS

STUDY POPULATION

In total, 367 patients with pSS who visited the Cardiology Department or Rheumatology Department of the First Affiliated Hospital of Wenzhou Medical University between January 2010 and January 2016 were enrolled in this study. Another 367 age- and gender-matched people who received annual medical examinations in the same hospital were enrolled as a control group. The 2002 classification criteria were used for the diagnosis of pSS[24]. Patients with other CTDs, chronic Hepatitis C Virus/Human Immunodeficiency Virus (HCV/HIV) infections and previous lymphoproliferative process diagnoses were excluded from the study. This study was approved by the Ethical Committee of the First Affiliated Hospital of Wenzhou Medical University (approval # 16024). Written informed consent was provided by all patients and participants prior to their enrolment in the study.

CLINICAL AND LABORATORY EVALUATIONS

The clinical data of participants were collected from a review of their medical records. The clinical characteristics included age at diagnosis, internal organ involvement, central and peripheral nervous system involvement, and the presence of Raynaud's syndrome. The radiologic findings included chest computerized tomography (CT) scans, electrocardiograms (ECG) and echocardiographs, and the levels of markers such as antinuclear antibody, rheumatoid factor (RF), anti-SSA/Ro, anti-SSB/La antibodies, baseline immunoglobulin, and complements fractions C3 and C4. Disease manifestations were scored with the European League against Rheumatism Sjögren's syndrome patient reported index and a cumulative European League Against Rheumatism Sjögren's syndrome disease activity index (ESSDAI), summing the scores achieved per organ domain as previously reported[25]. The evaluation of extraglandular organ involvement was standardized by ESSDAI.

ASSESSMENT OF EXOCRINE GLAND INVOLVEMENT

Patients were assessed through a detailed history and physical examination at the first interview by a rheumatologist. Xerophthalmia was confirmed by an ophthalmologist with experience in pSS with Schirmer's test, breakup time of tear film (BUT) and cornea fluorescent pigmentation (FL)[26]. Xerostomia was diagnosed by testing timed whole unstimulated salivary flow (WUSF) and performing a minor salivary gland biopsy. The histopathological analysis was performed by two experienced pathologists for each patient. A lymphocytic focus score ≥ 1 was regarded as a positive biopsy, with more than 50 lymphocytes per 4 mm^2, based on the classification described previously[27,28].

CARDIOVASCULAR EVALUATION

All patients in this cohort underwent a chest CT scan, an ECGs and echocardiogram. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the receipt of antihypertensive therapy. Echocardiography was performed by experienced cardiologists; the left ventricular ejection fraction, right ventricular dimensions, and function were recorded. The systolic pulmonary arterial pressure was estimated by quantifying the tricuspid regurgitation maximal velocity and adding a two-dimensional estimate of the right atrial pressure. Finally, cardiovascular involvement was defined as 1) arrhythmia; 2) myocardial function limitation; 3) pericardial disease; 4) pulmonary arterial hypertension; 5) valvular disease; 6) coronary artery calcium; or 7) myocardial ischemia[29].

STATISTICAL ANALYSIS

Continuous variables are expressed as medians (interquartile range [IQR]), and categorical variables are

presented as percentages. The Shapiro-Wilk test was used for normally distributed continuous data. The comparisons of nonparametric and continuous variables were performed with the Mann-Whitney U-test. Categorical variables were compared using Pearson's Chi-squared test or Fisher's exact tests. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Univariate analysis was used to test the association between CVDs and the study variables. A multiple logistic regression analysis was used to determine which variables were independently associated with cardiovascular risk in pSS patients. Statistical significance was defined as a $p<0.05$. All statistical analyses were performed with the R v3.3.2 statistical software package.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF pSS PATIENTS

The main demographic and clinical data of the pSS patients are shown in Table I. The median age at diagnosis was 51 years (IQR 42–61). The male to female ratio was 1:8.4. The prevalence of systemic involvement is also reported in Table I; articular involvement was the most prevalent extraglandular manifestation, impacting 41.7% of pSS patients in our study. Nearly two-thirds of pSS patients (64.3%) had high levels of immunoglobulin G (IgG). Most of the patients were positive for antinuclear antibodies (89.4%), with anti-SSA/Ro present in 299 (82.6%) patients and anti-SSB/La present in 167 (41.6%).

TABLE I. DEMOGRAPHIC AND CLINICAL DATA OF pSS PATIENTS

	n	Value
Age at diagnosis, median (IQR) years	367	51.0 (42.0-61.0)
Female	367	328 (89.4%)
Fatigue	367	48 (13.1%)
Weight loss	367	22 (6.0%)
Decayed tooth	367	57 (15.5%)
Central neuropathy	367	33 (9.0%)
Peripheral neuropathy	367	46 (12.5%)
Arthritis	367	153 (41.7%)
Cutaneous involvement	367	52 (14.2%)
Pulmonary involvement	367	74 (20.2%)
Renal involvement	367	52 (14.2%)
Muscular involvement	367	56 (15.3%)
Raynaud phenomenon	367	28 (7.6%)
Hypoalbuminemia (< 40g/L)	367	104 (28.3%)
High glucose level (≥126 mg/dl)	367	27 (7.4%)
High IgG level (>17g/L)	367	236 (64.3%)
Low C3 level (<90 mg/dl)	367	116 (31.6)
Low C4 level (<16 mg/dl)	367	110 (30.0)
Rheumatoid factor positive (>10 IU/ml)	367	226 (61.6)
Antinuclear antibodies positive (>1:160)	367	328 (89.4)
Anti-SSA/Ro antibody positive	362	299 (82.6)
Anti-SSB/La antibody positive	362	167 (46.1)

* Values are the number (percentage) unless indicated otherwise.
IQR: interquartile range; IgG: immunoglobulin G; C: complement

COMPARISONS BETWEEN pSS PATIENTS AND HEALTHY CONTROLS

Compared with the age- and sex-matched controls, pSS patients had a higher prevalence of hyperlipemia (41.9% versus 17.2%; $p<0.01$), with higher levels of total cholesterol and low-density lipoprotein (LDL) and lower levels of high-density lipoprotein cholesterol (HDL) ($p<0.01$). However, compared to the healthy controls, pSS patients had less hypertension (18.8% versus 30.5%; $p<0.01$), with lower average systolic pressures (123.15 ± 19.49 vs. 135.87 ± 21.66mmHg; $p<0.01$) but similar diastolic pressures (74.85 ± 11.04 vs. 76.01 ± 10.12mmHg; $p>0.05$). Compared with the controls, pSS patients had lower levels of albumin and triglycerides ($p<0.05$). As shown in Table II, compared with the controls, pSS patients had a higher proportion of cardiovascular involvement, including higher rates of cardiac function failure, pericardial disease, pulmonary arterial hypertension (PAH) and myocardial ischemia and higher levels of coronary artery calcium ($p<0.01$).

COMPARISON BETWEEN pSS PATIENTS WITH AND WITHOUT CARDIOVASCULAR INVOLVEMENT

As shown in Table III and Figure 1 and Figure 2, compared with pSS patients without cardiovascular involvement, pSS patients with cardiovascular involvement were older and had higher incidence rates of hypertension, diabetes mellitus, hypoalbuminemia, hyperlipemia, and extraglandular organ involvement (mainly pulmonary or renal involvement) and were more likely to have a higher body mass index (BMI) and CRP level ($p<0.05$). There was no significant difference between the two groups with regard to the ESSDAI.

TABLE II. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDY COHORT

Characteristic	Controls (n=367)	pSS (n=367)	p value
Age, years	51.8 (42.1-61.0)	51.0 (42.0-61.0)	0.985
Female	328 (89.4)	328 (89.4)	1
Body mass index, kg/m^2	22.4 (20.5-25.2)	22.2 (20.1-24.2)	0.142
Hypertension, no. (%)	112 (30.5)	69 (18.8)	<0.001
Diabetes mellitus, no. (%)	27 (7.5)	25 (6.8)	0.698
Albumin, g/L	37.9 (34.5-41.4)	37.4 (34.4-40.3)	0.009
Hyperlipemia, no. (%)	63 (17.2)	147 (41.9)	<0.001
Total cholesterol, mg/dl	3.5 (3.3-4.0)	4.4 (3.8-5.0)	<0.001
Triglyceride, mg/dl	1.4 (1.0-2.0)	1.3 (0.9-1.9)	0.611
High-density lipoprotein, mg/dl	1.1 (1.0-1.3)	1.0 (0.8-1.3)	<0.001
Low-density lipoprotein, mg/dl	2.1 (1.7-2.7)	2.5 (2.0-3.0)	<0.001
Uric acid, mg/dl	280.3 (228.1-356.9)	267.0 (223.8-327.0)	0.044
C-reactive protein >8mg/dl, no. (%)	97 (26.4)	92 (25.1)	0.651
Cardiovascular involvement	110 (29.7)	226 (61.6)	<0.001
Arrhythmia abnormal	48 (12.1)	42 (11.4)	0.792
Cardiac function failure	49 (13.3)	145 (39.5)	<0.001
Pericardial disease	8 (2.0)	24 (6.5)	0.002
Pulmonary arterial hypertension	9 (2.5)	52 (21.0)	<0.001
Coronary artery calcium	22 (5.9)	46 (12.5)	0.001
Myocardial ischemia	33 (8.9)	80 (21.8)	<0.001

Data are presented as the median (interquartile range) or as n (%) unless indicated otherwise

TABLE III. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF pSS PATIENTS ACCORDING TO CARDIOVASCULAR INVOLVEMENT

Cardiovascular involvement	Without (n=141)	With (n=226)	P-vale
Age, year	46.0 (37.0-54.0)	55.5 (47.0-64.0)	<0.001
Body mass index, kg/m2	20.8 (19.6-23.3)	22.6 (20.5-24.8)	0.002
Hypertension	5 (3.5)	64 (28.7)	<0.001
Diabetes mellitus	3 (2.1)	22 (9.9)	0.003
Extraglandular organ involvement	130 (92.2)	221 (97.8)	0.016
Hypoalbuminema	27 (19.1)	77 (34.1)	0.002
Hyperlipemia, no. (%)	46 (34.8)	101 (46.1)	0.038
Total cholesterol, mg/dl	1.2 (0.9-1.6)	1.3 (1.0-1.9)	0.017
High-density lipoprotein, mg/dl	1.1 (0.9-1.4)	1.0 (0.8-1.2)	0.008
C-reactive protein >8 mg/L	21 (16.8)	61 (29.3)	0.010

Data are presented as the median (interquartile range) or as n (%) unless indicated otherwise

SPECIFIC FACTORS ASSOCIATED WITH CARDIOVASCULAR INVOLVEMENT IN pSS

As shown in Table IV, an unadjusted univariate analysis was used to detect clinical and serologic factors potentially associated with cardiovascular involvement in pSS. Age, BMI, total cholesterol level, high-density lipoprotein level, the presence of hypertension, the presence of diabetes mellitus, extraglandular organ involvement and the presence of hypoalbuminemia were significantly associated with cardiovascular involvement in pSS patients ($p<0.05$).

To avoid interference from potential confounding factors, a multivariate logistic regression analysis was performed with all the significant factors from the uni-

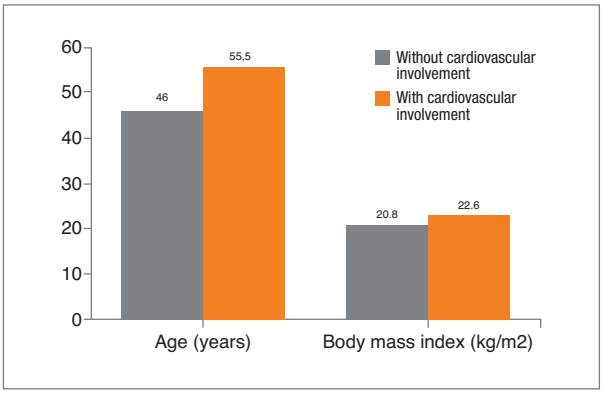

FIGURE 1. Demographic characteristics of pSS patients according to cardiovascular involvement.

pSS patients with cardiovascular involvement is older and more likely to have higher BMI (p<0.05).

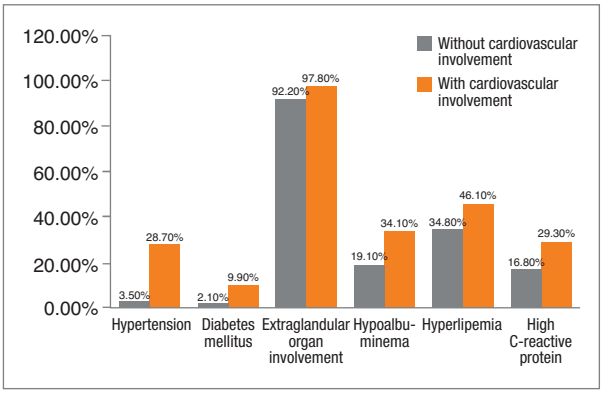

FIGURE 2. Inflammation and metabolic characteristics of pSS patients according to cardiovascular involvement.

pSS patients with cardiovascular involvement had a higher frequency of hypertension, diabetes mellitus, hypoalbuminema, and hyperlipemia, extraglandular organ involvement (mainly pulmonary or renal involvement) and raised higher CRP level than those without cardiovascular involvement (p<0.05)

variate analysis. As shown in Table V, we found that only age, hypertension, and extraglandular organ involvement were independently associated with cardiovascular involvement in pSS patients (p<0.05).

DISCUSSION

In the present study, we found that compared with the controls, pSS patients had a significantly higher rate of cardiovascular involvement, which is consistent with previous reports and recent meta-analyses[30-32]. In addition, a higher prevalence of hyperlipemia and a lower prevalence of hypertension were observed in pSS patients than in controls in our cohort, which is partly supported by the results of a previous case-control study[30]. However, compared to the controls, pSS patients had a lower prevalence of diabetes mellitus in Italian and English cohorts, while a higher prevalence was shown in some studies from Spanish pSS cohorts[30,33]. However, there was no significant difference in the prevalence of diabetes mellitus between the two groups in our cohort. Such conflicting results may be partially due to differences in genetic and metabolic backgrounds, diets, lifestyle habits and treatments for DM.

As a traditional CVD risk factor, hypertension was found to be associated with cardiovascular involvement in patients with pSS, which is in accordance with the

TABLE IV. UNIVARIATE ANALYSES OF FACTORS ASSOCIATED WITH CARDIOVASCULAR INVOLVEMENT IN PRIMARY SJOGREN'S SYNDROME

Cardiovascular involvement	Odds ratio (95% confidence interval) p value
Age, year	1.1 (1.0, 1.1) <0.001
Body mass index, kg/m2	1.1 (1.0, 1.2) 0.005
Hypertension	10.7 (4.2, 27.5) <0.001
Diabetes mellitus	5.0 (1.5, 16.9) 0.010
Extraglandular organ involvement	3.7 (1.3, 11.0) 0.017
Hypoalbuminema	2.2 (1.3, 3.6) 0.002
Total cholesterol, mg/dl	1.3 (1.0, 1.8) 0.037
High-density lipoprotein, mg/dl	0.5 (0.3, 0.9) 0.016
CRP positive (>8 mg/L)	2.1 (1.2, 3.6) 0.011

CRP: C-reactive protein

TABLE V. MULTIVARIATE ANALYSES OF FACTORS ASSOCIATED WITH CARDIOVASCULAR INVOLVEMENT IN PRIMARY SJOGREN'S SYNDROME

Cardiovascular involvement	Odds ratio (95% confidence interval) p value
Age, year	1.0 (1.0, 1.1) <0.001
Hypertension	6.9 (2.6, 17.7) <0.001
Extraglandular organ involvement	4.6 (1.1, 13.5) 0.033

latest report on this subject[34]. In addition, instead of the expected relationship between glandular involvement and CVDs, we found a novel independent association between extraglandular organ involvement and CVDs in pSS patients. Glandular involvement, especially a positive histological pattern of LSGB, is commonly used for diagnostic and prognostic purposes in clinical practice[35,36]. However, in our study, there was no significant association between glandular involvement and cardiovascular involvement in patients with pSS. Among the involved extraglandular organs, joints, lungs, skin and peripheral nerves were those most frequently involved in pSS[37]. This finding suggests that cardiovascular risk factors might worsen or trigger inflammatory processes in patients with pSS, contributing to the involvement of these main internal organs[30]; our data suggests that the reverse might also be true. Patients with multiple affected systems are more likely to experience involvement of the cardiovascular system due to their enhanced inflammatory and autoimmune responses, which has also been observed in patients with other autoimmune diseases, such as SLE and RA[38]. Therefore, extraglandular organ involvement and CVDs are not isolated in patients with pSS but are instead mutually reinforcing.

To protect pSS patients from CVDs, a number of techniques might need to be utilized at an early stage to identify pSS patients at risk for cardiovascular events. Radiographic identification of coronary calcium levels, which serve as a specific indicator of coronary atherosclerotic plaques[39], carotid ultrasound to identify increased carotid wall thickness or carotid artery plaque formation[40], and methods of quantify endothelial dysfunction[41] should be implemented in future clinical practice.

LIMITATIONS

Limitations of this study should be considered. This study included a homogenous group of participants from one center and cannot therefore support strong causal conclusions. Therefore, to further evaluate the role of cardiovascular involvement in pSS, more data from heterogeneous pSS patients with consecutive follow-up visits are highly recommended.

CONCLUSIONS

Our data showed that compared with the controls, pSS patients had a higher incidence of cardiovascular involvement. Given the close interactions between the cardiovascular system and other extraglandular organs and the potential relationship between those interactions and the outcomes of pSS patients, early detection and close monitoring of subclinical atherosclerosis and appropriate therapies are needed for these patients, especially in those with extraglandular organ involvement.

CORRESPONDENCE TO
Xun Li
Department of Cardiology,
The First Affiliated Hospital of Soochow University,
Suzhou, China
E-mail: xunli58@126.com

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