

Concise report

Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients

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Abstract

Objective. The aims of this study were to describe the clinical presentation of primary SS (pSS) in a large cohort of patients by assessing the prevalence of the patient subgroups at high risk for severe extraglandular manifestations and to explore the influence of the patients' serological profile on disease severity and on immunosuppressive drug utilization.

Methods. Cumulative demographic, clinical, serological, histological and therapeutic data of 1115 pSS patients were retrospectively evaluated. Independent serological markers for glandular and extraglandular disease manifestations were identified by logistic regression.

Results. The cohort included 1115 (1067 female, 48 male) pSS patients. Severe extraglandular manifestations were detectable in 15% of the patients and were represented by active synovitis (11%), axonal sensory-motor neuropathy (2%), severe leucocytopenia (14%), cutaneous vasculitis (6%) and non-Hodgkin's lymphoma (4.5%). We found that low C3/C4, hypergammaglobulinaemia, RF and cryoglobulinaemia were markers of severity for pSS. According to the number of serological variables, the patients were subdivided into three distinct groups: favourable (no serological markers), intermediate (one serological marker) and poor (two or more serological markers). In comparison with the other two patient groups, pSS patients presenting with two or more adverse determinants had a higher frequency of severe visceral disease complications and required more aggressive therapeutic interventions.

Conclusion. This study confirmed that the prevalence of the pSS high-risk subset for severe systemic manifestations is ~15%. Serological markers might help in the early identification of patients who are candidates to receive more aggressive treatments.

Key words: Sjögren's syndrome, epidemiology, disease severity.

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Introduction

Primary SS (pSS) is a complex systemic autoimmune disease primarily characterized by a focal chronic inflammation of the salivary and lachrymal glands; however, a certain percentage of patients might also develop severe extraglandular disease manifestations [1]. Thus the spectrum of pSS can vary from a benign slowly progressive autoimmune exocrinopathy to a heterogeneous potentially

life-threatening systemic disorder also characterized by an increased risk for non-Hodgkin's lymphoma (NHL) [1, 2]. Recently the availability of novel biologic agents [3] has made it increasingly important to accurately assess the exact prevalence of so-called high-risk patients who are candidates to receive more aggressive treatments [1]. Moreover, great interest has arisen in identifying serological markers of severity for pSS that might help to improve the stratification of pSS patients in clinical practice. To date, a number of clinical and serological features have been linked with pSS severity [1, 4, 5]. However, all these markers have appeared of limited value in isolation and the impact of their combination with one another on pSS clinical presentation and long-term outcomes has scarcely been investigated in large cohorts of patients in real life.

This study was therefore aimed at describing the clinical and serological features of a cohort of 1115 patients with pSS in order to assess the prevalence of high-risk patient subgroups and the influence of the patient's serological profile on disease severity and treatment. More specifically, we elaborated a stratification model, based on a combination of different markers of disease severity, that might represent a step forward in personalized medicine for pSS.

Patients and methods

Study design and study population

We conducted an observational, retrospective, cross-sectional multicentre study involving four Italian reference centres with substantial experience in the management of pSS. The case records of 1115 patients with a diagnosis of pSS were reviewed. All patients fulfilled four or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993 and 926/1115 also satisfied the American-European Consensus Group (AECG) 2002 criteria. Patients with a potentially associated defined CTD (i.e. RA, SLE) [6] or overlap syndromes (i.e. patients with ACAs and/or patients with RP and capillaroscopy suggestive for scleroderma pattern [7, 8]) were excluded. Data collected included (i) age at diagnosis (i.e. when the patient fulfilled the classification criteria), (ii) age at inclusion in the study, (iii) cumulative clinical and immunological features during disease evolution (from the diagnosis), including presence of dry eyes/mouth, ocular test results, parotid enlargement and signs or symptoms of extraglandular involvement that were defined according to previous studies [9–13]: active articular involvement (arthralgias, i.e. appearance or worsening of joint pain accompanied by morning stiffness >30 min, and arthritis, i.e. the presence of synovitis), interstitial lung disease (confirmed by imaging or an altered pattern on pulmonary function studies), RP, skin vasculitis (palpable purpura and/or rash with limited cutaneous vasculitis involving <18% of the body surface area and diffuse cutaneous vasculitis involving >18% of the body surface area), peripheral neurological involvement (sensory or motor peripheral neuropathy) diagnosed

either by electrophysiology or biopsy, myositis (i.e. active muscular involvement proven by abnormal creatine kinase, abnormal EMG or biopsy, excluding weakness due to corticosteroid; the presence of myositis was considered in the spectrum of pSS whenever these signs and symptoms occurred during the follow-up, long after the diagnosis of the disease had been established) and renal involvement (persistent proteinuria >0.5 g/day, tubular acidosis, interstitial nephritis, glomerulonephritis). Among laboratory abnormalities, information was collected on cytopenia with neutropenia (<1500/mm³), and/or anaemia (haemoglobin <12 g/dl), and/or thrombocytopenia (<150 000/mm³) or lymphopenia (<1000/mm³), low levels of C3 (<90 mg/dl) and C4 (<20 mg/dl) by nephelometry and hypergammaglobulinaemia (IgG >16 g/l), thyroid function and hepatitis C or B seropositivity.

Statistical analysis was based on the serological test results retrieved from the lab records of the participating rheumatology centres at diagnosis and not prospectively reassessed in a centralized lab. Immunological tests included ANA determined by IIF assay on HEp-2 cells (a titre ≥1.160 was considered positive), RF detected by nephelometry and cryocrit level measured as a percentage of packed cryoglobulins after cold centrifugation of the serum, as previously described [14]. Regarding the antibodies to the extractable nuclear antigens Ro/SSA and La/SSB, the four Italian rheumatology centres utilized either commercial kits for the ELISA tests locally validated and/or counter-immunoelectrophoresis. The counter-immunoelectrophoresis was performed as previously described [15]. Anti-Ro60 and Ro52 antibodies were detected by a fluorescence enzyme immunoassay employing human recombinant antigens (Thermo Fisher Scientific, Waltham, MA, USA). The ELISA results were defined as positive or negative according to the manufacturer's instructions.

The severity of the disease clinical manifestations was assessed using the European League Against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) glossary [13]. All patients gave informed consent for all procedures, which were carried out with local ethics committee (Comitato Etico per la Sperimentazione Clinica dei Medicinali, Azienda Ospedaliero-Universitaria Pisana) approval. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Chi-square, analysis of variance (ANOVA) and logistic regression were performed. Patients with missing data were excluded from the respective analysis. Bonferroni correction was used for multiple comparisons. Statistical analysis was carried out using SPSS 13 (SPSS, Chicago, IL, USA).

Results

Patients' characteristics

The cohort consisted of 1115 (1067 female, 48 male) pSS patients with a mean age at diagnosis of 51.6 years (s.d. 13.8) and a mean follow-up of 5.8 years (s.d. 6.5).

All the patients included satisfied the European classification criteria for pSS, while the AECG criteria were fulfilled in 926/1115 cases. The diagnosis was supported by a minor salivary gland biopsy in 708/1115 patients with a positive focus score ($FS \geq 1$) detected in 81.5% (577/708) of the cases. Patients' demographic, clinical and serological features are compared to the largest cohorts from the literature in Table 1 [9–12, 16]. Visceral systemic extraglandular pSS features were detectable in 520/1115 patients (46.6%), while the remaining 230/1115 (20.6%) presented only sicca symptoms. Generally the extraglandular manifestations presented by the patient cohort were mild, including arthralgias, RP, modest autoimmune cytopenia, limited cutaneous vasculitis, mild to moderately active pure sensory axonal polyneuropathy and mild to moderately active pulmonary involvement with radiological or high-resolution CT (HRCT) evidence of interstitial lung disease and normal or slightly abnormal lung function tests generally indicating a restrictive pattern [i.e. 70% with a carbon monoxide diffusing capacity (DLCO) >40% or 80% with a forced vital capacity (FVC) >60%]. Obstructive small airway physiological abnormalities were also observed in ~1.2% of the patients. The most frequent HRCT findings that we detected were ground-glass attenuation (2.3%), reticular pattern/small nodules (1.8%), bronchiectasis (1.3%) and honey-combing (0.3%). Severe extraglandular manifestations requiring immunosuppressive drugs were detected in 15% of the patients and were mostly represented by active synovitis (11.0%), axonal sensory-motor neuropathy (2.0%), severe neutropenia or lymphopenia (14.0%) and diffuse purpura or ulcers related to cutaneous vasculitis (6.0%). A minority of patients presented tubular acidosis with or without renal failure (1.0%) or glomerular involvement with proteinuria and histology findings indicating mesangial/mesangioproliferative chronic glomerulonephritis (0.7%), myositis (0.5%) or highly active cerebral vasculitis with cerebrovascular accident or transient ischaemic attack (0.5%) and transverse myelitis (0.2%). Finally, 50 cases of NHL were documented with an overall prevalence of 4.5%. Mucosa-associated lymphoid tissue NHL of the salivary glands constituted the majority of NHL subtypes, followed by diffuse large B cell lymphomas and nodal marginal zone lymphomas.

Impact of serological biomarkers on pSS severity

We identified independent risk factors associated with each single pSS extraglandular manifestation (see supplementary Table S1, available at *Rheumatology* Online). Younger age at diagnosis and longer disease duration were generally associated to severe systemic pSS manifestations. We identified the following pSS serological biomarkers as markers of disease severity: low levels of C3/C4; RF positivity; hypergammaglobulinaemia and cryoglobulins, which were more frequently observed in patients with salivary gland enlargement; skin vasculitis; and renal, neurological and haematological involvement, including the cases of NHL. In contrast, patients with anti-Ro/SSA positivity presented a higher frequency of

leucocytopenia compared with anti-Ro/SSA-negative patients. Similarly, patients with anti-La/SSB were distinguished by a higher prevalence of pericarditis when compared with anti-La/SSB-negative patients.

In order to further explore the impact of serology on pSS clinical presentation and treatment, we stratified the patients according to the number of the adverse laboratory results into three categories: favourable ($n=0$ serological markers), intermediate ($n=1$) and poor ($n \geq 2$) (Table 2). We found that in comparison with the other two patient groups, pSS patients included in the poor group had a higher frequency of severe visceral disease manifestations, including NHL. We consistently documented a significant increase in the utilization of immunosuppressive drugs and corticosteroids in these patients. In contrast, patients without any adverse serological markers satisfied less frequently the AECG criteria and were distinguished by a benign sicca-limited disease course over the follow-up (Table 2). Intriguingly, the patients in the intermediate group compared with the favourable group still showed a greater number of extraglandular pSS manifestations requiring immunosuppressive drugs.

Discussion

This study describes the prevalence of pSS clinical phenotypes in a large cohort of patients focusing, in particular, on the impact of serological abnormalities on the severity of the disease presentation and on the consequent requirement of aggressive treatment interventions. Overall, in line with the existing literature, the results of this study confirmed that the clinical course of pSS is characterized by significant interpatient heterogeneity [9–12, 16]. In the present study, severe extraglandular manifestations were observed in 15% of the patients, consistent with the results of the larger cohorts in the literature, which reported an overall prevalence of severe systemic disease features in ~10–20% of pSS patients [9–12, 16]. We also found that the frequency of NHL in our cohort was 4.6%, in line with the most recent studies published by Martel *et al.* [16], Solans-Laqué *et al.* [17] and Voulgarelis *et al.* [18], who reported an overall prevalence of lymphoma ranging from 4 to 9% in pSS.

Since severe pSS extraglandular complications generally occurred late in the disease course [4, 18], in this study we tried to identify any potential serological determinants of outcome for pSS. It has been previously reported that low C3 and C4 levels, cryoglobulins, monoclonal paraproteinaemia, anti-Ro/SSA, anti-La/SSB, RF and hypergammaglobulinaemia represent poor prognostic serological factors in pSS associated with lymphoma and severe extraglandular features [1, 5, 17, 18]. In this study, we verified the statistical association between the most severe disease manifestations and single laboratory abnormalities. In addition, some interesting information has emerged from the analysis of our data. First, we found that the positivity for anti-Ro/SSA and anti-La/SSB had a limited poor prognosis value, especially for lymphoproliferative complications. This observation is

TABLE 1 Patients' demographic, clinical and serological features

	Study cohort	Pertovaara <i>et al.</i> , 2001 [9]	Garcia-Carrasco <i>et al.</i> , 2002 [11]	Alamanos <i>et al.</i> , 2006 [10]	Ramos-Casals <i>et al.</i> , 2008 [19]	Martel <i>et al.</i> , 2011 [16]
Patients, <i>n</i>	1115	110	400	422	1010	445
Female	1067 (95.7)	107 (97)	373 (93)	402 (95)	937 (93)	400 (90)
Age at diagnosis, mean (s.d.), years	51.6 (13.8)	62 (13)	52.7 (0.85)	55.4 (12.5)	53 (0.48)	53.6 (1.4)
Age at inclusion, mean (s.d.), years	57.5 (13.7)	—	58.7 (0.72)	—	58.7 (0.46)	—
Follow-up, mean (s.d.), years	5.8 (6.5)	—	—	—	6 (0.3)	—
Xerostomia	1033 (92.6)	97 (88)	390 (98)	—	975 (96)	371 (86)
Xerophthalmia	1054 (94.5)	86 (72)	371 (93)	—	968 (96)	380 (86)
Salivary glands enlargement, <i>n</i> (%)	346 (31.0)	50 (46)	73 (18)	110 (26)	269 (27)	113 (23)
Ocular tests positive	982 (88.1)	—	351 (95)	422 (100)	398 (94)	373 (85)
Arthralgias	683 (61.3)	82 (75)	147 (37)	165 (39)	490 (48)	222 (50)
Arthritis	123 (11)	24 (22)	—	—	150 (15)	—
RP	239 (21.4)	55 (50)	62 (16)	146 (34.6)	187 (18)	189 (42)
Lung involvement	60 (5.4)	—	37 (9)	—	112 (11)	55 (12)
PNS involvement	59 (5.3)	23 (21)	29 (7)	—	110 (11)	70 (16)
Skin involvement	106 (9.5)	22 (20)	47 (12)	20 (4.7)	91 (9)	70 (16)
Lymphoma	50 (4.5)	—	—	—	—	18 (4)
ANA positive, <i>n</i> (%)	941 (84.4)	—	288 (74)	397 (94)	859 (85)	347 (78)
Anti-Ro/SSA	762 (68.3)	—	153 (40)	203 (50.5)	518 (52)	221 (48)
Anti-La/SSB	410 (36.8)	—	102 (26)	160 (40)	343 (34)	139 (31)
RF positive	582 (52.2)	—	146 (38)	136 (32.2)	467 (48)	184 (41)
Cryoglobulinaemia positive	59 (5.3)	—	27 (9)	107 (28)	62 (10)	68 (15)
Low C3	176 (15.8)	—	10 (3)	—	67 (9)	—
Low C4	124 (11.1)	—	23 (8)	—	66 (9)	—
Hypergammaglobulinaemia	530 (47.5)	—	—	—	—	225 (50)

All values are *n* (%) unless stated otherwise. Ocular tests positive: positivity of Schirmer's test and/or Rose Bengal/Green Lissamine staining; PNS: peripheral nervous system.

TABLE 2 Impact of serological markers of disease severity on pSS clinical presentation and treatment

Variable	Favourable, no markers (n = 469)	Intermediate, 1 marker (n = 427)	Poor, > 1 marker (n = 219)	P-value
AECG criteria	364 (77.6)	372 (87.1)	190 (86.8)	0.000
Salivary gland enlargement	106 (22.6)	150 (35.2)	90 (41.1)	0.000
Purpura	15 (3.2)	35 (8.3)	56 (25.7)	0.000
Kidney	2 (0.4)	12 (2.8)	10 (4.6)	0.001
Haematological manifestations	88 (19)	152 (35.6)	118 (54)	0.000
Lung	20 (4.3)	21 (4.9)	19 (8.7)	0.05
Peripheral nervous system	21 (4.5)	18 (4.2)	20 (9.1)	0.01
Lymphoma	9 (1.9)	10 (2.3)	31 (14.2)	0.000
Anti-Ro/SSA	239 (51.5)	336 (79.4)	187 (85.4)	0.000
Anti-La/SSB	96 (20.7)	200 (47.3)	114 (52.1)	0.000
Focus score ≥ 1	240 (77.9)	226 (82.2)	111 (88.8)	0.03
Glucocorticoids	168 (36.3)	166 (39.1)	104 (47.9)	0.01
Immunosuppressive drugs	42 (9.3)	62 (14.7)	69 (30.1)	0.0001

All values are n (%). Markers of severity for pSS included in the model: low C3/C4, hypergammaglobulinaemia, cryoglobulins and RF positivity. AECG: American-European Consensus Group.

particularly intriguing considering the controversy that has recently arisen regarding pSS classification criteria and anti-Ro/SSA antibodies as a mandatory criterion for pSS diagnosis [19, 20]. It is to be stressed, however, that the value of the comparison between our data and the existing literature might be hampered by the use of different methods of detection of these autoantibodies. In addition, in the present study, data on the specificity of anti-Ro/SSA (i.e. the 60 kDa SSA/Ro target antigen or the 52 kDa target) were available only in a minority of the patients and thus their clinical value will be the objective of a future centralized prospective study.

The second original aspect of our study was that, given that biomarkers may be of limited relevance in isolation, we examined the significance of a combination of the identified markers of severity in the prognostic stratification of pSS and found that the higher the number of laboratory abnormalities that the patient presented, the higher the prevalence of pSS systemic manifestations and complications were over the follow-up. Patients with two or more serological adverse biomarkers were more prone to develop severe disease manifestations and NHL over the follow-up and consequently required a more aggressive treatment.

In conclusion, even if pSS is generally a benign systemic disorder, severe systemic manifestations might occur in about one-fifth of patients. Overall, our results suggest that the subset of patients at high risk of systemic complications is specifically characterized by an active serological profile suggestive for B cell chronic activation. Therefore, in clinical practice, serological markers of disease severity should be taken into account in the management of pSS. Patients presenting two or more laboratory abnormalities should be more closely monitored and be more deserving candidates for early aggressive immunosuppressive drugs. Undoubtedly our findings should be validated in prospective longitudinal cohort

studies. However, considering the large amount of data collected and the inclusion in the stratification model of well-known markers of disease severity, this study might provide a solid body of information on the different clinical and serological faces of pSS and its subsets, thus representing a promising starting point towards individualized medicine for the disease.

Rheumatology key messages

- Severe systemic manifestations might occur in about one-fifth of Italian patients with primary SS.
- Patients with primary SS and signs of B cell activation may deserve aggressive treatment.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

- 1 Skopouli FN, Dafni U, Ioannidis JP *et al*. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. *Semin Arthritis Rheum* 2000;29:296–304.
- 2 Quartuccio L, Salvin S, Fabris M *et al*. BLYS upregulation in Sjögren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal

- expansion in the salivary glands. *Rheumatology* 2013;52: 276–81.
- 3 Bowman SJ. Biologic therapies in primary Sjogren's syndrome. *Curr Pharm Biotechnol* 2012;13:1997–2008.
 - 4 Baldini C, Pepe P, Luciano N *et al.* A clinical prediction rule for lymphoma development in primary Sjogren's syndrome. *J Rheumatol* 2012;39:804–8.
 - 5 Theander E, Henriksson G, Ljungberg O *et al.* Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006;65:796–803.
 - 6 Vitali C, Bombardieri S, Jonsson R *et al.* Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
 - 7 Bournia VK, Diamanti KD, Vlachoyiannopoulos PG *et al.* Anticentromere antibody positive Sjogren's syndrome: a retrospective descriptive analysis. *Arthritis Res Ther* 2010; 12:R47.
 - 8 Baldini C, Mosca M, Della Rossa A *et al.* Overlap of ACA positive systemic sclerosis and Sjogren's syndrome: a distinct clinical entity with mild organ involvement but at high risk of lymphoma. *Clin Exp Rheumatol* 2013;31: 272–80.
 - 9 Pertovaara M, Pukkala E, Laippala P *et al.* A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects. *Ann Rheum Dis* 2001;60:467–72.
 - 10 Alamanos Y, Tsifetaki N, Voulgari PV *et al.* Epidemiology of primary Sjogren's syndrome in north-west Greece, 1982–2003. *Rheumatology* 2006;45:187–91.
 - 11 Garcia-Carrasco M, Ramos-Casals M, Rosas J *et al.* Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine* 2002; 81:270–80.
 - 12 Ramos-Casals M, Solans R, Rosas J *et al.* Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine* 2008;87: 210–9.
 - 13 Seror R, Mariette X, Bowman S *et al.* Accurate detection of changes in disease activity in primary Sjogren's syndrome by the European League Against Rheumatism Sjogren's Syndrome Disease Activity Index. *Arthritis Care Res* 2010; 62:551–8.
 - 14 Bombardieri S, Paoletti P, Ferri C *et al.* Lung involvement in essential mixed cryoglobulinemia. *Am J Med* 1979;66: 748–56.
 - 15 Wu DH, Tavoni A, Garzelli C *et al.* A simple method for the biochemical purification of Ro/SS-A antigen. *J Immunol Methods* 1989;121:219–24.
 - 16 Martel C, Gondran G, Launay D *et al.* Active immunological profile is associated with systemic Sjogren's syndrome. *J Clin Immunol* 2011;31:840–7.
 - 17 Solans-Laquerie R, Lopez-Hernandez A, Bosch-Gil JA *et al.* Risk, predictors, and clinical characteristics of lymphoma development in primary Sjogren's syndrome. *Semin Arthritis Rheum* 2011;41:415–23.
 - 18 Voulgarelis M, Ziakas PD, Papageorgiou A *et al.* Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. *Medicine* 2012;91:1–9.
 - 19 Ramos-Casals M, Brito-Zeron P, Perez-De-Lis M *et al.* Sjogren syndrome or sjogren disease? The histological and immunological bias caused by the 2002 criteria. *Clin Rev Allergy Immunol* 2010;38:178–85.
 - 20 Shiboski SC, Shiboski CH, Criswell L *et al.* American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res* 2012;64: 475–87.

Supplementary Table S1: Extraglandular manifestations of pSS and independent serologic markers of disease severity (multivariate logistic analysis)

Clinical manifestations	Independent Factors	OR	95% CI	
Salivary gland enlargement (SGE)	Age at diagnosis	.983	.971	.995
	Disease duration	1.053	1.026	1.080
	AECG criteria	2.060	1.198	3.540
	Low C4	1.857	1.197	2.880
Articular involvement	Age at diagnosis	1.018	1.006	1.030
	Disease duration	1.081	1.052	1.111
Skin vasculitis	Age at diagnosis	1.026	1.006	1.046
	Disease duration	1.085	1.044	1.127
	Low C3	2.356	1.316	4.218
	Hypergammaglobulinemia	2.176	1.231	3.848
	Rheumatoid factor	2.642	1.406	4.964
	Cryoglobulins	7.233	3.747	13.963
Renal Involvement	Age at diagnosis	0.960	0.931	0.990
	Cryoglobulins	6.453	2.498	16.674
Neurological involvement	Disease duration	1.093	1.045	1.143
	Low C4	2.729	1.179	6.318
	Hypergammaglobulinemia	0.422	0.204	0.871
	Cryoglobulins	4.609	1.889	11.247
Heart Involvement	Anti-La/SSB	5.241	1.890	14.528
Leukocytopenia	Low C3	2.217	1.478	3.324
	Hypergammaglobulinemia	1.832	1.282	2.619
	Anti-Ro/SSA	1.656	1.076	2.549
	Cryoglobulins	3.137	1.744	5.643
Non-Hodgkin's lymphoma	Salivary gland	7.675	3.600	16.364
	Low C4	4.684	2.252	9.741
	Male sex	3.437	1.177	10.040
	Cryoglobulins	2.870	1.200	6.864

CI: Confidence Interval for odds ratios (OR)