

Title: Comorbidities in patients with Primary Sjögren's Syndrome and Systemic Lupus

Erythematosus: A comparative registries-based study

Subtitle: Comorbidities in Sjögren's Syndrome and Systemic Lupus Erythematosus

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Abstract

Objective: To compare the prevalence of the main comorbidities in two large cohorts of patients with Primary Sjögren's Syndrome (pSS) and Systemic Lupus Erythematosus (SLE), with focus on cardiovascular (CV) diseases.

Methods: Cross-sectional multicenter study where the prevalence of more relevant comorbidities in two cohorts was compared. Patients under follow-up from the SJOGRENSER (Spanish Rheumatology Society Register of pSS) and RELESSER (Spanish Rheumatology Society Register of SLE) registries, and who fulfilled the 2002-AECG and 1997-ACR classification criteria, respectively, were included. A binomial logistic regression analysis was carried out to explore potential differences, making

general adjustments for age, sex and disease duration and specific adjustments for each variable, including CV risk factors and treatments, when it was judged appropriate.

Results: A total of 437 pSS patients (95% female) and 2,926 SLE patients (89% female) were included. Mean age: 58.6 (p55-p75: 50.0-69.9) and 45.1 years (36.4-56.3), respectively ($p < 0.001$). Disease duration: 10.4 (6.0-16.7) and 13.0 years (7.45-19.76), respectively ($p < 0.001$). Smoking, dyslipidemia and arterial hypertension were associated less frequently with pSS [OR: 0.36 (95%CI:0.28-0.48), OR: 0.74 (0.58-0.94) and OR: 0.50 (0.38-0.66), respectively] as were life-threatening CV events (i.e., stroke or myocardial infarction) [OR: 0.57 (0.35-0.92)]. Conversely, lymphoma was associated more frequently with pSS [OR 4.41 (1.35-14.43)]. The prevalence of severe infection was lower in pSS than in SLE (10.1% vs 16.9%, $p < 0.001$; OR: 0.54 (0.39-0.76).

Conclusions: pSS patients have consistently less serious CV comorbidity burden and a lower prevalence of severe infection than those with SLE. In contrast, their risk of lymphoma was greater.

Key words

Primary Sjögren's syndrome, Systemic Lupus Erythematosus, comorbidity, cardiovascular diseases, infection

Significance and Innovations: -

- This first large-scale comparative study between pSS and SLE contributes to a better understanding of the differences and similarities between two systemic immune-mediated inflammatory rheumatic conditions
- pSS patients have consistently less serious CV comorbidity burdens than those with SLE

- In contrast, the risk of lymphoma in pSS exceeds that seen in SLE patients

Primary Sjögren's syndrome (pSS) is an autoimmune disorder characterized by chronic multisystem inflammation that shares certain pathophysiology and clinical features with Systemic Lupus Erythematosus (SLE). Although pSS is one of the most common rheumatic autoimmune diseases (1), reliable data regarding the prevalence of specific medical comorbidities in patients with pSS remain scarce (2).

Although increased atherosclerotic risk has been well established in other rheumatic autoimmune systemic diseases such as SLE (3, 4) only limited evidence is available for pSS. A higher prevalence of several cardiovascular (CV) risk factors, including hyperlipidemia, hypertension and metabolic syndrome has been noted in patients with pSS compared to age- and sex-matched healthy controls (5-7). Furthermore, higher prevalence of early subclinical atherosclerosis in pSS has similarly been observed in several studies (8,9,10). However, the issue of whether the presence of certain cardiovascular risk factors translates into an increased likelihood of CV events in pSS patients has not been studied in sufficient detail.

There are no comparative studies examining the most relevant comorbidities in patients with pSS versus those with SLE. Such studies could contribute not only to a better delineation of CV and/or lymphoma risk factors and other comorbidities, but also improve our understanding of the similarities and differences between these two immune-mediated, systemic rheumatic diseases.

In this study we analyzed the differences and similarities concerning the prevalence of certain comorbidities conditions in two large nation-wide cohorts of patients suffering SLE or pSS drawn from the Spanish Rheumatology Society SLE (RELESSER) and Spanish Rheumatology Society pSS (SJOGRENSER) Registries. This study was

conducted under the aegis of the Autoimmune Systemic Disease Study Group of the Spanish Society of Rheumatology (EAS-SER) and took advantage of the identical definitions of comorbidities used in the two registers, as well as the same network of researchers involved in both. In the present analysis, we have made a special emphasis on CV diseases.

Methods

The methodology used, the definitions of the disease-related variables, and general characteristics of both registries (RELESSER and SJOGRENSER) have been previously described in detail (11,12). Briefly, the RELESSER is a nation-wide multicenter, hospital-based registry. It has 2 parts: an initial cross-sectional phase (RELESSER-TRANS) and a further prospective cohort study (RELESSER-PROS) that remains ongoing. This study included patients from 45 rheumatology departments across Spain with substantial experience in the management of SLE. Moreover, it includes comprehensive clinical data for every patient. Only the cumulative data from the RELESSER-TRANS were used in the current analysis. The procedure of inclusion was not random in RELESSER and the centers were invited to include all patients whose medical records were available.

SJOGRENSER is also a multicenter descriptive transversal study of pSS patients under active follow-up at 33 rheumatology departments similarly distributed throughout Spain. Patients under active follow-up were included randomly from an anonymized list provided by each department.

The two cohorts were assembled by the EAS-SER Group. Both shared the same network of researchers and both were built using a high degree of standardization in defining their respective variables (11,12).

Both registries were approved by the institutional research review boards at all participating centers. Informed consent was obtained from every patient included. The studies were conducted in accordance with the Helsinki Declaration.

All pSS and secondary SS (sSS) patients fulfilled the 2002-American-European Consensus Group (AECG) criteria for the classification of SS (13), and all SLE patients met the 1997-ACR criteria (14).

In both registries, extensive information about cumulative comorbidity conditions was collected, using identical definitions for all of the comorbidities included in this analysis, as detailed below.

Design

Cross-sectional multicenter study where the cumulative prevalence of comorbidities between two patient cohorts was compared.

Definitions

CV risk factors were defined as follows: Smoking was categorized as follows: current or ex-smoker, and never smoked. Diabetes: previous diagnosis or 2 fasting serum glucose levels 126 mg/dL and/or antidiabetic drugs. Dyslipidemia: total cholesterol 240 mg/dL and/or low-density lipoprotein > 130 mg/dL and/or triglycerides 160 mg/dL and/or intake of lipid-lowering drugs. Hypertension was classified using the following World Health Organization (WHO) definitions: systolic blood pressure 140 mm Hg and/or a diastolic blood pressure 90 mm Hg on 2 occasions or receiving antihypertensive treatment (15).

On the other hand, a CV event was defined as the presence of at least 1 of following: ischemic heart disease, including myocardial infarction and/or angina pectoris based on clinical diagnosis and ischemic changes in the electrocardiogram and/or specific changes in cardiac enzymes and/or typical findings in a coronary angiography; clinically diagnosed heart failure and/or based on chest radiography; cerebral vascular accident based on an unequivocal previous diagnosis or on the presence of clinical manifestations and/or supported by an imaging procedure; and peripheral artery disease supported by the presence of clinical manifestations confirmed by an imaging procedure.

Other comorbidity definitions include: Fibromyalgia (FM) according to the 1990-ACR criteria (16); severe infection: infections requiring hospitalization; osteoporotic fractures: if clinically recorded as such; lymphoma: through involved tissue biopsy.

Statistical analysis

With the aim of improving comparability between the two cohorts, we performed the main analysis, including only those patients under active follow-up from the RELESSER cohort, since the SJOGRENSER registry include only living patients under active follow-up. However, given that around one-third of SLE patients die due to CV causes and since - in contrast to pSS - CV mortality is higher in SLE patients than in the general population, we decided to conduct a sensitivity analysis, including also those patients who had died. In this manner, we sought to avoid any bias related to the loss of patients that died due to severe CV events in the SLE cohort.

Additionally, to avoid “overlapping” patients, we decided to exclude from the main analysis those patients with sSS from the SLE group.

Values related to categorical variables are expressed as percentages. Continuous variables are considered as medians and interquartile ranges. Comparisons were done using a chi-square test for categorical data and Kruskal-Wallis tests for continuous data. Associations were studied through a binomial logistic regression analysis. Results are expressed as crude Odds Ratio (OR) and adjusted OR. All of the comparisons were adjusted for age, sex and disease duration; specific adjustments for each variable, including CV risk factors and treatments, were made when deemed appropriate. All analyses were carried out using Stata 13.1 and SPSS 21.0.

Results

A total of 437 patients with pSS were included, 95% of them women and 93% Caucasian, with a median age at inclusion of 59 years and a median age at diagnosis of 50 years. The median score for ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) was 2 (p25-p75:0-4). Less than 5% of patients developed visceral involvement, using ESSDAI items, and 56% exhibited hematologic involvement. A total of 102 patients (23.3%) had hypocomplementemia (low C3 or low C4, anytime) and 26 (6 %) carried some type of antiphospholipid antibodies.

In parallel, all patients fulfilling the ACR-97 SLE criteria included in RELESSER under active follow-up were included in the analysis. Thus, there was a total of 2,926 patients of whom 2,523 (89.9% female) were SLE patients without sSS.

A comprehensive description of clinical characteristics and comorbidities of the entire RELESSER cohort has previously been published (17).

A total of 2,926 SLE patients (89% female) were included in this analysis, 93.3% of them Caucasian, with a mean age at inclusion of 45.1 years (36.4-56.3). The main clinical characteristics of this RELESSER subgroup, namely, SLE patients under active follow-up and without sSS (corresponding to the present analysis) at the time of

inclusion in the registry were as follows: median score for SELENA-SLEDAI (SELENA-Systemic Lupus Erythematosus Disease Activity Index) 2 (p25-p75:0-4), SLICC/ACR Damage Index: 0 (0-1); lupus nephritis was present in 29.9%, 1.3% of patients were in a dialysis program and 1.5 % had undergone renal transplant. A total of 1934 patients (78 %) had hypocomplementemia (low C3 or low C4, anytime) and 960 (55.1%) any kind of antiphospholipid antibodies.

The comparative sociodemographic and chronological characteristics of pSS versus SLE without sSS are shown in Table 1. It is worth noting the differences in the mean age of patients upon enrollment in the registry (median: 58.6 years in pSS versus 44.5 years for SLE, $p < 0.001$). Remarkable differences between SLE and pSS were also observed in cumulative treatments, as shown in Table 2, with more SLE patients undergoing some glucocorticoid, antimalarial and/or immunosuppressive treatment, except in the case of rituximab. Moreover, significantly fewer patients with pSS were hospitalized due to disease activity, compared with SLE patients [(17.2% vs. 53.2%, $p < 0.001$; OR: 0.19 (95%CI: 0.15-0.24)].

A comparative analysis of the prevalence of comorbidities is shown in Table 3. Classic CV risk factors such as tobacco use, dyslipidemia and arterial hypertension were less prevalent in pSS and the adjusted ORs were: 0.39 (95%CI:0.29-0.51), 0.77 (0.61-0.98) and 0.51 (0.39-0.66), respectively as were life-threatening CV events (i.e., stroke or myocardial infarction) [adjusted OR: 0.61 (0.38-0.93)] (Table 3). When we also adjusted for hypocomplementemia, no relevant changes in the Odd Ratios were observed. Conversely, adjusting for antiphospholipid antibodies resulted in the loss of statistical significance for all CV event differences.

The prevalence of severe infection was lower in pSS than in SLE (10.1% vs 16.9%, $p < 0.001$; crude OR: 0.55 (0.40-0.77) and the OR adjusted for age, sex, disease duration

was :0.62 (0.44-0.86) ($p=0.008$), although this difference lost statistical significance when also adjusted for treatments (glucocorticoids, hydroxychloroquine and immunosuppressives). Conversely, lymphoma was associated more frequently with pSS [adjusted OR 4.41 (95%CI: 1.35-14.43)]. On the other hand, FM was also more frequently observed in pSS patients [adjusted OR: 2.43 (1.70-3.49)].

An alternative analysis was carried out that included patients with sSS who also existed in the SLE group, and the results are shown in Supplementary Materials (Table 4). In short, only one difference lost statistical significance; i.e., stroke, with an adjusted OR of 0.56 (95%CI: 0.30-1.04). Additionally, it is worth noting that the OR of FM prevalence in pSS patients versus those with SLE decreased [from 2.43 (1.70-3.49) to 1.98 (1.42-2.76)] when the former were included in the analysis.

Finally, an additional sensitivity analysis was carried out that also took into account those patients in SLE group who had died. This was done in an attempt of improve the capture of serious CV events in SLE by reducing bias related to CV death in SLE patients. These results are shown in Table 5 (Supplementary Materials). The adjusted ORs (pSS/SLE) for cardiac failure prevalence and severe infection reached statistical significance when the dead patients from the RELESSER registry were included in the analysis [ORs: 0.49 (95%CI: 0.27-0.89) and 0.66 (95%CI: 0.46-0.96), respectively].

Interestingly, the OR for differences in the presence of lymphoma decreased, losing the statistical significance [from 4.41 (1.35-14.43) to 2.50 (0.92-6.80)].

Discussion

In our comparative analysis, we found a higher prevalence of serious CV comorbidities in patients with SLE than in those with pSS. These results are in line with the absence

of an increase of mortality in pSS, suggested by several studies (18, 19) as well as with a lesser degree of damage observed in pSS when comparing with SLE. (20).

Furthermore, the lower rate of disease-related hospitalization observed in our study seems to confirm that pSS is a less severe disease than SLE, at least in our environment and as defined by the 2002-AECG criteria. In fact, this feature probably has an impact on the development of comorbidities. It is worth noting that the difference in the prevalence of severe CV comorbidities was more consistent when SLE patients without sSS were compared against those with pSS. This last observation is consistent with the less severe SLE in patients with associated sSS versus those without sSS, which has been reported by several groups (21,22).

The prevalence of lymphoma constitutes an exception, being more frequently observed in pSS in the current comparative analysis. However, the prevalence of lymphoma (1.6%) was not markedly high in the SJOGRENSER registry. This result is in line with the low prevalence of lymphoma reported by Malladi et al, who used the same 2002-AECG classification criteria in analyzing a large international registry of pSS patients (23). The use of alternative classification criteria may, obviously, lead to differences in the observed prevalence of this complication in pSS. The ratio for lymphoma was approximately 4 times higher in pSS compared with SLE in our analysis, a difference that did not change significantly when adjusted for immunosuppressor and antimalarial use. Interestingly, when patients with sSS from the RELESSER cohort were included, the difference in the prevalence of lymphoma did not change in any relevant way. This observation suggests that in SLE, the risk of lymphoma is not linked to the presence of sSS. Our results are consistent with a recent case-control study from a large SLE cohort, in which no difference was found in the prevalence of sSS between SLE patients with or without B-cell lymphoma (24).

While several lines of evidence support an increase of CV events in SLE (25- 28), this is not the case, at least not to the same extent as with pSS. Although classic CV risk factors are indeed higher in pSS patients, a corresponding increase in CV events is less clear. Bartoline et al. actually observed that cerebrovascular events and myocardial infarction were significantly more common in patients with pSS versus age-matched healthy women (2.5% vs. 1.4% and 1.0% vs. 0.4%, respectively) when analyzing a large multicenter cohort of pSS (27). In contrast, several studies have not found any differences in the prevalence of CV events when compared with the general population (2, 29-31).

In our study, we found that the OR of CV events was around 50% less in patients with pSS versus those with SLE. These results are consistent with the absence of increased CV mortality associated with pSS when compared with general population and conform to most studies carried out to date (18,19). In contrast, the mortality rate is clearly higher in SLE patients and CV diseases remain a principal cause of death in this condition (32).

Several classical CV risk factors were more prevalent in SLE (namely arterial hypertension, dyslipidemia and tobacco smoking) in our study. Worth noting is the fact that the difference between pSS and SLE across all types of CV events was not entirely explained by differences in the classic CV risk factors included in our analysis, suggesting that SLE-intrinsic factors are probably involved. In contrast and interestingly, a study carried out comparing pSS with a control group did not find any differences in intima medial thickness after adjusting for classical cardiovascular risk factors. This suggests that perhaps the disease-related factors are not as important in atherosclerosis associated with pSS (8).

Although some studies have found higher mean levels of C-reactive protein (CRP) in

pSS (31), it can be assumed in general terms that pSS is, in fact, a disease in which the concentration of acute-phase protein serum CRP is not elevated (35). It is tempting to speculate that the inflammatory burden might be lower in pSS than SLE. In fact, many patients with SLE increased levels of CRP, particularly with arthritis and serositis, and CRP is associated with disease activity in these organs (35,37). Bearing in mind that CRP, particularly high-sensitivity CRP, has been associated with atherosclerosis both in the general population (38) and in SLE patients (39, 40), this difference could plausibly explain the prevalence of CV disease in pSS and SLE. Unfortunately, we do not have comparative data about CRP in our cohorts.

Additionally, complement activation is more prevalent in SLE than in pSS (38), which is confirmed in our own study. The complement system has been associated with subclinical arteriosclerosis and atheroma plaque progression in SLE (39, 40). However, when we adjusted for hypocomplementemia, the Odd Ratios did not change in a relevant way for any CV event, suggesting that this variable does not explain the differences between pSS and SLE. In fact, the association of hypocomplementemia with CV events in SLE remains controversial (25, 26).

On the other hand, there is a higher risk of thrombosis in patients with SLE compared to pSS, at least in terms of venous thrombosis. This suggests the existence of a prothrombotic state in SLE, which would be less relevant in pSS (42).

In this regard, several research groups have noted an increase in homocysteine in SLE patients, a risk factor of CV diseases apparently not present in pSS. In fact, homocysteine's role in the progression of atherosclerosis in SLE has been posited by several longitudinal studies (39, 43, 44). Additionally, the prevalence of antiphospholipid antibodies and antiphospholipid syndrome is higher in SLE than in pSS patients (45), a difference again clearly shown in our study. Further to this, our

group has recently published an analysis concerning CV events in patients from the RELESSER registry, in which antiphospholipid antibody positivity was associated with CV events in a multivariate analysis (25). Remarkably, at least in the present analysis, adjusting for antiphospholipid antibodies entails the loss of statistical significance for all Odd Ratios corresponding to CV events.

Another interesting finding of our study relates to tobacco smoking. Several reports indicate that tobacco smoking serves as a protective factor for pSS (30, 46). In contrast, tobacco is well known risk factor for SLE (47). Our own study is a clear confirmation of the opposite impact of smoking on two rheumatic immune-mediated inflammatory diseases. However, when we adjusted our analysis for tobacco use, differences in CV events between LES and pSS remained.

In contrast with SLE, the prevalence of severe infection in pSS is largely unknown. We have found a prevalence of infection of 10% in our pSS cohort. Based on our analysis, the OR of this serious complication was approximately 40% less in pSS than in SLE, although the difference did not maintain statistical significance when adjusted for therapies (immunosuppressant drugs, GC and antimalarial use). This observation suggest that factors related to treatments, more than the disease itself, could be involved in the greater risk for infection recorded in SLE patients. The discovery that significant differences were more evident when dead patients were included in the SLE group suggests that the prevalence of severe infection in SLE is under-estimated in this analysis.

FM is a comorbidity condition that negatively impacts the quality of life in patients with SLE and pSS (48). Most, but not all, of the observational cohort studies that have included patients with both SLE and pSS patients have observed a higher prevalence of FM in pSS versus SLE (49-51). However, only in this comparative analysis were

adjustments for sex, age and disease duration carried out, thus confirming and reinforcing previous data. Recently, the relationship between pSS and FM was further underscored by the findings in a specifically conducted analysis drawing from RELESSER cohort, in which sSS was identified as a risk factor for fibromyalgia in SLE (52). Furthermore, when we included patients with sSS from the RELESSER cohort in the present analysis, the OR comparing the prevalence of FM in pSS versus SLE decreased, while still favoring pSS. Although it is clear from the literature that FM and/or chronic widespread pain is frequently observed in all autoimmune systemic rheumatic diseases (48), the prevalence of and pathogenic factors involved in each probably differ.

Very limited information is available on the occurrence of fracture rates in patients with pSS. Gravani et al found a prevalence of fractures of 12.5%, a percentage not significantly different compared to healthy controls (9). In our study, which involved a larger and more representative sample of pSS using the same classification criteria, the prevalence of fracture was not very different; i.e., 8.6%. Despite the prolonged use of GCs in SLE patients, we did not find any differences in the prevalence of osteoporotic fractures between the pSS and SLE cohorts. This somewhat unexpected result deserves explanation, but unfortunately, the lack of covariates related to fracture risk in our study does not allow for further analysis.

Our study has certain limitations that must be pointed out. First of all, the results of this analysis are limited by the bias inherent to its transversal design. Second, the registries from which the cohorts are derived, RELESSER and SLOGRENSER, were not specifically designed for the purposes of comorbidities comparative analysis and thus several covariates are missing.

There are certain differences in the design of both registries that deserve further mention. Patients included in SJOGRENSER were randomly selected, thus forming a highly representative sample of pSS from Spanish rheumatology clinics. In contrast, RELESSER was a consecutive patients registry, including deceased individuals and those lost to follow up. In our view, however, the large number of patients ultimately included in RELESSER assures its representativeness. To enable a comparative analysis, we exclude from the RELESSER group all deceased individuals and those lost for follow-up. However, this selection, given the well-known low mortality rate associated with pSS, could result in an infra-estimation of serious comorbidity in the SLE group as well as severity differences. In fact, as is shown in Supplementary Materials, the adjusted OR for cardiac failure and infection reached significance when these patients were included in the analysis, increasing the prevalence differences, and favoring SLE. Interestingly, no changes appeared in the OR of strokes.

In addition, it is plausible that patients with more severe pSS have higher levels of comorbidity, as has been observed in studies examining the prevalence of lymphoma (19). Despite the random nature of their selection, the number of severe pSS patients was not sufficient in our cohort to address this question. Nonetheless it is important to note that there are no universally accepted criteria for defining severe pSS, making it difficult to carry out this type of analysis.

In summary, we have shown that pSS patients have a consistently less serious CV and infectious comorbidity burden compared to those with SLE. In contrast, their risk of lymphoma exceeds that seen in SLE patients.

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Table 1: Sociodemographic differences (pSS vs. SLE without sSS)

	pSS	SLE	OR (95%CI)
Female sex, N (%)	416 (95.2)	2,268 (89.9)	0.45 (0.28 -0.71)
Caucasian, N (%)	408 (93.4)	2,274 (92.9)	-
Age at diagnosis, median (p25–p75)	50.2 (41.9-59.3)	32.0 (23.6-42.1)	1.08 (1.07-1.09)
Age at inclusion , median (p25–p75)	58.6 (50.0-69.9)	44.5 (35.6-54.9)	1.06 (1.06-1.07)
Disease duration , median (p25–p75)	10.4 (6.0-16.7)	12.7 (7.2-19.6)	0.98 (0.97-0.99)

pSS: primary Sjögren's syndrome; sSS: secondary SS; SLE: Systemic Lupus Erythematosus.

Table 2: pSS and SLE (without sSS) cumulative treatment comparisons

	pSS	SLE	OR (95%CI)
HCQ (current or ever) : N(%)	219 (50.9)	2,085 (87.5)	0.15 (0.12-0.19)
GC (current or ever) : N(%)	213 (49.4)	2,108 (87.9)	0.13 (0.11-0.17)
Current GC dosage *			
<= 10mg/daily : N(%)	114 (62.3)	151 (47.9)	ref
10-30 mg/daily : N(%)	29 (15.8)	102 (32.4)	0.38 (0.23-0.61)
> 30mg/daily : N(%)	40 (21.9)	62 (19.7)	0.85 (0.54-1.36)
Azathioprine: N(%)	45 (10.1)	753 (31.8)	0.25 (0.18-0.35)
Methotrexate : N(%)	57 (13.5)	407 (17.1)	0.75 (0.55-1.01)
Mycophenolate : N(%)	17 (3.9)	385 (16.3)	0.21 (0.13-0.35)
Ciclophosphamide : N(%)	13 (3.0)	521 (21.9)	0.11 (0.06-0.20)
Rituximab : N(%)	31 (7.3)	158 (6.6)	1.10 (0.74-1.63)

*Prednisone or equivalent

pSS: primary Sjögren's syndrome; sSS: secondary SS; SLE: Systemic Lupus Erythematosus.

HCQ: hydroxychloroquine; GC: glucocorticoids.

Table 3: Comparative prevalence of comorbidities (pSS vs. SLE without sSS): Results from logistic regression analysis

Comorbidities	pSS N (%)	SLE N (%)	Crude OR (95%CI)	OR adjusted* (95%CI)	specific adjustments **
Hypertension	112 (25.6)	673 (26.8)	0.94 (0.75-1.19)	0.50 (0.38-0.66)	-
Diabetes	28 (6.4)	106 (4.2)	1.54 (1.00-2.37)	0.79 (0.49-1.27)	-
Dyslipidemia	145 (33.2)	732 (30.2)	1.15 (0.92-1.43)	0.74 (0.58-0.94)	-
Heart failure	13 (2.9)	66 (2.64)	1.13 (0.62-2.07)	0.70 (0.37-1.33)	ND
Ischemic heart disease	4 (0.92)	63 (2.5)	0.36 (0.13-0.99)	0.27 (0.09-0.81)	GC, smoking HBP, dyslipidemia
Peripheral artery disease	14 (3.2)	48 (1.93)	1.68 (0.92-3.07)	0.98 (0.44-2.07)	GC, smoking HBP, dyslipidemia
Stroke	15 (3.4)	120 (4.8)	0.70 (0.41-1.22)	0.51 (0.27-0.96)	GC, smoking HBP, dyslipidemia
Any CV event	30 (6.8)	203 (8.0)	0.84 (0.57-1.26)	0.57 (0.35-0.93)	GC, smoking HBP, dyslipidemia
Fibromyalgia	64 (14.6)	129 (5.2)	3.10 (2.26-4.27)	2.43 (1.70-3.49)	ND
Osteoporotic fracture	37 (8.6)	139 (5.7)	1.56 (1.07-2.28)	0.94 (0.61-1.46)	GC
Smoking (any time)	110 (25.3)	951 (41.2)	0.33 (0.25-0.43)	0.36 (0.28-0.48)	-
Cancer (except lymphoma)	21 (4.8)	104 (4.11)	1.18 (0.73-1.91)	0.72 (0.43-1.21)	-
Lymphoma	7 (1.6)	10 (0.4)	4.10 (1.55-10.83)	4.41 (1.35-14.43)	IS, HCQ
Severe infection	44 (10.1)	403 (16.9)	0.55 (0.40-0.77)	0.85 (0.58-1.25)	GC, IS, HCQ

*OR pSS vs. SLE, adjusted just by sex, age and disease duration, if not otherwise stated in the right column

**further specific adjustments for each variable when applicable. ND: not done.

pSS: primary Sjögren's syndrome. sSS: secondary SS; SLE: Systemic Lupus Erythematosus. CV: cardiovascular;

HBP: high blood pressure; HCQ: hydroxychloroquine; GC: glucocorticoids; IS: immunosuppressors

Table 4: Comparative prevalence of comorbidities (pSS versus SLE , including patients with sSS)

Comorbidities	pSS N (%)	SLE N (%)	<i>p</i> value	OR (95%CI)	<i>p</i> value	OR adjusted*	specific adjust**
Hypertension,	112 (25.6)	800 (27.5)	0.410	0.91 (0.72-1.14)	< 0.001	0.51 (0.39-0.66)	-
Diabetes	28 (6.4)	127 (4.2)	0.066	1.49 (0.97-2.27)	0.416	0.82 (0.52-1.30)	-
Dyslipidemia	145 (33.2)	863 (30.6)	0.285	1.12 (0.90-1.39)	0.031	0.77 (0.61-0.98)	-
Heart failure	13 (2.9)	75 (2.6)	0.637	1.15 (0.64-2.10)	0.358	0.74 (0.40-1.40)	ND
Ischemic heart disease	4 (0.92)	74 (2.55)	0.044	0.35 (0.13-0.97)	0.021	0.28 (0.10-0.83)	GC, smoking HBP, Dyslipidemia
Peripheral artery disease	14 (3.2)	54 (1.9)	0.071	1.73 (0.95-3.15)	0.753	1.13 (0.53-2.38)	GC, smoking HBP, Dyslipidemia
Stroke	15 (3.4)	139 (4.8)	0.208	0.71 (0.41-1.21)	0.068	0.56 (0.30-1.04)	GC, smoking HBP, Dyslipidemia
Any CV event	30 (6.8)	238 (8.12)	0.366	0.83 (0.56-1.24)	0.040	0.61 (0.38-0.98)	GC, smoking HBP, Dyslipidemia
Fibromyalgia	64 (14.6)	186 (6.5)	<0.001	2.47 (1.82-3.35)	<0.001	1.98 (1.42-2.76)	ND
Osteoporotic fracture	37 (8.6)	192 (6.75)	0.064	1.30 (0.90-1.87)	0.517	0.87 (0.57-1.33)	GC
Smoking (any time)	110 (25.3)	1.088 (40.9)	<0.001	0.34 (0.26-0.44)	<0.001	0.39 (0.29-0.51)	-
Cancer (except lymphoma)	21 (4.8)	129 (4.4)	0.695	1.10 (0.69-1.76)	0.234	0.74 (0.45-1.22)	-
lymphoma	7 (1.6)	13 (0.4)	0.004	3.96 (1.55-10.11)	0.004	4.77 (1.56-14.75)	IS, HCQ
Severe infection	44 (10.1)	606 (18.5)	<0.001	0.51 (0.37-0.70)	0.214	0.79 (0.54-1.15)	GC, IS, HCQ

*OR pSS versus SLE, adjusted just by sex, age and disease duration, if not otherwise stated in the right column

**further specific adjust for each variable when applicable

pSS: primary Sjögren's syndrome. sSS: secondary SS; SLE: Systemic Lupus Erythematosus. CV: cardiovascular; HBP: high blood pressure; HCQ: hydroxychloroquine; GC: glucocorticoids; IS: immunosuppressors

Table 5: Comparative prevalence of comorbidities (pSS versus SLE without sSS but including all RELESSER dead patients)

Comorbidities	pSS N (%)	SLE N (%)	<i>p</i> value	OR (95%CI)	<i>p</i> value	OR adjusted*	specific adjust**
Hypertension,	112 (25.6)	891 (28.6)	0.112	0.86 (0.68-1.08)	< 0.001	0.46 (0.35-0.60)	-
Diabetes	28 (6.4)	149 (4.8)	0.02	1.61 (1.06-2.46)	0,376	0.81 (0.50-1.30)	-
Dyslipidemia	145 (33.2)	1101 (31.3)	0.435	1.09 (0.88-1.34)	0.075	0.84 (0.67-1.06)	-
Heart failure	13 (2.9)	127 (4.1)	0.220	0.72 (0.40-1.28)	0.015	0.47 (0.26-0.86)	ND
Ischemic heart disease	4 (0.92)	113 (3.6)	0.003	0.25 (0.09-0.67)	0.004	0.21 (0.07-0.60)	GC, smoking HBP
Peripheral artery disease	14 (3.2)	71 (2.3)	0.185	1.40 (0.79-2.51)	0.816	1.09 (0.53-2.27)	GC, smoking HBP
Stroke	15 (3.4)	178 (5.7)	0.045	0.58 (0.34-0.99)	0.077	0.57 (0.31-1.02)	GC, smoking HBP
Any CV event	30 (6.8)	315 (10.0)	0.036	0.66 (0.45-0.98)	0.009	0.54 (0.34-0.86)	GC, smoking HBP
Fibromyalgia,	64 (14.6)	153 (5.0)	<0.001	3.26 (2.39-4.45)	<0.001	2.41 (1.76-3.30)	ND
Osteoporotic fracture	37 (8.6)	187 (6.2)	0.353	3.41 (2.57-4.54)	0.714	0.92 (0.60-1.41)	GC
Smoking (any time)	110 (25.3)	1519 (48.3)	<0.001	0.25 (0.20-0.32)	<0.001	0.50 (0.40-0.64)	-
Cancer (except lymphoma)	21 (4.8)	151 (4.8)	0.791	1.00 (0.63-1.40)	0.073	0.66 (0.40-1.07)	-
lymphoma,	7 (1.6)	16 (0.5)	0.01	3.18 (1.30-7.78)	0.046	2.92 (1.02-8.32)	IS, HCQ
Severe infection	44 (10.1)	593 (20.0)	<0.001	0.42 (0.31-0.59)	0.028	0.66 (0.46-0.96)	GC, IS, HCQ

*OR pSS versus SLE, adjusted just by sex, age and disease duration, if not otherwise stated in the right column

**further specific adjust for each variable when applicable

pSS: primary Sjögren's syndrome. sSS: secondary SS; SLE: Systemic Lupus Erythematosus. CV: cardiovascular;

HBP: high blood pressure; HCQ: hydroxychloroquine; GC: glucocorticoids; IS: immunosuppressors