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ORIGINAL ARTICLE

Risk factors for cardiovascular disease in primary Sjögren's syndrome (pSS): a 20-year follow-up study

Cristiana Sieiro Santos[1] · Ruben Rego Salgueiro[2] · Clara Moriano Morales[1] · Carolina Álvarez Castro[1] · Elvira Díez Álvarez[1]

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Abstract

Introduction Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by a chronic grade of inflammation. Cardiovascular events represent the major causes of morbidity and mortality in patients with inflammatory rheumatic diseases; however, the significance and prevalence of cardiovascular disease in patients with pSS remain unclear.

Objective To determine the clinical significance of cardiovascular disease in pSS and analyze the risk of cardiovascular disease according to glandular/extraglandular involvement and positivity to anti-Ro/SSA and/or anti-La/SSB autoantibodies.

Methods A retrospective study including patients diagnosed with pSS fulfilling the 2016 ACR/EULAR classification criteria was followed and evaluated in our outpatient clinic between 2000 and 2022. The prevalence of cardiovascular risk factors with pSS was evaluated, and a possible association with clinical and immunological characteristics, the treatments received, and the impact on cardiovascular disease were determined. Univariate and multivariate regression analyses were performed in an attempt to determine potential risk factors associated with cardiovascular involvement.

Results A total of 102 pSS patients were included. Eighty-two percent were female, with a mean age of 65±24 years and a disease duration of 12.5 ±6 years. Thirty-six patients (36%) had at least one cardiovascular risk factor. Arterial hypertension was diagnosed in 60 (59%) patients, dyslipidemia in 28 (27%), diabetes in 15 (15%), obesity in 22 (22%), and hyperuricemia in 19 (18%). History of arrhythmia was found in 25 (25%), conduction defects in 10 (10%), arterial peripheral vascular disease in 7 (7%), venous thrombosis in 10 (10%), coronary artery disease in 24 (24%), and cerebrovascular disease in 22 (22%) of patients. Patients with extraglandular involvement had a higher prevalence of arterial hypertension (p=0.04), dyslipidemia (p=0.003), LDL mean values (p=0.038), hyperuricemia (p=0.03), and coronary artery disease (p=0.01) after adjusting for age, sex, disease duration, and the significant variables in the univariate analysis. Patients with Ro/SSA and La/SSB autoantibodies had a substantially higher risk of hyperuricemia (p=0.01), arrhythmia (p=0.01), coronary artery disease (p=0.02), cerebrovascular disease (p=0.02), and venous thrombosis (p =0.03). In the multivariate logistic regression analysis, higher odds of cardiovascular risk factors were associated with extraglandular involvement (p=0.02), treatment with corticosteroids (p=0.02), ESSDAI>13 (p=0.02), inflammatory markers including ESR levels (p 0.007), and serologic markers such as low C3 levels (p=0.03) and hypergammaglobulinemia (p=0.02).

Conclusions Extraglandular involvement was associated with a higher prevalence of arterial hypertension, dyslipidemia, hyperuricemia, and coronary artery disease. Anti-Ro/SSA and anti-La/SSB seropositivity was associated with a higher prevalence of cardiac rhythm abnormalities, hyperuricemia, venous thrombosis, coronary artery disease, and cerebrovascular disease. Raised inflammatory markers, disease activity measured by ESSDAI, extraglandular involvement, serologic markers including hypergammaglobulinemia and low C3, and treatment with corticosteroids were associated with a higher risk for cardiovascular comorbidities.

Key Points

- *Patients with pSS are vulnerable to cardiovascular risk factors. There is an interconnection between extraglandular involvement, disease activity, inflammatory markers, and cardiovascular risk comorbidities.*
- *Anti-Ro/SSA and anti-La/SSB seropositivity was associated with a higher frequency of cardiac conduction abnormalities, coronary artery disease, venous thrombosis, and stroke.*
- *Hypergammaglobulinemia, elevated ESR, and low C3 are associated with a higher prevalence of cardiovascular comorbidities.*
- *Valid risk stratification tools to help with prevention and consensus on the management of CVDs in pSS patients are warranted.*

Extended author information available on the last page of the article

Keywords Autoantibodies · Cardiovascular disease · Sjogren

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by the lymphocytic infiltration of secretory glands, which results in sicca syndrome [1]. The spectrum of the disease can extend to extraglandular manifestations, including renal, lung, and neurological involvement and associate a higher risk of lymphoma [2].

Cardiovascular diseases were found to be major causes of morbimortality in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) [3–6]. The interaction between the innate and adaptive systems and immune-mediated mechanisms related to the pathogenesis of autoimmune diseases play an important role in inducing and perpetuating vascular atherosclerotic damage [7]. Pro-inflammatory cytokines, adhesion molecules, and chronic inflammation lead to endothelial damage and ischemia of arterial wall and ultimately to plaque formation and rupture.

In the general population, traditional cardiovascular risk factors, such as cholesterol levels, smoking, diabetes mellitus, and arterial hypertension, play a role in the pathogenesis of cardiovascular damage. Stratification algorithms have been validated to properly assess the cardiovascular risk of individuals in the general population developing cardiovascular diseases; meanwhile, in patients with systemic autoimmune diseases such as RA, the systemic coronary risk estimation (SCORE) should be multiplied by 1.5 to assess the cardiovascular risk. In several other systemic autoimmune diseases and/or chronic inflammatory diseases, the estimation of cardiovascular morbidity and mortality is limited due to the difficulty to quantify the role of chronic inflammatory burden and immune deregulation to the atherosclerotic damage [8, 9].

Primary Sjögren's syndrome shares several clinical and pathophysiologic characteristics with SLE and RA; however, the prevalence and significance of cardiovascular disease in pSS remain unclear. Several studies have found that patients have a higher risk of comorbidities in pSS compared to the general population [10, 11]. Furthermore, the impact of anti-Ro/SSA and anti-La/SSB autoantibodies on the risk of cardiovascular disease has not been evaluated. Anti-Ro/SSA and anti-La/SSB autoantibodies are very prevalent in autoimmune diseases and have arrhythmogenic effects on the cardiac conductive system, which can result in a higher risk for congenital atrioventricular block in children of seropositive mothers. This association to conduction defects in seropositive adults has not been properly evaluated [12].

The purpose of our work was to assess the cardiovascular risk associated to pSS, including traditional and modifiable cardiovascular risk factors, determine predictors of cardiovascular events in pSS, and develop an approach for risk assessment in a clinical practice setting in order to fill some gaps in the knowledge about cardiovascular disease in pSS. We have investigated the prevalence of cardiovascular events and risk factors in patients with pSS with a follow-up period of 20 years, stratified by glandular and extraglandular involvement and anti-Ro/SSA and/or anti-La/SSB autoantibody positivity.

Materials and methods

Patients

A retrospective study was performed by including pSS fulfilling the 2016 ACR/EULAR criteria for primary Sjögren's syndrome followed in our unit from January 2000 to December 2022 [13]. Patients not fulfilling the 2016 ACR/EULAR criteria and/or missing data regarding the diagnosis of pSS, patients with overlapping syndromes, and patients with a history of chronic hepatitis C, human immunodeficiency virus (HIV), and lymphoproliferative diagnoses were excluded from the study. Patients diagnosed before 2016 were reclassified according to the 2016 ACR/EULAR criteria. We have included patients and stratified them according to the presence of extraglandular involvement and autoantibody positivity. Collection of sociodemographic, clinical, and analytical data was performed at inclusion. Clinical data, traditional cardiovascular risk, and cardiovascular events were also collected during regular visits and by review of medical records for each patient.

Data collection

Sociodemographic features including age at inclusion, age at diagnosis, sex, disease duration, and clinical data including dry eye and dry mouth, glandular and extraglandular involvement, including articular involvement, skin, lung, hematological, renal and gastrointestinal involvement, and central and peripheral nervous system involvement were registered. Analytical patterns including anti-SSA/Ro antibody, anti-SSB/La antibody, rheumatoid factor (RF), immunoglobulins, complement fractions C3 and C4, beta-2microglobulin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were also retrieved.

Treatment history with hydroxychloroquine (HCQ), methotrexate (MTX), mycophenolate (MMF), rituximab (RTX), and glucocorticoids (GC) was included.

Disease manifestations were scored according to the European League Sjögren's syndrome disease activity index (ESSDAI) [14].

Assessment of exocrine gland involvement

A medical history, anamnesis, and physical examination at our outpatient clinic were taken. An experienced ophthalmologist performed the following test: Schirmer's test, Van Bijsterveld Score using Rose Bengal/Lissamine Green, and/or Ocular Staining using fluorescein. Whole unstimulated salivary flow (WUSF) and/or minor salivary gland biopsy was also performed. The biopsy tissue was evaluated by two experienced pathologists and considered positive with a lymphocytic focus score ≥1, with more than 50 lymphocytes per 4 mm [13, 15].

Assessment of extraglandular involvement

The following information regarding extraglandular manifestations was collected: (1) *cutaneous involvement*: xerosis, angular cheilitis, cutaneous vasculitis, erythematous annular plaques, cryoglobulinemia, polycyclic annular erythema, erythema elevatum diutinum, Sweet's syndrome, multiform-like erythema, granulomatous panniculitis, and erythema nodosum-like; (2) *articular involvement*: inflammatory arthralgia with subclinical synovitis evaluated by ultrasound and clinical arthritis; (3) *renal involvement*: renal tubular acidosis and/or glomerulonephritis defined as proteinuria of over 0.5 g/day and presence of hematuria which was confirmed by renal histology; (4) *lung involvement*: interstitial lung disease (ILD using high-resolution computerized tomography); (5) *gastrointestinal involvement*: autoimmune hepatitis (altered hepatic function and presence of autoantibodies antinuclear antibodies, anti-smooth muscular antibodies, anti-microsomal antibodies) confirmed by liver biopsy, after exclusion of alternative causes of hepatitis; (6) peripheral nervous system: peripheral neuropathy diagnosed by electrophysiology and/or biopsy; (7) central nervous system: brainstem and/or cerebellar syndrome, acute or subacute encephalopathy, aseptic meningitis, chronic progressive myelitis, transverse myelitis, Brown-Sequard syndrome, and optic neuropathy; (8) *hematologic*: leukopenia, thrombocytopenia, and autoimmune hemolytic anemia. The diagnosis of extraglandular manifestations relied on the exclusion of other causes.

Definition of traditional cardiovascular risk

Cardiovascular risk factors were established using the following World Health Organization (WHO) definitions:

- Arterial hypertension: systolic blood pressure (SBP) over 140 mmHg or diastolic blood pressure (DBP) over 90 mmHg or receiving antihypertensive treatment. Blood pressure was considered as the mean of 3 measurements.
- Dyslipidemia: cholesterol, low-density lipoprotein, (LDL), triglycerides, and high-density lipoprotein (HDL) imbalance.
    - Hypercholesterolemia as total cholesterol level >250 mg/dl on two or more prospective occasions.
    - Hypertriglyceridemia as serum triglyceride level >150 mg/dl on two or more prospective occasions.
    - High-density lipoprotein (HDL) as <40 mg/dl and low-density lipoprotein (LDL) defined as >130 mg/dl.
- Obesity was defined as body mass index (BMI) over 30 kg/m^2.
- Smoking was defined as current smoker, ex-smoker, and never smoker.
- Diabetes mellitus was defined as diabetes requiring insulin/oral antidiabetic drugs treatment and/or the presence in at least two determinations of fasting glycemia higher than 126 mg/dl.
- Hyperuricemia was defined as high level of uric acid in the blood. Serum uric acid concentrations over 6 mg/dl for females, 7 mg/dl for men or patients under uric acid lowering drugs treatment.

Definition of cardiovascular events

Cardiovascular events were evaluated retrospectively and included:

- Cerebrovascular disease including ischemic attacks confirmed by brain CT and/or brain MRI and carotid artery disease on sonography.
- Coronary artery disease included heart infarction defined by elevated cardiac enzyme levels and/or electrocardiogram; silent myocardial ischemia defined as myocardial ischemia in the absence of chest discomfort or other anginal equivalents; stable angina and unstable angina defined clinically during physical exertion.
- Arrhythmia: including supraventricular arrhythmias, ventricular tachyarrhythmias and ventricular fibrillation, atrial fibrillation, and bradyarrhythmia.
- Conduction defects: first-degree heart block, left anterior fascicular block, right and left, bundle branch block, and second- or third-degree AV block.
- Arterial peripheral vascular disease
- Venous thrombosis: deep vein thrombosis and pulmonary embolism.

The levels of biomarkers were measured using standardized laboratory methods.

Charlson comorbidity index

The Charlson comorbidity index (CCI) assesses the presence of comorbidities by taking into account both the number and severity of pre-defined comorbid conditions: myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate or several renal disease, diabetes with end organ damage, any tumor, leukemia, lymphoma, moderate or severe liver disease, metastatic solid tumor, AIDS. It can be used to predict short-term and long-term outcomes such as function, hospital length of stay, and mortality rates. Based on the CCI score, the severity of comorbidity was categorized into three grades: mild, with CCI scores of 1–2; moderate, with CCI scores of 3–4; and severe, with CCI scores ≥5.

Ethical concerns

The institutional ethics committee of the Complejo Asistencial Universitario de León approved the study (CEIMN°2211). Participants have given their written consent to participate in this study, and this was notified in the patient's medical history.

Statistical analysis

Categorical data were compared using Fisher's exact test or chi-squared test. Continuous data were compared using the unpaired *t*-test or ANOVA for normally distributed data and the Mann-Whitney test or Kruskal-Wallis for non-normally distributed data. Multivariate logistic regression models were used to determine associations between demographic, clinical, serological, and treatment characteristics and cardiovascular disease in pSS. These results are presented as odds ratios and 95% confidence intervals. The significance level was set at $p < 0.05$. All statistical analyses were conducted with SPSS.

Results

Sociodemographic, clinical and treatment characteristics

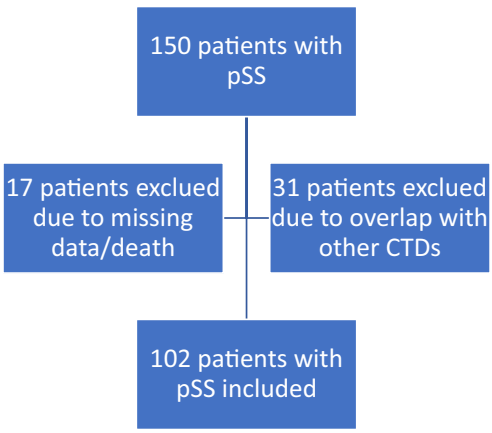
A total of 150 patients were diagnosed with primary Sjögren's syndrome. At inclusion, 17 patients were excluded due to missing data and/or death and 31 patients were excluded due to overlap with other connective tissue diseases. A total of 102 patients with pSS were enrolled in the registry (Flowchart 1). Eighty-two percent were female, with a mean age of 65±24 years and a mean time since diagnosis of 12.5 ±6 years. Sociodemographic, clinical, serological, and antibody positivity, treatment, and disease activity are summarized in supplemental data.

Cardiovascular risk factors

Thirty-six patients (36%) had at least one cardiovascular risk factor. Arterial hypertension was diagnosed in 60 (59%) patients, dyslipidemia in 28 (27%), diabetes in 15 (15%), obesity in 22 (22%), and hyperuricemia in 19 (18%). Hisory of arrhythmia was found in 25 (25%), conduction defects in 10 (10%), arterial peripheral vascular disease in 7 (7%), venous thrombosis in 10 (10%), coronary artery disease in 24 (24%), and cerebrovascular disease in 22 (22%) of patients. The mean values of LDL were 108±46, HDL was 56±21, triglycerides were 101±43, and uric acid was 5.44±1.4. Cardiovascular risk factors and cardiovascular events are summarized in supplemental data.

Comparison between pSS with extraglandular and glandular involvement

Compared with age-, sex-, and disease duration-matched controls, pSS with extraglandular involvement had a higher frequency of arterial hypertension (68% vs 49%, OR 2.28 (1.01–5.09), p=0.04) and dyslipidemia (41% vs 14%, OR 4.4, 95% CI (1.67–11.6), p=0.003), higher level of low-density lipoprotein (116±48 vs 99±44, p=0.038), higher frequency of hyperuricemia (27% vs 9%, OR 3.48, 95% CI (1.15–10.6), p=0.03), higher prevalence of coronary artery disease (35% vs 12%, OR 4.09, 95% CI (1.46–11.4), p=0.01), higher levels of C-reactive protein (14±8.8 vs 9±0.6, p 0.006), and higher levels of erythrocyte sedimentation rate (25.7±24 vs 17.4±14, p 0.04) compared to patients with glandular involvement only. Table 1 represents the results in patients with pSS based on extraglandular and glandular-only involvement.



Flowchart 1 Patients included in the study

Comparison between pSS with anti-Ro/SSA and anti-La/SSB involvement

Compared with age-, sex-, and disease-matched controls, pSS with anti-Ro/SSA+ and anti-La/SSB+ or anti-Ro/SSA+ and anti-La/SSB− had a higher frequency of hyperuricemia (31% vs 8%, OR 5.47, 95% CI (1.65–17.5), p=0.01); higher prevalence of arrhythmia (35% vs 14%, OR 3.42, 95% CI (1.28–9.16), p=0.01), coronary artery disease (24% vs 8%, OR 3.62, 95% CI (1.07–12.07, p=0.04), cerebrovascular disease (39% vs 10%, OR 3.83, 95% CI (1.27–11.5), p =0.02), venous thrombosis (18% vs 2%, OR 10.23, 95% CI (1.24–21.5), p=0.03); and higher levels of CRP (23±10.9 vs 10±4.9, p 0.01) and ESR (21±22 vs 16.7±15, p 0.94), than seronegative patients for anti-Ro/SSA− and/or anti-La/SSB antibodies. Table 2 represents the results in patients with pSS based on autoantibody positivity.

Clinical, immunological, treatment, and disease activity characteristics of patients according to the Charlson comorbidity index (CCI)

Table 3 represents significant differences found comparing the demographic, clinical, and treatment characteristics and disease activity of pSS patients according to the score obtained in the Charlson comorbidity index (CCI). pSS patients with a severe comorbidity score, in comparison with the other two groups, had a higher frequency of extraglandular involvement, including renal involvement (42% vs 31% vs 24%, p=0.04) and central nervous system (29% vs 17% vs 12%, p=0.02). In addition, elevated CRP (67% vs 39% vs 29%, p=0.002), elevated ESR (75% vs 61% vs 36%, p=0.03), higher levels of beta2microglobulin (5.3±2.3 vs 2.3±1.9 vs 1.02±2.4, p=0.003), low C3 (83% vs 67% vs 29%, p=0.02), higher frequency of hypergammaglobulinemia (79% vs 56% vs 33%, p=0.02), and higher frequency of anti-Ro/SSA antibodies (75% vs 56% vs 59%, p=0.04). Regarding treatment, patients with pSS with severe comorbidity score had received corticosteroids more frequently (67% vs 42% vs 38%, p=0.02) and hydroxychloroquine less frequently (25% vs 33% vs 52%, p=0.03). Interestingly, significant differences regarding disease activity measured by ESSDAI and CCI were also found, as 45% of patients with severe comorbidity score had an ESSDAI>13 compared to 19% and 11% of the two groups.

Cardiovascular disease stratified by hydroxychloroquine (HCQ) treatment

Table 4 represents cardiovascular disease in pSS patients stratified by HCQ treatment. No significant difference was found regarding the occurrence of arrhythmia, conduction defects, arterial peripheral vascular disease, venous thrombosis, and cerebrovascular disease. Patients under HCQ treatment exhibited a lower frequency of coronary artery disease (7.5% vs 21%, OR 0.18, 95% CI (0.04–0.84), p 0.03).

Table 1 Cardiovascular risk factors and acute phase reactants in patients with pSS in patients with extraglandular and glandular involvement

Cardiovascular risk factor	Without extraglandular involvement	With extraglandular involvement	OR (95% CI)	p value
Arterial hypertension (n, %)	25 (49%)	35 (68%)	2.28 (1.01–5.09)	**0.04**
Dyslipidemia(n, %)	7 (14%)	21 (41%)	4.4 (1.67–11.6)	**0.003**
Diabetes (n, %)	5 (9%)	10 (20%)	2.29 (0.72–7.3)	0.16
Cholesterol (mg/dl)	182±48	166±68	-	0.17
Low-density lipoprotein (mg/dl)	99±44	116±48	-	**0.038**
High-density lipoprotein (mg/dl)	58±15	54±26	-	0.11
Triglycerides (mg/dl)	78±40	87±49	-	0.18
Smoking history (n, %)	21 (42%)	21 (31%)	1 (0.45–2.2)	1
Obesity (n, %)	10 (19%)	12 (24%)	1.26 (0.49–3.25)	0.64
Hyperuricemia	14 (27%)	5 (9%)	3.48 (1.15–10.6)	**0.03**
Arrhythmia (n, %)	10 (20%)	15 (29%)	1.71 (0.68–4.27)	0.25
Conduction defects (n, %)	4 (8%)	6 (12%)	1.56 (0.42–5.92)	0.51
Arterial peripheral vascular disease (n, %)	3 (6%)	4 (8%)	1.36 (0.29–6.41)	0.67
Venous thrombosis (n, %)	4 (8%)	6 (12%)	1.56 (0.41–5.9)	0.51
Coronary artery disease (n, %)	6 (12%)	18 (35%)	4.09 (1.46–11.4)	**0.01**
Cerebrovascular disease (n, %)	7 (14%)	15 (29%)	2.61 (0.96–7.12)	0.06
C-reactive protein, CRP (mean±SD)	14±18.8	9±10.6	-	**0.006**
Erythrocyte sedimentation rate, ESG (mean±SD)	25.7±24	17.4±14	-	**0.04**

Bold values are significant p values

Table 2 Cardiovascular risk factors and acute phase reactants in patients with pSS in patients based on autoantibody status

Cardiovascular risk factor	Anti-Ro/SSA+/anti-La− and anti-Ro+/anti-La/SSB−	Anti-Ro/SSA− and anti-La/SSB−	OR (95% CI)	*p* value
Arterial hypertension (*n*, %)	31 (61%)	29 (57%)	1.18 (0.53–2.6)	0.69
Dyslipidaemia (*n*, %)	15 (29%)	13 (26%)	1.22 (0.51–2.91)	0.66
Diabetes (*n*, %)	8 (16%)	7 (14%)	1.17 (0.39–3.50)	0.78
Total cholesterol (mg/dl)	174±51	162±57	-	0.86
Low-density lipoprotein (mg/dl)	105±39	102±42	-	0.62
High-density lipoprotein (mg/dl)	50±12	59±28	-	0.12
Triglycerides (mg/dl)	101±32	100±43	-	0.42
Smoking (*n*, %)	22 (43%)	18 (35%)	1.39 (0.63–3.09)	0.42
Obesity (*n*, %)	22 (43%)	19 (37%)	1.27 (0.58–2.82)	0.55
Hyperuricemia (*n*, %)	16 (31%)	4 (8%)	5.47 (1.65–17.5)	**0.01**
Arrhythmia (*n*, %)	18 (35%)	7 (14%)	3.42 (1.28–9.16)	**0.01**
Conduction defects (*n*, %)	7 (14%)	3 (6%)	1.5 (0.37–6.24)	0.56
Arterial peripheral vascular disease (*n*, %)	4 (8%)	3 (6%)	2.54 (0.62–10.5)	0.19
Venous thrombosis (*n*, %)	9 (18%)	1 (2%)	10.23 (1.24–21.5)	**0.03**
Coronary artery disease (*n*, %)	12 (24%)	4 (8%)	3.62 (1.07–12.07)	**0.04**
Cerebrovascular disease (*n*, %)	15 (39%)	5 (10%)	3.83 (1.27–11.5)	**0.02**
C-reactive protein, CRP (mean±SD)	23±10.9	10±4.9	-	**0.01**
Erythrocyte sedimentation rate, ESG (mean±SD)	21±22	16.7±15	-	**0.04**

Bold values are significant *p* values

Multivariate analysis

A multivariate logistic regression analysis with all the significant factors from the univariate analysis was performed. The dependent variable in our analysis was the presence of cardiovascular disease, which was defined of at least one of the following: cerebrovascular disease, coronary artery disease, arrhythmia, conduction defects, arterial peripheral vascular disease, and venous thrombosis. We have run 4 different models including disease-related data, serological data, inflammatory markers, and treatment data. As shown in Table 5, a higher odds of cardiovascular risk factors was associated with extraglandular involvement (OR 7.2, 95% CI (2.34–15.7), p=0.02), treatment with corticosteroids (OR 7.2, 95% (CI 2.34–15.7), p=0.02), hypergammaglobulinemia (OR 10.2, 95% CI (4.5–15.7), p=0.02), ESSDAI>13 (OR 1.5, 95% CI (1.2–4.52), p=0.02), ESR levels (2.9, 95% CI (1.42–3.45), p 0.007) and low C3 levels (1.32, 95% CI (1.02–3.42), p=0.03). Treatment with hydroxychloroquine (0.82, 95% CI (0.46–0.92), p=0.03) was associated with a lower odds of cardiovascular risk factors.

Discussion

Our study analyzes the prevalence of cardiovascular risk factors in a series of 102 patients with pSS. We have determined the influence of extraglandular involvement and antibody positivity on cardiovascular risk. Our results show that patients with extraglandular involvement exhibited a higher prevalence of arterial hypertension, dyslipidemia, hyperuricemia, and coronary artery disease and patients with anti-Ro/SSA and anti-La/SSB had a higher prevalence of cardiac rhythm abnormalities, hyperuricemia venous thrombosis, coronary artery disease, and cerebrovascular disease.

Several studies have shown an interconnection between extraglandular involvement, disease activity, and disease duration with cardiovascular events [16]. A meta-analysis analyzing the cardiovascular disease risk burden in pSS showed an increase in the risk of major adverse cardiovascular events (MACEs), including cerebrovascular events and coronary events, with clinical and immunological markers playing a role in promoting CV events, despite traditional cardiovascular risk factors [17, 18]. In several studies, hypertension, hypertriglyceridemia, and metabolic syndrome were also more prevalent in patients with pSS and smoking, obesity, and diabetes are less prevalent [19–21].

Hypertension was detected very frequently in pSS, present in 59% of the patients in our study; however, 65% of these patients were under anti-hypertensive drugs. In patients with extraglandular involvement, a higher prevalence of hypertension was found; however, no significant differences were found regarding antibody positivity [10, 11]. Hypertension in pSS is estimated in literature to range from 13 to 52% [22–24]. Interestingly, the prevalence of hypertension is also increased in pSS patients aged less

Table 3 Epidemiological features, clinical and immunological features, and treatments received in patients with pSS according to Charlson comorbidity index (CCI)

	Mild comorbidity score (*n*=42)	Moderate comorbidity score (*n*=35)	Severe comorbidity score (*n*=25)	*p* value
Male	3 (5%)	5 (14%)	10 (42%)	**0.03**
Mean age at diagnosis	59.2 ±12	60.5±17.4	59.5±15	0.147
Xerostomia	29 (69%)	22 (61%)	17 (71%)	0.237
Xerophthalmia	27 (64%)	28 (77%)	18 (75%)	0.12
Parotid enlargement	23 (55%)	14 (39%)	10 (42%)	0.08
Arthritis	23 (55%)	19 (53%)	13 (58%)	0.132
Cutaneous involvement	12 (29%)	14 (39%)	8 (33%)	0.82
Interstitial lung disease	12 (29%)	8 (22%)	9 (37.5)	0.06
Gastrointestinal	15 (36%)	12 (33%)	10 (42%)	0.26
Hematological	12 (29%)	10 (27%)	8 (33%)	0.18
Central nervous system	5 (12%)	6 (17%)	7 (29%)	**0.02**
Peripheral nervous system	14 (33%)	10 (28%)	9 (38%)	0.37
Renal	10 (24%)	11 (31%)	10 (42%)	**0.04**
Elevated CRP	12 (29%)	14 (39%)	16 (67%)	**0.002**
Elevated ESR	15 (36%)	22 (61%)	18 (75%)	**0.03**
Low C3	12 (29%)	24 (67%)	20 (83%)	**0.02**
Low C4	5 (12%)	17 (47%)	10 (42%)	0.23
Elevated rheumatoid factor	12 (29%)	16 (44%)	11 (46%)	0.34
Hypergammaglobulinemia	14 (33%)	25 (56%)	19 (79%)	**0.02**
Beta2microglobulin	1.02±2.4	2.3±1.9	5.3±2.3	**0.003**
ANTI-SSA/Ro	25 (59%)	20 (56%)	18 (75%)	**0.04**
ANTI-SSB/La	13 (31%)	16 (44%)	10 (42%)	0.19
ESSDAI 0–5	24 (57%)	12 (33%)	7 (29%)	0.22
ESSDAI 5–13	10 (24%)	20 (77%)	6 (25%)	0.34
ESSDAI >13	8 (19%)	4 (11%)	11 (45%)	**0.02**
Hydroxychloroquine (HCQ)	22 (52%)	12 (33%)	6 (25%)	**0.03**
Methotrexate (MTX)	10 (24%)	7 (19%)	8 (33%)	0.18
Rituximab (RTX)	9 (21%)	5 (14%)	8 (33%)	0.23
Mycophenolate (MYF)	11 (26%)	12 (33%)	7 (29%)	0.15
Glucocorticoids (GC)	16 (38%)	15 (42%)	16 (67%)	**0.02**

Bold values represent significant *p* values

Table 4 Cardiovascular risk factors in patients with pSS in patients stratified by HCQ treatment

Cardiovascular risk factor	HCQ group	Non-HCQ group	OR (95% CI)	*p* value
Arrhythmia (*n*, %)	12 (30%)	13 (21%)	1.61 (0.65–4.02)	0.30
Conduction defects (*n*, %)	5 (12.5%)	5 (8%)	1.63 (0.44–6.03)	0.46
Arterial peripheral vascular disease (*n*, %)	3 (7.5%)	4 (6%)	1.17 (0.25–5.56)	0.83
Venous thrombosis (*n*, %)	2 (5%)	8 (13%)	0.34 (0.07–1.77)	0.21
Coronary artery disease (*n*, %)	3 (7.5%)	13 (21%)	0.18 (0.04–0.84)	**0.03**
Cerebrovascular disease (*n*, %)	7 (17.5%)	13 (21%)	0.79 (0.28–2.21)	0.67
C-reactive protein, CRP (mean±SD)	11±9.5	10±4.2	-	0.15
Erythrocyte sedimentation rate, ESG (mean±SD)	18±12	15.3±11	-	0.10

Bold values represent significant *p* values

than 50 years, thus suggesting that other disease-related pathogenic mechanisms including genetics and inflammatory factors could be a determining factor in elevating blood pressure. In our study, a proportion of hypertensive patients were not under antihypertensive medications before Sjogren's diagnosis. We may think that hypertension in pSS is underdiagnosed and suboptimally treated and blood pressure should be routinely monitored in outpatient clinics.

Table 5 Multivariate logistic regression models to analyze the association between demographic, clinical, serological, and treatment characteristics and cardiovascular disease in pSS

Variable	OR 95% CI	*p* value
Male sex	1.04 (0.95–3.21)	0.70
Age at diagnosis	2.1 (0.81–4.25)	0.22
Extraglandular involvement	7.2 (2.34–15.7)	**0.02**
ESSDAI>13	1.5 (1.2–4.52)	**0.02**
Hypergammaglobulinemia	10.2 (4.5–21.2)	**0.02**
ESR	2.9 (1.42–3.45)	**0.007**
Low C3	1.32 (1.02-3.42)	**0.03**
Anti-Ro/SSA	2.1 (0.82–3.45)	0.32
Anti-La/SSB	1.32 (1.02–3.27)	0.58
HCQ	0.82 (0.46–0.92)	**0.03**
Corticosteroids	7.2 (2.34–15.7)	**0.02**
Rituximab	2.1 (0.92–3.92)	0.42

Bold values represent significant *p* values

Dyslipidemia was present in 27% of the patients of our series and 30% of these patients were taking statin treatment. Mean LDL and triglycerides were higher than 100 mg/dl and mean HDL was lower than 50 mg/dl in the patients included. Patients with extraglandular involvement exhibited a higher prevalence of dyslipidemia and higher levels of LDL. Increased total cholesterol and triglyceride have been associated with reduced HDL levels in pSS patients, as previously demonstrated in SLE and RA patients [25–27]. Disease-related inflammatory features were associated with impaired lipid profile in pSS. Regarding antibody positivity, several studies have found that patients with circulating anti-Ro/SSA and anti-La/SSB had higher total cholesterol and LDL levels; however, we did not find significant results compared to negative patients [28, 29].

Diabetes was observed in 15%. The prevalence of diabetes in pSS is variable, ranging from 0 to 28%, due to the different definitions and assessments of diabetes among the studies [30]. Our results were not conclusive regarding the influence of antibody positivity and extraglandular involvement and the prevalence of diabetes. Regarding obesity, we found a prevalence of 22%; however, no differences were found regarding antibody positivity and extraglandular involvement. Smoking history was present in 21% of the patients. We did not find a significant difference regarding extraglandular involvement and antibody status. In pSS, it makes sense that there is a lower proportion of smokers as smoking could be related to the exacerbation of oral and ocular symptoms.

Hyperuricemia was detected in 18% of patients. When we investigated patients with extraglandular involvement and antibody positivity, we found out that in both cases, there was a higher frequency of hyperuricemia and also higher levels of uric acid. Serum uric acid is a cardiovascular risk factor, strongly associated with peripheral, carotid, and coronary vascular disease. Several studies have shown that elevated serum uric acid is associated with a higher risk of hypertension in the general population. It was also suggested that uric acid could lead to an increase in blood pressure by promoting the liberation of inflammatory factors and lead to endothelial dysfunction. Recent studies found a significant dose-effect association between serum uric acid and hypertension in pSS and a correlation between levels of uric acid >4.7 mg/dl and the presence of cardiovascular risk factors and a higher disease activity [31, 32].

Twenty-four percent of our patients had coronary artery disease and we found significant differences regarding extraglandular involvement and autoantibody positivity. A meta-analysis of observational cohort studies demonstrated that pSS patients had a 1.5-fold increased risk of myocardial ischemia, angina, and cerebrovascular events [9]. A study of 624 patients with pSS patients also found that antibody positivity and extraglandular involvement were associated with higher cardiovascular risk factors [23]. Mofors et al. have found a higher risk of cerebrovascular disease and venous thromboembolism in pSS patients with anti-SSA/Ro and anti-SSB/La antibodies [33]. Likewise, we found that patients positive for anti-SSA/Ro and anti-SSB/La antibodies had a higher prevalence of stroke, peripheral arterial disease, and venous thrombosis. Several studies have shown that pSS patients have an increased risk of venous thrombosis, ranging from deep vein thrombosis and pulmonary thromboembolism and less typical sites such as cerebral venous thrombosis. These events usually happened in the first years after diagnosis when disease activity is higher [34, 35].

We also found a higher prevalence of arrhythmia in patients with anti-Ro/SSA and anti-La/SSB positivity. While it is very well established that neonates of seropositive mothers have an increased risk for congenital atrioventricular block, the association of anti-Ro/SSA and anti-La/SSB seropositivity with cardiac rhythm abnormalities in adult patients is very much unknown. A recent study published in the *European Heart Journal* examined the association of anti-Ro/SSA and anti-La/SSB seropositivity with cardiac rhythm and conduction disturbances. They found that patients with anti-Ro positivity exhibited abnormal conduction and rhythm disturbances, while patients who tested positive for anti-La alone did not demonstrate an association with arrhythmias [36]. Anti-SS-A/SS-B antibodies can interact with potassium channels, which can affect the ventricular repolarization and the QT interval, and behave like an autoimmune cardiac channelopathy [37].

Almost 25% of our pSS patients had a severe comorbidity score calculated by CCI. Forty-two percent of these patients were male and exhibited a higher prevalence of extraglandular manifestations, with a higher prevalence of central nervous system and renal involvement. Besides that, a relationship between the number of comorbidities and extraglandular involvement was also observed. Bartoloni et al. showed that pSS patients with cardiovascular events are more likely to associate extraglandular involvement, and that central nervous system involvement is independently associated with CV events after adjusting for age and disease duration [7]. This suggests a correlation between systemic involvement and cardiovascular risk factors. Inflammatory markers were higher in this group of patients. Disease activity was also higher in patients with 3 or more cardiovascular risk factors. Inflammatory markers such as CRP are well-recognized risk factors for CV, such as SLE and RA, and play a pivotal role in atherosclerosis. Given that CRP and ESR have a role in atheromatosis, it seems logical to think that elevated levels may indicate an increased risk for atherosclerotic cardiovascular damage in pSS [22]. Severe systemic involvement usually requires treatment with glucocorticoids to control disease activity, and this can be a contributing factor to the risk of MACEs development.

A higher prevalence of hypergammaglobulinemia and higher levels of beta2microglobulin were also found in patients with severe comorbidity score. This does not come as a surprise, since immunoglobulin G serum is a marker of B lymphocyte hyperactivity which can be associated with an increase in cardiovascular risk [25, 26].

We also found that the prevalence of cardiovascular risk factors in patients with pSS was lower in those receiving antimalarials. Hydroxychloroquine has been previously associated wih a cardiovascular protective effect in several studies in SLE patients, by lowering the risk of coronary artery disease and death in patients with SLE but there is no data in pSS patients [38–40]. In our study, patients with pSS under HCQ treatment had lower coronary artery disease, showing the significant cardiovascular protective effect of HCQ by modulating endothelial dysfunction and pro-inflammatory cytokines.

No significant associations between HCQ treatment and arrhythmia or conduction abnormalities were found in our study. There were several concerns recently about the use of HCQ and cardiac arrhythmia, as it was stated that HCQ could prolong QT interval; however, several studies showed that HCQ did not increase the risk of ventricular arrhythmia regardless of duration of treatment and cumulative dose in patients with autoimmune diseases, including pSS.

Corticosteroid therapy has been associated with a higher prevalence of cardiovascular risk factors in patients with immune-mediated inflammatory diseases, increasing the risk of cardiovascular disease, stroke, and vascular disease [40]. Unsurprisingly, patients in our study under corticosteroid therapy exhibited a higher cardiovascular risk. Several studies have found a corticosteroid dose-dependent risk of myocardial infarction, heart failure, atrial fibrillation, and cerebral disease in patients diagnosed with rheumatic diseases [41, 42]. Evidence also suggests that a dose of less than 5 mg of prednisolone was considered relatively safe; however, even at a low dose, patients with immune-mediated inflammatory diseases exhibit an underlying risk of cardiovascular disease [43].

We think our results can shed some light on the importance to screen cardiovascular risk factors in patients with pSS, especially hypertension, hyperuricemia, and dyslipidemia. It is important to determine periodically lipid panel profiles and fasting glucose and to measure blood pressure in outpatient clinics in the routine follow-up of pSS patients. Collaboration with specific preventive units and with primary care is also encouraged to initiate appropriate therapy to prevent or reduce sequelae from cardiovascular risk factors. As with other rheumatological diseases, such as RA and SLE, assessing and managing traditional and modifiable cardiovascular risk factors are essential to prevent cardiovascular events.

Further longitudinal studies with long follow-up periods as well as larger cohorts are warranted to establish the prevalence of cardiovascular risk factors in pSS and to develop valid risk stratification tools to help with the prevention and management of cardiovascular diseases in pSS patients.

One of the strengths of our study was the follow-up duration and the fact that we have only included primary SS, excluding secondary SS. Longer follow-up periods are necessary to exhibit an association with cardiovascular risk factors and thus correctly estimate the prevalence of cardiovascular events. We must address some limitations. First, only a few comorbidities were investigated in our registry; second, the presence of comorbidities was confirmed by medical history and some data might have been missed, which could underestimate the prevalence of cardiovascular risk factors; third, patients with severe extraglandular involvement were treated with glucocorticoids which can be associated with the development of comorbidities; fourth, we were unable to incorporate carotid and femoral artery ultrasonography in pSS patients to measure intima-media thickness, an indicator for subclinical atherosclerosis and MACE events; and fifth, the lack of a healthy control group limits the comparison of the results to the general population.

There is no general consensus on the management of cardiovascular risk in Sjogren's patients. Our results show that pSS patients have a higher risk of

cardiovascular events, particularly patients with extraglandular organ involvement, with disease activity, with inflammatory markers, and with a history of treatment with glucocorticoids. Anti-Ro/SSA and anti-La/SSB were associated with a higher prevalence of cardiac conduction abnormalities, arterial and venous thrombosis, and stroke.

In conclusion, pSS is associated with an overall risk of cardiovascular comorbidities, as demonstrated for other systemic autoimmune diseases such as RA and SLE. Patients with extraglandular involvement exhibited a higher prevalence of arterial hypertension, dyslipidemia, hyperuricemia, and myocardial ischemia and patients with anti-Ro/SSA and anti-La/SSB had a higher prevalence of arterial and venous thrombosis, hyperuricemia, stroke, and cardiac rhythm abnormalities. Raised inflammatory markers, presence of hypergammaglobulinemia, beta2microglobulin levels, and low C3 levels were associated with a higher risk for cardiovascular comorbidities. Corticosteroid use was also associated with cardiovascular risk factors, while hydroxychloroquine was a protective factor. Our results suggest that cardiovascular risk factors should be considered in the management of patients with pSS.

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Data availability All data are available in the article.

Compliance with ethical standards

Ethics This study was approved by Complejo Asistencial Universitario de León's Ethical Committee. Participants gave written consent to participate in the study before taking part.

Disclosures None.

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Authors and Affiliations

Cristiana Sieiro Santos[1] · Ruben Rego Salgueiro[2] · Clara Moriano Morales[1] · Carolina Álvarez Castro[1] · Elvira Díez Álvarez[1]

✉ Cristiana Sieiro Santos
cristysieirosantos@gmail.com

[1] Rheumatology Department, Complejo Asistencial Universitario de León, Altos de Nava S/N, 24008 León, Spain

[2] Internal Medicine, Unidade Local de Saúde da Guarda, Guarda, Portugal