Characterization of a subset of patients with primary Sjögren’s syndrome initially presenting with C3 or C4 hypocomplementemia

Patricia Jordán-González¹, Ricardo Gago-Piñero¹, Noemí Varela-Rosario¹, Naydi Pérez-Ríos², Luis M. Vilá¹

Abstract

Objective: This study aimed to determine the association of C3 and C4 hypocomplementemia at the diagnosis of primary Sjögren’s syndrome (pSS) with clinical manifestations, disease activity, and disease damage.

Methods: A cross-sectional study was conducted in 94 Puerto Ricans with pSS. Patients were aged ≥21 years and met the 2012 American College of Rheumatology Classification Criteria for pSS. Demographic characteristics, health-related features, cumulative extraglandular manifestations, serologic tests at pSS diagnosis, comorbidities, disease activity (per European League Against Rheumatism Sjögren’s Syndrome Disease Activity Index [ESSDAI]), and pharmacologic therapy were determined. Serum C3 and C4 levels were measured at pSS diagnosis by immunoturbidimetry. Patients with and without hypocomplementemia were analyzed using bivariate and multivariate logistic regression analyses adjusted for age, sex, and disease duration.

Results: The mean age and disease duration of the study population were 52.4±12.4 years and 5.9±4.8 years, respectively; of the total study population, 94% were female. C3 and C4 hypocomplementemia were observed in 9.6% and 13.8% of the patients, respectively. In the multivariate analysis, C3 hypocomplementemia was associated with leukocytoclastic vasculitis, interstitial lung disease, higher SSDDI score, and exposure to rituximab. C4 hypocomplementemia was associated with leukocytoclastic vasculitis, interstitial lung disease, and higher ESSDAI and SSDDI scores.

Conclusion: In this population of patients with pSS, low C3 and C4 levels at diagnosis were associated with extraglandular manifestations such as vasculitis and interstitial lung disease, as well as disease activity and damage accrual. These results suggest that complements C3 and C4 have clinical and prognostic value in patients with pSS.

Keywords: Sjögren’s syndrome, C3 complement, C4 complement

Introduction

Primary Sjögren’s syndrome (pSS) is a progressive autoimmune disease characterized by lymphocytic infiltration primarily of the exocrine glands (1). Clinical presentation ranges from sicca symptoms to extraglandular manifestations such as musculoskeletal, pulmonary, renal, and nervous system involvement, among others (2). In contrast to other rheumatic autoimmune diseases such as systemic lupus erythematosus, the association of serologic markers with clinical features of pSS has not been well established, except for C3 and C4 hypocomplementemia, which has been identified as a risk factor for lymphoma (3). Few studies have shown that low serum C3 and C4 levels correlate with specific extraglandular manifestations such as vasculitis, disease activity, and damage accrual (4-6). It is likely that these serologic markers are not frequently used in this clinical setting because low C3 and C4 levels are found at diagnosis in only 1%-15% of patients with pSS and in about 20% during the course of the disease (7, 8). Nonetheless, those who present with C3 and C4 hypocomplementemia could represent a subset of patients with a poorer disease course and outcome. Hence, we sought to evaluate the association of low C3 and C4 levels at pSS diagnosis with clinical manifestations, disease activity, and disease damage.

Methods

Patient population

We performed a cross-sectional study in 94 Puerto Ricans with pSS evaluated from August 2014 to August 2017. Patients were adults (aged ≥21 years), and all met the 2012 American College of Rheumatology...
Classification Criteria for pSS (9). As stated in this classification, patients with the following conditions were excluded: secondary Sjögren’s syndrome, IgG4 disease, sarcoidosis, lymphoma, history of head and neck radiation, graft-versus-host disease, and infection with hepatitis C virus and human immunodeficiency virus. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (Approval Date: May 19, 2014; Approval Number: A6310114). Signed consent was waived because this research presented no more than minimal risk of harm to subjects, and involved no procedures for which written consent is normally required as the information gathered for this the study was obtained during routine medical visits and it was within standards of care for pSS patients.

Variables
Factors from the following domains were determined: demographic features, lifestyle behaviors, extraglandular manifestations, serologic markers, disease activity, disease damage, comorbidities, and pharmacologic profile. Age, gender, and disease duration (period between pSS diagnosis and study visit) were included in the demographic domain. Lifestyle behaviors such as alcohol intake (≥1 drink per day for women and ≥2 drinks per day for men), exercise (structured or planned physical activity at least 3 times per week), and tobacco use were noted at the study visit. At any time during the course of pSS, the presence of the following extraglandular manifestations was determined: arthralgia, arthritis, urticarial rash, major clinical manifestations such as leukocytoclastic vasculitis and interstitial lung disease (diagnosed by high-resolution chest computed tomography), autoimmune hepatitis (diagnosed by liver biopsy), renal tubular acidosis, anemia, leukopenia (<4,000/mm³), neutropenia (<1,500/mm³), lymphopenia (<1,000/mm³), thrombocytopenia (<100,000/mm³), and hypergammaglobulinemia. The following serologic markers were measured at the diagnosis: antinuclear antibodies, rheumatoid factor, anti-Ro and anti-La antibodies, and C3 and C4 complements. Serum C3 and C4 levels were measured by immunoturbidimetry. These levels were defined as low according to the standard laboratory parameters. Normal range for serum C3 and C4 was 80-160 mg/dL and 16-48 mg/dL, respectively.

Disease activity was determined at the study visit using the 2010 European League Against Rheumatism Sjögren’s Syndrome Disease Activity Index (ESSDAI) (10) and disease damage was determined using the Sjögren’s Syndrome Disease Damage Index (SSDDI) (11). Cumulative selected comorbidities and pSS pharmacologic treatments (muscarnic agonists, nonsteroidal anti-inflammatory drugs, corticosteroids, hydrochloroquine, and immunosuppressive drugs) were ascertained at the study visit.

Statistical analysis
Patients with and without low C3 and C4 levels were compared using Fisher’s exact test, Chi-square test, Student’s t test, and Mann-Whitney test, as appropriate. Factors that were significant in the bivariate analysis were entered into the multivariate logistic regression analyses adjusted for age, sex, and disease duration. Statistical significance was established at p<0.05. Statistical analysis was performed using the STATA v.15 (StataCorp; College Station, TX, USA).

Results
A total of 94 patients were studied, of whom 88 (93.6%) were females. The mean (standard deviation [SD]) age of the study population was 52.4 (12.4) years. The mean (SD) disease duration was 5.9 (4.8) years. At pSS diagnosis, low C3 and C4 levels were found in 9 (9.6%) and 13 (13.8%) patients, respectively. Moreover, 7 (7.4%) patients had both C3 and C4 hypocomplementemia.

Table 1 shows the demographic features, lifestyle behaviors, clinical manifestations, serologic tests, disease activity, and damage accrual in patients with and without hypocomplementemia. No significant differences were observed for age, gender, disease duration, and health-related behaviors between the study groups. Patients with low C3 levels were more likely to have leukocytoclastic vasculitis (44.4% vs. 8.2%, p=0.010), interstitial lung disease (33.3% vs. 12.9%, p=0.002), and higher SSDDI scores (2.2±2.2 vs. 0.5±0.9, p=0.002) than those with normal C3 levels. In contrast, leukocytoclastic vasculitis (38.5% vs. 7.4%, p=0.007), interstitial lung disease (23.1% vs. 1.2%, p=0.008), and higher ESSDAI (1.5±1.7 vs. 0.6±0.8, p=0.013) and SSDDI (2.0±2.2 vs. 0.4±0.76, p=0.003) scores were more commonly seen in patients with low C4 levels compared with those with normal levels.

Selected comorbid conditions are shown in Table 2. Patients with low C3 levels had asthma (33.3% vs. 7.1%, p=0.039) more frequently than those with normal C3 levels. No significant differences were found for other comorbidities. Patients with low C3 levels were more frequently exposed to rituximab treatment (22.2% vs. 2.4%, p=0.045) than those with normal C3 levels. No significant differences were found for other pharmacologic therapies (Table 3).

Table 4 depicts the multivariate logistic regression of features associated with low C3 and C4 levels. Low C3 levels were related to leukocytoclastic vasculitis (odds ratio [OR]: 9.53, 95% confidence interval [CI]: 3.13-30.30), interstitial lung disease (OR: 43.43, 95% CI: 3.15-536.80), SSDDI score ≥1 (OR: 3.11, 95% CI: 1.49-6.47), and rituximab therapy (OR: 112.63, 95% CI: 5.1-234.04). Low C4 levels were associated with leukocytoclastic vasculitis (OR: 5.41, 95% CI: 1.02-27.80), interstitial lung disease (OR: 40.87, 95% CI: 3.21-519.77), ESSDAI score ≥1 (OR: 1.86, 95% CI: 1.05-3.29), and SSDDI score ≥1 (OR: 2.71, 95% CI: 1.37-5.35).

Discussion
This study evaluated the relationship of C3 and C4 hypocomplementemia with extraglandular manifestations, disease activity, and disease damage in patients with pSS initially presenting with C3 or C4 hypocomplementemia. We found that low C3 and C4 levels seem to have a significant clinical and prognostic value in patients with pSS. Our data show that C3 and C4 hypocomplementemia are associated with major clinical manifestations such as leukocytoclastic vasculitis and interstitial lung disease and with damage accrual. C4 hypocomplementemia, but not C3, was also associated with disease activity.

Our study confirms the association of C3 and C4 hypocomplementemia with vasculitis (12). For example, in a Spanish cohort of patients with pSS, leukocytoclastic vasculitis was found to be the main histologic diagnosis in 95% of patients with vasculitis, and 49% of them had C3 and C4 hypocomplementemia (13). This association is not surprising because leukocytoclastic vasculitis is an immune complex disease; thus, complement fixation and consumption are expected.
Table 1. Demographic features, lifestyle behaviors, clinical manifestations, serologic tests, disease activity, and damage accrual in patients with pSS.

| Features                        | C3 complement levels | C4 complement levels |
|---------------------------------|----------------------|----------------------|
|                                 | Normal (n=85)       | Low (n=9)            | Normal (n=81)       | Low (n=13)            |
|                                 | Mean (SD)           | Mean (SD)           | Mean (SD)           | Mean (SD)           |
| Age, mean (SD) years            | 52.7 (12.6)         | 49.3 (10.3)         | 0.443               | 53.3 (12.4)         | 45.7 (12.4)         | 0.047               |
| Gender, % female                | 94.1                | 88.9                | 0.463               | 93.8                | 92.3                | 0.999               |
| Disease duration, mean years (SD)| 5.6 (4.2)           | 8.7 (8.4)           | 0.568               | 5.5 (4.2)           | 8.7 (7.2)           | 0.160               |
| Alcohol consumption             | 5.9                 | 11.1                | 0.463               | 4.9                 | 15.4                | 0.192               |
| Cigarette smoking               | 4.7                 | 0.0                 | 0.999               | 3.7                 | 7.7                 | 0.454               |
| Exercise                        | 28.2                | 33.3                | 0.713               | 27.2                | 38.5                | 0.510               |
| Arthralgia                      | 82.4                | 88.9                | 0.999               | 82.7                | 84.6                | 0.999               |
| Arthritis                       | 24.7                | 44.4                | 0.240               | 24.7                | 38.5                | 0.321               |
| Urticarial rash                 | 4.7                 | 22.2                | 0.100               | 4.9                 | 15.4                | 0.192               |
| Pure sensory neuropathy         | 17.7                | 44.4                | 0.078               | 21.0                | 15.4                | 0.999               |
| Mixed polyneuropathy            | 10.6                | 0.0                 | 0.593               | 11.1                | 0.0                 | 0.352               |
| Leukocytoclastic vasculitis     | 8.2                 | 44.4                | 0.010               | 7.4                 | 38.5                | 0.007               |
| Interstitial lung disease       | 1.2                 | 33.3                | 0.002               | 1.2                 | 23.1                | 0.008               |
| Autoimmune hepatitis            | 2.4                 | 0.0                 | 0.999               | 2.5                 | 0.0                 | 0.999               |
| Renal tubular acidosis          | 1.2                 | 0.0                 | 0.999               | 1.2                 | 0.0                 | 0.999               |
| Anemia                          | 37.7                | 22.2                | 0.480               | 34.6                | 46.2                | 0.536               |
| Leukopenia (<4,000/mm$^3$)      | 32.1                | 22.2                | 0.715               | 32.1                | 25.0                | 0.748               |
| Neutropenia (<1,500/mm$^3$)     | 7.1                 | 11.1                | 0.522               | 6.2                 | 16.7                | 0.222               |
| Lymphopenia (<1,000/mm$^3$)     | 26.2                | 33.3                | 0.698               | 25.0                | 38.5                | 0.325               |
| Thrombocytopenia (<100,000/mm$^3$) | 7.1             | 0.0                 | 0.999               | 6.2                 | 8.3                 | 0.574               |
| Hypergammaglobulinemia          | 28.2                | 11.1                | 0.436               | 24.7                | 38.5                | 0.321               |
| Antinuclear antibodies          | 84.3                | 77.8                | 0.637               | 83.7                | 83.3                | 0.999               |
| Rheumatoid factor               | 57.3                | 50.0                | 0.723               | 56.4                | 58.3                | 0.900               |
| Anti-Ro antibodies              | 85.9                | 77.8                | 0.618               | 86.4                | 76.9                | 0.403               |
| Anti-La antibodies              | 37.7                | 44.4                | 0.728               | 37.0                | 46.2                | 0.530               |
| Anti-Ro and anti-La antibodies  | 36.5                | 44.4                | 0.723               | 35.8                | 46.2                | 0.543               |
| ESSDAI                          |                      |                     |                     |                     |                     |                     |
| Activity index score, mean (SD) | 0.6 (0.9)           | 1.1 (1.5)           | 0.248               | 0.6 (0.8)           | 1.5 (1.7)           | 0.013               |
| Activity index score ≥1, %     | 42.4                | 66.7                | 0.290               | 39.5                | 76.9                | 0.012               |
| SSDDI                           |                      |                     |                     |                     |                     |                     |
| Damage index score, mean (SD)   | 0.5 (0.9)           | 2.2 (2.2)           | 0.002               | 0.5 (0.8)           | 2.0 (2.2)           | 0.003               |
| Damage index score ≥1, %        | 36.5                | 77.8                | 0.028               | 35.8                | 69.2                | 0.023               |

ESSDAI: European League Against Rheumatism Sjögren’s Syndrome Disease Activity Index; pSS: primary Sjögren’s syndrome; SD: standard deviation; SSDDI: Sjögren’s Syndrome Disease Damage Index.
We found that patients with C3 and C4 hypo-complementemia at diagnosis were more likely to have interstitial lung disease than those with normal complement levels. However, previous studies are conflictive regarding this association. In a multicenter cohort study of Chinese patients with pSS, hypocomplementemia was not found to be a risk factor for interstitial lung disease (14). Another study in Asian patients with pSS, did not find any differences in C3 and C4 levels in patients with and without interstitial lung disease (15). On the contrary, studies performed in populations from Spain, Argentina, and Italy have reported associations of C3 or C4 hypocomplementemia with interstitial lung disease in pSS (16-18). The discrepancies observed between these studies, including ours, could be related to geographic and ethnic factors.

In the bivariate analysis, we found an association between C3 hypocomplementemia and asthma. Interestingly, patients with pSS appear to have a higher risk of developing asthma compared with those without pSS (19). In fact, other investigators have reported the association of low C3 levels in the general population of patients who have asthma (20). It has been shown that C3a plays a critical role by regulating the interaction between mast cells and bronchial smooth muscle cells in lung inflammation in patients who have asthma (21). Therefore, the activation of complement cas-

### Table 2. Comorbid conditions in patients with pSS.

| Comorbidities, % | C3 complement levels | C4 complement levels |
|------------------|----------------------|----------------------|
|                  | Normal (n=85) | Low (n=9) | p  | Normal (n=81) | Low (n=13) | p  |
| Hypertension     | 37.7         | 44.4     | 0.728 | 40.7         | 23.1      | 0.224 |
| Type 2 diabetes mellitus | 12.9     | 0.0      | 0.592 | 13.6         | 0.0       | 0.352 |
| Dyslipidemia     | 36.5         | 11.1     | 0.160 | 38.3         | 7.7       | 0.054 |
| Overweight/obesity (BMI ≥25.0) | 66.2     | 55.6     | 0.713 | 65.7         | 61.5      | 0.761 |
| Coronary artery disease | 4.7      | 0.0      | 0.999 | 4.9          | 0.0       | 0.999 |
| Hypothyroidism   | 32.9         | 44.4     | 0.484 | 34.6         | 30.8      | 0.999 |
| Asthma           | 7.1          | 33.3     | 0.039 | 7.4          | 23.1      | 0.107 |
| Osteoarthritis   | 42.4         | 44.4     | 0.999 | 45.7         | 23.1      | 0.126 |
| Osteoporosis     | 12.9         | 33.3     | 0.129 | 16.1         | 7.7       | 0.683 |
| Fibromyalgia     | 18.8         | 0.0      | 0.349 | 19.8         | 0.0       | 0.115 |
| Depression       | 25.9         | 33.3     | 0.696 | 25.9         | 30.8      | 0.740 |
| Headaches        | 5.9          | 11.1     | 0.463 | 6.2          | 7.7       | 0.999 |
| Peptic ulcer disease/gastritis | 22.4 | 0.0      | 0.196 | 21.0         | 15.4      | 0.999 |
| Infections (any cause) | 27.1 | 33.3 | 0.704 | 25.9         | 38.5      | 0.339 |
| Neoplasia        | 7.1          | 0.0      | 0.999 | 4.9          | 16.7      | 0.171 |

BMI: body mass index; pSS: primary Sjögren’s syndrome.

### Table 3. Pharmacologic treatment in patients with pSS.

| Medications, % | C3 complement levels | C4 complement levels |
|----------------|----------------------|----------------------|
|                | Normal (n=85) | Low (n=9) | p  | Normal (n=81) | Low (n=13) | p  |
| Pilocarpine    | 8.4          | 11.1     | 0.576 | 7.5         | 16.7      | 0.279 |
| Cevimeline     | 44.7         | 33.3     | 0.727 | 44.4        | 38.5      | 0.686 |
| Cyclosporine (ophthalmic) | 27.1 | 33.3 | 0.704 | 29.6        | 15.4      | 0.504 |
| NSAIDs         | 48.2         | 55.6     | 0.737 | 50.6        | 38.5      | 0.416 |
| Prednisone     | 31.8         | 55.6     | 0.265 | 30.9        | 53.9      | 0.123 |
| Hydroxychloroquine | 89.4 | 77.8 | 0.283 | 87.7        | 92.3      | 0.999 |
| Methotrexate   | 7.1          | 12.5     | 0.479 | 6.2         | 16.7      | 0.222 |
| Azathioprine   | 4.7          | 11.1     | 0.402 | 4.9         | 7.7       | 0.533 |
| Rituximab      | 2.4          | 22.2     | 0.045 | 2.5         | 15.4      | 0.091 |

NSAIDs: Nonsteroidal anti-inflammatory drugs; pSS: Primary Sjögren’s syndrome.
cide is fundamental in the pathophysiology of asthma. On the contrary, patients with pSS may present with asthmatic symptoms that in many instances are secondary to small airway disease, frequently falsely interpreted as bronchial asthma (22, 23). Based on the cohort and case-control studies, small airway disease is the most common respiratory manifestation in pSS (22, 23). To the best of our knowledge, there are no previous studies evaluating the association of C3 hypocomplementemia in patients who have asthma and are suffering from pSS. We do not have an explanation for these results other than speculate that the association with C3 hypocomplementemia could be related to pSS and/or asthma itself; thus, further investigation is warranted.

As previously reported by our group, we found an association between C3 and C4 hypocomplementemia and damage accrual (4). Similarly, in a cohort study of Italian patients with pSS, low C4 levels were associated with systemic damage (24). In agreement with other studies, we also found that low C4 levels are associated with higher disease activity (25). Thus, our results confirm the prognostic value of these serologic markers in terms of disease activity and damage in pSS.

Our patients with low C3 levels were more likely to receive therapy with rituximab. This finding is expected because of the relationship of hypocomplementemia with interstitial lung disease. In a Spanish cohort of patients with pSS, more than 20% of patients with severe systemic disease received rituximab as an immunosuppressive treatment (26). Furthermore, in a French registry, researchers reported that rituximab was effective for patients with pSS presenting with systemic manifestations (27). Specifically, adequate clinical response was observed in 78% of patients who presented with pulmonary involvement. Rituximab has been frequently used off-label in patients with rheumatic diseases complicated with interstitial lung disease, including pSS.

This study had some limitations that need to be highlighted. This was a cross-sectional study and we had to take into consideration the disadvantages inherent of its design. We had a small number of patients with pSS; consequently, the association with other manifestations that occur in a relatively low frequency could not be fully ascertained. For example, we could not confirm the relationship with lymphoma because in our study, only one patient had this lymphoproliferative disorder. The low number of patients also limited the multivariate analyses and induced large CIs. Our population had a relatively short disease duration (nearly 6 years); therefore, the association with comorbidities that occur in the long term, such as cardiovascular events, could not be determined. Additionally, disease activity was only evaluated at the study visit and not during the course of the disease. Finally, serum C3 and C4 levels were not measured throughout the disease course. We do not know if the immunomodulatory or immunosuppressive therapy would have an effect on these levels or if follow-up levels could be related or not with the clinical associations observed with hypocomplementemia at pSS diagnosis. Nonetheless, because C3 and C4 levels were measured at diagnosis before pSS therapy, they appear to have a prognostic value for the development of systemic involvement.

We conclude that patients with pSS presenting with low serum C3 and C4 levels at diagnosis may represent a subset of patients with a worse clinical outcome when compared with those with normal complement levels. The patients who presented with low levels of C3 and C4 at diagnosis were more likely to have small vessel vasculitis and interstitial lung disease and had higher disease activity and damage accrual. Our results suggest that clinicians should evaluate serum C3 and C4 levels in patients with pSS to determine those at high risk for disease progression and damage.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (Approval Date: May 19, 2014; Approval Number: A6310114).

**Informed Consent:** Informed consent was not obtained due to the nature of this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - P.J.G., L.M.V.; Design - P.J.G., L.M.V.; Supervision - L.M.V.; Resources - L.M.V.; Materials - R.G.P., N.V.R., L.M.V.; Data Collection and/or Processing - P.J.G., N.P.R., R.G.P., L.M.V., N.V.R.; Analysis and/or Interpretation - P.J.G., N.P.R., R.G.P., L.M.V., N.V.R.; Literature Search - P.J.G., L.M.V.; Writing Manuscript - P.J.G., L.M.V., Critical Review - P.J.G., N.P.R., R.G.P., L.M.V., N.V.R.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Financial Disclosure:** The authors declared that this study was supported by the National Institute on Minority Health and Health Disparities and the National Institute of Allergy and Infectious Diseases of the National Institute of Health under award number U54MD007587.

**References**

1. Rischmueller M, Tieu J, Lester S. Primary Sjögren’s syndrome. Best Pract Res Clin Rheumatol 2016; 30: 189-220. [Crossref]
2. Malladi AS, Sack KE, Shiboski SC, Shiboski CH, Baer AN, Banushree R, et al. Primary Sjögren’s syndrome: characteristic clinical features and outcomes among a diverse spectrum of patients. J Rheumatol 2016; 43: 1578-86. [Crossref]

---

**Table 4. Logistic regression of characteristics associated with C3 and C4 hypocomplementemia in patients with pSS.**

| Characteristics                  | Low C3 complement levels OR (95% CI) | Low C4 complement levels OR (95% CI) |
|----------------------------------|-------------------------------------|-------------------------------------|
|                                  | Unadjusted                         | Adjusted                            |
|                                  |                                    |                                     |
| Leukocytoclastic vasculitis      | 8.91 (1.94-40.98)                  | 9.53 (1.73-52.48)                   |
| Interstitial lung disease        | 11.86 (1.44-97.44)                  | 43.43 (3.51-536.80)                 |
| ESSDAIb                          | -                                   | -                                   |
| SSDDI score                      | 6.10 (1.19-31.19)                  | 3.11 (1.49-6.47)                    |
| Asthmaa                          | 6.58 (1.31-33.11)                  | 5.00 (0.76-33.14)                   |
| Rituximabb                       | 11.86 (1.44-97.44)                  | 112.63 (5.51-2,304.04)              |

**Notes:**

a Variables adjusted for sex, age, and disease duration.

b Logistic regression model was not performed for ESSDAI with low C3 levels and asthma and rituximab with low C4 levels because there was no statistical significance in the bivariate analyses.

CI: confidence interval; ESSDAI: European League Against Rheumatism Sjögren’s Syndrome Disease Activity Index; OR: odds ratio; pSS: Primary Sjögren’s syndrome; SSDDI: Sjögren’s Syndrome Disease Damage Index.
syndrome as a systemic disease: A study of participants enrolled in an international Sjögren’s syndrome registry. Arthritis Care Res (Hoboken) 2012; 64: 911-8. [Crossref]

3. Ramos-Casals M, Brito-Zerón P, Yagüe J, Akasbi M, Bautista R, Ruano M, et al. Hypocomplementemia as an immunological marker of morbidity and mortality in patients with primary Sjögren’s syndrome. Rheumatology (Oxford) 2005; 44: 89-94. [Crossref]

4. Jordán-González P, Gago-Piñero R, Vázquez-Sanabria I, Pérez-Ríos N, Vilá LM. Factors associated with disease damage in puer-to-ricans with primary sjögren syndrome. J Clin Rheumatol 2019 Mar 12. doi: 10.1097/RHU.0000000000001023. [Epub ahead of print]. [Crossref]

5. García-Carrasco M, Mendoza-Pinto C, Jiménez-Hernández C, Jiménez-Hernández M, Nava-Zavala A, Riebeling C. Serologic features of primary Sjogren’s syndrome. Clinical and prognostic correlation. Int J Clin Rheum Dis 2012; 7: 651-9. [Crossref]

6. Ramos-Casals M, Brito-Zerón P, Solans R, Camps MT, Casanovas A, Sopeña B, et al. Systemic involvement in primary Sjögren’s syndrome evaluated by the EULAR-SS disease activity index: Analysis of 921 Spanish patients (GEAS-SS Registry). Rheumatology (Oxford) 2014; 53: 321-31. [Crossref]

7. Skopoulou FN, Dafni U, Ioannisidis JP, Moutsopoullos HM. Clinical evolution, and morbidity and mortality of primary Sjögren’s syndrome. Semin Arthritis Rheum 2000; 29:296-304. [Crossref]

8. Horvath IF, Szanto A, Papp G, Zehner M. Clinical course, prognosis, and cause of death in primary Sjögren’s syndrome. J Immunol Res 2014; 2014: 647507. [Crossref]

9. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. Sjögren’s International Collaborative Clinical Alliance (SICCA) Research Groups. American College of Rheumatology classification criteria for Sjogren’s syndrome: A data-driven, expert consensus approach in the Sjögren’s International Collaborative Clinical Alliance cohort. Arthritis Care Res (Hoboken) 2012; 64: 475-87. [Crossref]

10. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al. EULAR Sjögren’s Task Force. EULAR Sjogren’s syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren’s syndrome. Ann Rheum Dis 2010; 69: 1103-9. [Crossref]

11. Vitali C, Palombi G, Baldini C, Benucci M, Bombardieri S, Covelli M, et al. Sjögren’s Syndrome Disease Damage Index and disease activity index: Scoring systems for the assessment of disease damage and disease activity in Sjögren’s syndrome, derived from an analysis of a cohort of Italian patients. Arthritis Rheum 2007; 56: 2223-31. [Crossref]

12. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, et al. GEMESS Study Group. Primary Sjögren syndrome in Spain: Clinical and immunologic expression in 1010 patients. Medicine (Baltimore) 2008; 87: 210-9. [Crossref]

13. Ramos-Casals M, Anaya JM, García-Carrasco M, Rosas J, Bové A, Claver G, et al. Cutaneous vasculitis in primary Sjögren’s syndrome: Classification and clinical significance of 52 patients. Medicine (Baltimore) 2004; 83: 96-106. [Crossref]

14. Liu Z, Li M, Wang Q, Zhao Y, Xu D, Zeng X. The risk factors and prognosis of interstitial lung disease associated with primary Sjögren’s syndrome: A multi-center cohort study [abstract]. Arthritis Rheumatol 2018; 70 (suppl 10). 2020 Oct 18. Available from: https://acrabstracts.org/abstract/the-risk-factors-and-prognosis-of-Interstitial-lung-disease-associated-with-primary-sjogren-sindrome-a-multi-center-cohort-study/. [Crossref]

15. Wang Y, Hou Z, Qiu M, Ye Q. Risk factors for primary Sjögren syndrome-associated interstitial lung disease. J Thorac Dis 2018; 10: 2108-17. [Crossref]

16. Paixa X, Bosch JA, Pallisa E, Martinez-Valle F, Ramontol M, Bujan S, et al. AB0548 Interstitial Lung Disease (ILD) in primary Sjögren syndrome: Clinical, immunological and radiological features and outcome. Ann Rheum Dis 2014; 73: 987. [Crossref]

17. Manfredi A, Sebastiani M, Cerri S, Cassone G, Bellini P, Casa GD, et al. Prevalence and characterization of non-sicca onset primary Sjögren syndrome with interstitial lung involvement. Clin Rheumatol 2017; 36: 1261-8. [Crossref]

18. Velez SD, Zazzetti F, Galván LS, Gallacher A, Maye M, Rivero M, et al. THU0028 Interstitial lung disease in primary Sjögren syndrome: A Gessor analysis. Ann Rheum Dis 2014; 73(Suppl 2): 186. [Crossref]