

# A Clinical Prediction Rule for Lymphoma Development in Primary Sjögren's Syndrome

CHIARA BALDINI, PASQUALE PEPE, NICOLETTA LUCIANO, FRANCESCO FERRO, ROSARIA TALARICO, SARA GROSSI, ANTONIO TAVONI, and STEFANO BOMBARDIERI

**ABSTRACT. Objective.** To develop and validate a practical prediction rule for the progression from primary Sjögren's syndrome (pSS) to B cell non-Hodgkin's lymphoma (B cell NHL) based on the combination of routinely available clinical and serological disease variables.

**Methods.** The case records of 563 patients with pSS were reviewed, and their demographic, clinical, and immunologic features were collected. Multivariate logistic regression analysis was performed to identify independent risk factors for lymphoma development and to create a propensity score for discrimination between patients at risk of B cell NHL and those patients not at risk. The model was internally validated by resampling procedures.

**Results.** Out of 563 patients with pSS, 387 fulfilling the American European Consensus Group criteria (12 with B cell NHL, 375 without B cell NHL) were included in our study. Salivary gland enlargement ( $p = 0.001$ ), low C3 ( $p = 0.035$ ) and/or C4 levels ( $p = 0.021$ ), and disease duration ( $p = 0.001$ ) were identified as independent risk factors for B cell NHL in pSS. The optimal threshold of the propensity score was determined at  $Y = 4.26$ , which allowed us to identify patients who develop B cell NHL with a sensitivity of 78% and specificity of 95%. The leave-one-out cross-validated prediction error was 6%, and the median bootstrapped sensitivity and specificity were 71% and 95%, respectively.

**Conclusion.** We created a "bedside" prediction model for the identification of patients with pSS who are at risk for B cell NHL, which revealed an excellent discriminative ability and a good internal and external reproducibility. (J Rheumatol First Release Feb 15 2012; doi:10.3899/jrheum.110754)

*Key Indexing Terms:*  
SJÖGREN'S SYNDROME  
PREDICTION MODEL

NON-HODGKIN'S LYMPHOMA  
PROGNOSIS

Primary Sjögren's syndrome (pSS) is a mild chronic autoimmune disease affecting mainly the exocrine glands and generally characterized by a slow progression and by low morbidity and mortality rates<sup>1</sup>. Although pSS clinical manifestations may be related to the functional impairment of salivary and lachrymal glands, several longitudinal studies have provided evidence on the significantly increased incidence of lymphoproliferative complications in pSS, suggesting that the disease might represent a link between autoimmunity and lymphoproliferation<sup>2</sup>. A recent metaanalysis has demonstrated that among rheumatic diseases, pSS displays the highest risk of malignant proliferation, with a standardized incidence rate of 18.9 (95% CI 9.4–37.9) compared with systemic lupus erythematosus and rheumatoid arthritis<sup>3</sup>. Overall, the prevalence of non-Hodgkin's lymphoma (B cell NHL) in pSS has been

estimated to be around 5%, and various histologic subtypes have been described, the most common being mucosa-associated lymphoid tissue lymphomas located in the parotid glands<sup>2,4,5,6,7,8</sup>. The transition to B cell NHL affects only a minority of patients with pSS, but it has been associated with an excess in the overall disease mortality rate, making it crucial to develop models for identification of NHL risk in clinical practice<sup>9</sup>. To date, a number of lymphoma risk factors have been described, including parotid gland enlargement, purpura, low C3 and C4, cryoglobulinemia, monoclonal gammopathy, increased  $\beta_2$ -microglobulin, lymphocytopenia, hypogammaglobulinemia, lymphadenopathy, and splenomegaly<sup>10,11,12,13,14,15</sup> (Table 1). However, despite this relatively large number of well characterized single risk factors, models for the prediction of lymphoma risk are not well established, and it is still difficult to identify the patients with pSS who will have a progression to lymphoma. Therefore, an accurate, objective, and simple clinical prediction rule may be helpful in guiding medical decision-making<sup>16</sup>. The aim of our study was thus to develop and validate such a rule for the risk of lymphoma in patients with pSS that relies only on readily available clinical measures.

## MATERIALS AND METHODS

*Patient population and eligibility criteria.* The study cohort consisted of

---

*From the Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy.*

*C. Baldini, MD; P. Pepe, MSc; N. Luciano, MD; F. Ferro, MD; R. Talarico, PhD; S. Grossi, MD; A. Tavoni, MD; S. Bombardieri, MD, Professor, Rheumatology Unit, Department of Internal Medicine, University of Pisa.*

*Address correspondence to Dr. C. Baldini, Rheumatology Unit, Department of Internal Medicine, University of Pisa, Via Roma 67, 56126 Pisa, Italy. E-mail: chiara.baldini74@gmail.com*

*Accepted for publication November 17, 2011.*

---

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2012. All rights reserved.

Table 1. Predictors of malignant lymphoma in primary Sjögren's syndrome (pSS).

Study	Country	No. pSS Patients	NHL, n	Risk Factors
Sutcliffe <sup>10</sup>	UK	72	5	Salivary gland enlargement, lymphadenopathy, leg ulcers
Voulgarelis <sup>11</sup>	Greece	765	33	Lymphadenopathy, skin vasculitis, peripheral nerve involvement, low-grade fever, anemia, lymphopenia
Skopouli <sup>12</sup>	Greece	261	11	Low C4, mixed monoclonal cryoglobulins, purpura
Ioannidis <sup>13</sup>	Greece	723	38	Parotid enlargement, low C4, palpable purpura
Theander <sup>14</sup>	Sweden	286	12	Purpura/skin vasculitis, CD4-penia, low C3/C4
Brito-Zerón <sup>15</sup>	Spain	266	9	Low C3

NHL: non-Hodgkin's lymphoma.

patients with a diagnosis of definite pSS who had attended our Rheumatology Unit between 1989 and 2009. Only patients who met the American-European Consensus Group (AECG) 2002 criteria<sup>17</sup> for the disease were included. Eligibility criteria also required an age at diagnosis > 18 years and the absence of a preexisting lymphoma.

The followup began when a diagnosis of pSS was made. In the cases of patients who had been seen before 2002, the followup started at the time of their first visit if they were retrospectively judged to have satisfied the AECG 2002 criteria<sup>17</sup>.

**Data collection.** Detailed medical charts going back to 1989 were available for all patients. The patients' demographic, clinical, immunologic, and histologic features at the first diagnosis of pSS and at regular intervals during the observation time were retrospectively collected, and the information was entered into structured data sheets.

Variables analyzed included sex, date of diagnosis, date of first study visit, date of last followup, disease duration, fulfillment of classification criteria, and documentation of lymphoma. The following data were also collected: presence of dry eyes and dry mouth, ocular signs (Schirmer's test, Rose-Bengal staining, or lissamine green), periodic parotid enlargement, and signs or symptoms suggestive of extraglandular involvement. We defined the following extraglandular manifestations according to previous studies<sup>10,11,12,13,14,15,18,19</sup>: nonerosive arthritis, interstitial lung disease (fibrosis or pneumonitis confirmed by radiograph or high-resolution computed tomography scan and/or histology, or altered pattern on pulmonary function study), skin vasculitis (palpable purpura or proven on biopsy), peripheral neurological involvement (polyneuropathy, mononeuropathy, dysautonomia), diagnosed either by electrophysiology or biopsy, and renal involvement (persistent proteinuria > 0.5 g/day, tubular acidosis, interstitial nephritis, glomerulonephritis).

Among laboratory abnormalities, information was collected on leukopenia (white blood cell count < 4000/mm<sup>3</sup>), neutropenia (neutrophils < 1500/mm<sup>3</sup>), low levels of C3 and C4 complement (< 90 mg/dl and < 20 mg/dl, respectively, by nephelometry), hypergammaglobulinemia (total gamma globulins > 2 g/l), rheumatoid factor, antinuclear antibodies, anti-Ro antibody, anti-La antibody positivity, cryoglobulinemia, and hepatitis C and B seropositivity.

The diagnosis of B cell NHL was histologically proven in all cases, and type and stage of the lymphoproliferative malignancies were classified according to the 2001 World Health Organization Classification for Tumors of Hematopoietic and Lymphoid Tissues, and the Ann Arbor Staging System<sup>20</sup>.

**Statistical analyses.** Data were expressed as median values (25th-75th percentiles) for continuous variables and as absolute frequencies and percentages for nominal variables. Patients with missing data were excluded from the respective analysis. Patients who developed B cell NHL were compared to those who did not develop B cell NHL using the Mann-Whitney U test for continuous variables and Fisher's exact test for nominal variables. In order to improve the homogeneity and the power of our prediction model, only the patients' clinical and biological variables recorded at the diagnosis of pSS (baseline) were taken into consideration for the statistical analyses. The final predictive model was developed by the stepwise forward selection method in

a multivariate logistic setting. Univariate and multivariate analyses were performed using SPSS 13 (SPSS Inc., Chicago, IL, USA)<sup>21</sup>.

The receiver-operation characteristic (ROC) curve of the selected model was then analyzed using the R package "EpiR" to develop a prediction score. In order to identify a good compromise between sensitivity and specificity, a cutoff point of this score was identified on the basis of the maximum Youden Index<sup>22</sup>. A 95% CI of sensitivity and specificity was also provided.

The predictive accuracy of the final classification rule was then validated by resampling procedures. Leave-one-out cross-validated prediction errors and bootstrapped sensitivity and specificity were calculated using the R package "boot"<sup>23,24</sup>.

## RESULTS

**Demographic, clinical, serological, and histological characteristics of patients with pSS.** A retrospective medical record review was performed in 563 patients with pSS who were recruited between 1989 and 2010 at one center in Italy. All the patients satisfied the European preliminary criteria<sup>25</sup>, and 387/563 also satisfied the AECG criteria. All the AECG patients had regularly attended our unit for a median followup of 6 years (range 2–12 yrs). Table 2 summarizes the 387 patients' clinical and demographic features.

Twelve cases of B cell NHL were diagnosed during the followup, translating into a 3.1% frequency of B cell NHL in our cohort. All patients were white. The median age at lymphoma diagnosis was 50.5 years (range 33.75–54.75 yrs). The median time from pSS diagnosis to lymphoma was 17.5 years (range 11.5–24 yrs). All patients but 1 had ocular and oral dryness. Table 3 summarizes NHL types and stages and the observed frequency of glandular and extraglandular signs and symptoms registered during the course of pSS disease. The patients' antibody profiles and the other laboratory-detected alterations are also shown in Table 3. In particular, cryoglobulins were present in 2 out of 12 patients, a monoclonal gammopathy was documented in only 1 patient, and increased  $\beta_2$ -microglobulin was found in 5 of 10 patients (for 2 patients, data were not available).

**Univariate analysis.** Parotid enlargement, low C3 and C4 levels, and disease duration were the variables associated with progression to lymphoma in univariate analysis (Table 2).

**Multivariate analysis and validation.** Multivariate analysis was performed on 318 patients, including 9 cases of B cell NHL (subjects showing missing values for at least 1 of the

Table 2. Clinical and laboratory features of patients with and without non-Hodgkin's lymphoma (NHL). Data are no. (%) unless otherwise specified.

Variables (collected at pSS diagnosis)	Total	No NHL	NHL	p
Age, yrs, median (IQR)	59 (47–70)	59 (47–70)	64 (47–70)	0.653
Disease duration, yrs, median (IQR)	6 (2–12)	6 (2–11)	14.5 (10–18)	0.002
Age at diagnosis, yrs, median (IQR)	51 (40–62)	51 (40–62)	50.5 (33.75–54.75)	0.262
Female	376/387 (97.1)	365 (97.3)	11 (91.6)	0.29
Smoker	30/289 (10.3)	29 (10.4)	1 (10)	1.000
Ocular symptoms	346/387 (89.4)	335 (89.3)	11 (91.6)	1.000
Oral symptoms	344/387 (89)	334 (89)	10 (83.3)	0.631
Ocular signs*	371/384 (96.6)	359/372 (96.5)	12 (100)	1.000
Positive histopathologic findings	261/308 (85)	252 (84.5)	9 (90)	0.72
Parotid enlargement	52/383 (13.6)	45 (12)	7 (60.0)	0.001
Arthritis	42/384 (11)	40 (10.7)	2 (16.6)	0.629
Skin vasculitis	20/386 (5)	18 (4.8)	2 (16.6)	0.123
Raynaud's phenomenon	84/384 (21.8)	80 (21.5)	4 (33.3)	0.476
Lung involvement	5/386 (1.6)	5 (1.3)	0 (0)	1.000
Peripheral nerve involvement	2/387 (0.5)	2 (0.5)	0 (0)	1.000
Kidney involvement	0 (0)	0 (0)	0 (0)	NA
Low C3	44/321 (14)	40 (13)	4 (40)	0.036
Low C4	23/320 (7.0)	20 (6.4)	3 (33)	0.021
Leukopenia	80/384 (21)	78 (21)	2 (16.6)	1.000
Neutropenia	13/382 (3.4)	13 (3.5)	0 (0)	1.000
Hypergammaglobulinemia	211/377 (56)	205 (53)	5 (6)	1.000
Monoclonal component	6/380 (1.5)	6 (1.6)	0 (0)	1.000
Antinuclear antibodies	349/387 (90)	338 (90)	11 (92)	1.000
Anti-Ro antibodies	292/387 (75)	282 (75)	10 (83)	0.738
Anti-La antibodies	139/387 (36)	133 (35)	6 (50)	0.363
Rheumatoid factor	241/375 (64)	234 (61)	7 (63.6)	1.000
Cryoglobulins	5/174 (2.8)	5 (3)	0 (0)	1.000

\* Evaluated by Rose-Bengal, lissamine green, and/or Schirmer test. IQR: interquartile range; NA: not applicable; pSS: primary Sjögren's syndrome.

variables associated with lymphoma at the univariate analysis were excluded from the analysis).

Salivary gland enlargement ( $X_1$ : OR 10.20,  $p = 0.002$ ), low C4 levels ( $X_2$ : OR 11.53,  $p = 0.008$ ), and disease duration ( $X_3$ : OR 1.14,  $p = 0.01$ ) were identified as independent risk factors for B cell NHL in pSS. The corresponding  $\beta$  coefficients were then used to calculate the linear predictor  $Y = 2.32X_1 + 2.446X_2 + 0.132X_3$ , ranging from 0 to 6.5, with a higher score indicating a greater risk of lymphoma development. Among patients with B cell NHL, the median prediction score was 4.6 (range 3.4–5.4), while among patients who did not develop B cell NHL, the median prediction score was 1.1 (range 0.4–2.5;  $p < 0.001$ ). The diagnostic performance of the model was evaluated by the ROC curve analysis. An area under the curve of 0.905 (95% CI 0.815–0.995) was found.

We used the optimal cutoff point of  $Y = 4.26$  to determine patients at risk of B cell NHL and those not at risk, with a sensitivity of 78% and a specificity of 95%.

The predictive performance of the proposed rule was assessed by resampling methods. The leave-one-out cross-validated prediction error was 6%. Finally, the median (interquartile range) of the bootstrapped distribution of the sensitivity

and specificity were 71 (56%–82%) and 96% (94%–97%), respectively.

## DISCUSSION

We developed and validated a practical prediction rule for lymphoma risk in pSS by retrospectively analyzing clinical charts of a large cohort of patients followed at our Rheumatology Unit. Our model, based on the combination of 3 simple, routine clinical measures (i.e., parotid enlargement, hypocomplementemia, and years of disease duration), allowed us to accurately discriminate between pSS patients at risk for B cell NHL and patients not at risk, with a sensitivity of 78% and specificity of 95%.

Moreover, when internally validated, the model also showed good stability and reproducibility.

Our prediction model is based on well known risk factors for lymphoma (Table 1)<sup>10,11,12,13,14,15</sup>. Nonetheless, the novelty of this study is that these well recognized poor prognosis risk factors have been combined for the first time in a practical rule that could correctly identify patients at higher risk of lymphoma.

The proposed prediction model has other apparent distinc-

Table 3. Clinical, laboratory, and histological features of patients with primary Sjögren's syndrome (pSS) developing non-Hodgkin's lymphoma (NHL).

Pts	Sex	Lymphoma Type	Stage	B-Cell Symptoms	Parotid Enlargement	Extraglandular Involvement	Serological Profile										Therapy	Clinical
							Hyper-g	MC	RF	ANA	SSA	SSB	Cryo	Low	HCV	B2M		
1	F	Gastric MALT-type	IE	Yes	No	Arthritis	Yes	No	No	Yes	Yes	Yes	No	No	No	ND	Surgery	Yes
2	M	DLBCL	IIIS	Yes	No	Arthritis	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	ND	CHOP	Yes
3	F	DLBCL	II	Yes	Yes	Skin vasculitis, PNS	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes	RTX + CHOP	Yes
4	F	Salivary MALT-type	IV	No	Yes	Leukopenia	No	No	No	Yes	No	No	No	No	No	Yes	RTX + CFX	Yes
5	F	Salivary MALT-type	IE	No	Yes	Leukopenia	Yes	No	Yes	Yes	Yes	No	No	No	No	No	RTX	Yes
6	F	Salivary MALT-type	IE	No	Yes	None	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	PDN, AZA	Yes
7	F	Salivary MALT-type	IE	No	Yes	Lung, leukopenia	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Parotidectomy	Yes
8	F	Salivary MALT-type	IE	No	Yes	None	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	Parotidectomy	Yes
9	F	Salivary MALT-type	IV	No	Yes	Lung, leukopenia	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	RTX + CHOP	Yes
10	F	Salivary MALT-type	IV	Yes	Yes	Leukopenia	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	RTX + CYC	Yes
11	F	NMZL	IV	Yes	Yes	PNS, leukopenia	No	No	Yes	Yes	Yes	No	No	Yes	No	No	CHOP	Yes
12	F	DLBCL	IV	Yes	Yes	Lung	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	RTX + CHOP	No

MALT: mucosa-associated lymphoid tissue; NHL: non-Hodgkin's lymphoma; NMZL: nodal marginal zone lymphoma; DLBCL: diffuse large B cell lymphoma; PNS: peripheral nervous system; Hyper-g: hypergammaglobulinemia; MC: monoclonal component; RF: rheumatoid factor; ANA: antinuclear antibodies; SSA: anti-Ro/SSA; SSB: anti-La/SSB; Cryo: cryoglobulins; HCV: hepatitis C virus; B2M:  $\beta_2$ -microglobulin; ND: not determined; CHOP: cyclophosphamide, hydroxydaunorubicin (also called doxorubicin), oncovin, prednisone; RTX: rituximab; CYC: cyclophosphamide; PDN: prednisone; AZA: azathioprine.

tive strengths. First, all the clinical measures are clearly defined, readily available predictors, and no laboratory tests or radiographic procedures not routinely performed in the management of patients with pSS are required. With this in mind, we decided not to extend the analysis to variables such as cryoglobulinemia,  $\beta_2$ -microglobulin, monoclonal gammopathy, or TCD4+ lymphocytopenia, which might not have been routinely investigated in clinical practice in patients with pSS, especially in those with an isolated benign autoimmune exocrinopathy. On the contrary, we focused attention on the presence of salivary enlargement and hypocomplementemia, which have been widely recognized as early predictors of outcome in patients with pSS.

Ramos-Casals, *et al*<sup>26</sup> and Brito-Zerón, *et al*<sup>15</sup>, in 2 different studies, identified low C3 and C4 levels among the presenting features indicating a poor prognosis for pSS that might be prospectively associated with adverse outcomes (i.e., vasculitis, B cell lymphomas, and death). In addition, Voulgarelis, *et al*<sup>11</sup> and Theander, *et al*<sup>14</sup> reported hypocomplementemia and parotid gland swelling as specific risk factors for lymphoma.

In our model, we also emphasized the association between B cell NHL and disease duration, outlining the general concept of lymphoma as a late complication of pSS, resulting from the transition from polyclonal B cell activation to monoclonal expansion of B lymphocytes<sup>5</sup>. Therefore, our data are in agreement with the results of the largest studies on lymphoproliferative complications in pSS.

In 1999, Voulgarelis, *et al*<sup>11</sup>, describing the disease characteristics, clinical course, and evolution of 33 patients with pSS and NHL who were followed in 9 European medical centers, reported a median time from SS diagnosis to lymphoma diagnosis of 7.5 years. Theander, *et al*<sup>14</sup>, describing a cohort of 507 patients, reported that during the first 5 years of the followup the standardized incidence ratios for NHL were 6.4 (95% CI 1.3–18.7), 11.1 (95% CI 3.0–28.5) during years 6–10, and 20.8 (95% CI 6.8–48.6) during years 10–15.

Another potential advantage is that our study population represented a broad disease spectrum, ranging from patients with an isolated autoimmune exocrinopathy to patients with severe systemic involvement, suggesting a potentially large applicability of the model to the other cohorts of patients with pSS.

Because the propensity score was derived retrospectively and validated in a single-center cohort of patients, the generalizability of the clinical rule we have developed may require a prospective confirmation in an independent test set of patients with pSS. However, based on our findings, our model might be seen as a feasible potential decision-making aid for the management of patients with pSS.

We constructed and validated a practical bedside prediction rule for detection of lymphoma risk that may be helpful in clinical practice to identify those patients with pSS who are at higher risk of B cell NHL and who may benefit from more intensive surveillance during the followup.

## ACKNOWLEDGMENT

We thank Laura Fatuzzo for her valuable contribution in reviewing the text.

## REFERENCES

1. Mavragani CP, Moutsopoulos HM. The geoepidemiology of Sjögren's syndrome. *Autoimmun Rev* 2010;9:A305-10.
2. Voulgarelis M, Skopouli FN. Clinical, immunologic, and molecular factors predicting lymphoma development in Sjögren's syndrome patients. *Clin Rev Allergy Immunol* 2007;32:265-74.
3. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: A meta-analysis. *Arch Intern Med* 2005;165:2337-44.
4. Pillemer SR. Lymphoma and other malignancies in primary Sjögren's syndrome. *Ann Rheum Dis* 2006;65:704-6.
5. Mariette X. Lymphomas in patients with Sjögren's syndrome: Review of the literature and physiopathologic hypothesis. *Leuk Lymphoma* 1999;33:93-9.
6. Voulgarelis M, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome. *Isr Med Assoc J* 2001;3:761-6.
7. Fietta P, Delsante G, Quaini F. Hematologic manifestations of connective autoimmune diseases. *Clin Exp Rheumatol* 2009;27:140-54.
8. Voulgarelis M, Moutsopoulos HM. Mucosa-associated lymphoid tissue lymphoma in Sjögren's syndrome: Risks, management, and prognosis. *Rheum Dis Clin North Am* 2008;34:921-33, viii.
9. Voulgarelis M, Tzioufas AG, Moutsopoulos HM. Mortality in Sjögren's syndrome. *Clin Exp Rheumatol* 2008;5 Suppl 51:S66-71.
10. Sutcliffe N, Inanc M, Speight P, Isenberg D. Predictors of lymphoma development in primary Sjögren's syndrome. *Semin Arthritis Rheum* 1998;28:80-7.
11. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: A multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. *Arthritis Rheum* 1999;42:1765-72.
12. Skopouli FN, Dafni U, Ioannidis JP, Moutsopoulos HM. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. *Semin Arthritis Rheum* 2000;29:296-304.
13. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. *Arthritis Rheum* 2002;46:741-7.
14. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LTH. Lymphoma and other malignancies in primary Sjögren's syndrome: A cohort study on cancer incidence and lymphoma predictors. *Ann Rheum Dis* 2006;65:796-803.
15. Brito-Zerón P, Ramos-Casals M, Bove A, Sentis J, Font J. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. *Rheumatology* 2007;46:1359-62.
16. Wittoek R, De Keyser F, Boonen A, De Vlam K, Vastesaeger N, Mielants H, et al. Classification models for disease: The effect of associations between markers on calculating the risk for disease by likelihood ratio products. *Clin Exp Rheumatol* 2009;27:272-6.
17. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: A revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-8.
18. Seror R, Mariette X, Bowman S, Baron G, Gottenberg JE, Boostma H, et al; European League Against Rheumatism Sjögren's Task Force. Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. *Arthritis Care Res* 2010;62:551-8.
19. Seror R, Ravaud P, Bowman SJ, Baron G, Tzioufas A, Theander E, et al; EULAR Sjögren's Task Force. EULAR Sjögren'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.
20. Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. The World Health Organization classification of neoplastic diseases of the haematopoietic and lymphoid tissues: Report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November 1997. *Histopathology* 2000;36:69-86.
21. The R Project for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria; 2005. [Internet. Accessed December 13, 2011.] Available from: <http://www.R-project.org>
22. Stevenson M, Nunes T, Sanchez J, Thornton R. epiR: Functions for analysing epidemiological data. R package version 0.9-27. 2010. [Internet. Accessed December 13, 2011.] Available from: <http://CRAN.R-project.org/package=epiR>
23. Henderson AR. The bootstrap: a technique for data-driven statistics using computer-intensive analyses to explore experimental data. *Clin Chim Acta* 2005;359:1-26.
24. Carpenter J. Bootstrap methods and their application. Davison AC, Hinkley DV, editors. Cambridge: Cambridge University Press; 1997. *Epidemiol Infection* 1998;121:485.
25. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;36:340-7.
26. Ramos-Casals M, Brito-Zerón P, Yagüe J, Akasbi M, Bautista R, Ruano M, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. *Rheumatology* 2005;44:89-94.