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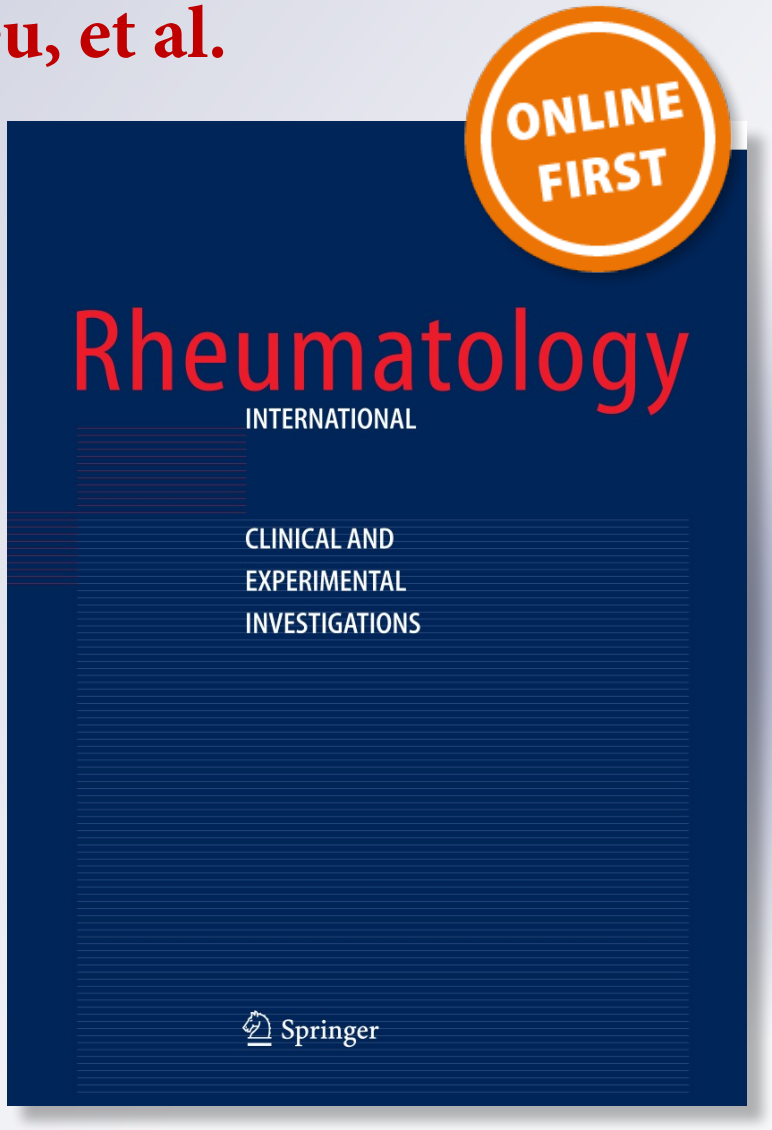

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REVIEW ARTICLE

Identification of lymphoma predictors in patients with primary Sjögren's syndrome: a systematic literature review and meta-analysis

Maria B. Nishishinya · Claudia A. Pereda · Santiago Muñoz-Fernández · José M. Pego-Reigosa · Iñigo Rúa-Figueroa · José-Luis Andreu · Mónica Fernández-Castro · José Rosas · Estibaliz Loza Santamaría

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Abstract To identify risk and predictors of lymphoma or lymphoproliferative disease in patients with primary Sjögren syndrome. Articles were identified through a comprehensive search strategy in Medline, Embase and Cochrane CENTRAL. Studies had to investigate primary Sjögren syndrome patients, 18 years of age or older, with the goal of examining potential clinical, immunological and hematological risk factors for lymphoma or lymphoproliferative disease. The quality of the studies was graded using the Oxford Levels of Evidence Scale. Whenever possible, the authors created evidence tables and performed meta-analysis. Of 900 studies identified, 18 were selected for inclusion. These studies provided data from over 15,000 patients (90 % female) for analysis. Lymphadenopathy, parotid enlargement, palpable purpura, low C4 serum levels and cryoglobulins were the most consistent non-Hodgkin´s lymphoma/lymphoproliferative disease predictors. Additionally, some of the studies identified splenomegaly, low C3 serum levels, lymphopenia and neutropenia as significant prognostic factors. The detection of germinal center-like lesions in primary Sjögren Syndrome diagnostic salivary biopsies was also proposed as highly predictive of non-Hodgkin´s lymphoma. In contrast, anemia, anti-Ro, anti-La, antinuclear antibodies, rheumatoid factor, male gender and hypergammaglobulinemia were not associated with lymphoma or lymphoproliferative disease. Patients with primary Sjögren syndrome have an increased risk of

Maria B. Nishishinya, Claudia A. Pereda, Santiago Muñoz-Fernández and Estibaliz Loza Santamaría belong to "Evidence based working group of the Spanish Society of Rheumatology—SER". Santiago Muñoz-Fernández, José M. Pego-Reigosa, Iñigo Rúa-Figueroa, José-Luis Andreu, Mónica Fernández-Castro and José Rosas belong to "Systemic Autoimmune Disease working group—SER".

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M. B. Nishishinya
Instituto Traumatológico Quirón, Barcelona, Spain

C. A. Pereda (✉)
Rheumatology Department, Clínica Mediterráneo, Avenida Mediterraneo 353 bloque 2 4 °C, 04009 Almería, Spain
e-mail: claudiapereda1963@yahoo.es; cpereda@reumatologo.net

S. Muñoz-Fernández
Reumatology Department, Hospital Universitario Infanta Sofía, Madrid, Spain

J. M. Pego-Reigosa
Rheumatology Department, Complejo Hospitalario Universitario de Vigo, Pontevedra, Spain

J. M. Pego-Reigosa
Instituto de Investigación Biomédica de Vigo (IBIV), Pontevedra, Spain

I. Rúa-Figueroa
Rheumatology Department, Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

J.-L. Andreu · M. Fernández-Castro
Rheumatology Department, Hospital Universitario de Puerta de Hierro-Majadahonda, Madrid, Spain

J. Rosas
Rheumatology Department, Hospital Marina Baixa, Villajoyosa, Alicante, Spain

E. Loza Santamaría
Institute for Musculoskeletal Health, Madrid, Spain

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lymphoma or lymphoproliferative disease compared to the general population. Ascertaining relevant and reliable predictors in this patient population would greatly facilitate the identification of patients at elevated risk for closer monitoring in the context of limited resources.

Keywords Sjögren syndrome · Lymphoma · Clinical markers · Immunological markers

Introduction

The association between primary Sjögren syndrome (pSS) and lymphoma, mostly non-Hodgkin´s lymphoma (NHL) or lymphoproliferative disease (LPD), has been documented for the past 40 years [1–6]. Though pSS is a relatively benign autoimmune disease, it increases the risk for malignant NHL/LPD; however, this association remains poorly understood. While almost 1 in 5 pSS patients death is caused by lymphoma [4], a pooled standardized incidence rate (SIR) analysis estimated a nearly 20-times increased incidence rate of NHL among these patients compared to the general population [7].

There is growing evidence that chronic antigenic stimulation by exo- or autoantigens might be strongly associated with the development of pSS-associated lymphoproliferation. Additional molecular oncogenic events such as microsatellite instability, loss of the B-cell cycle control, and possibly forced overproduction of specific B-cell biologic stimulators might also play a significant role [8–10]. Given the considerable impact of lymphoma and LPD on morbidity and mortality, it is essential to identify potential clinical or immunological markers, concurrently with the pSS diagnosis in order to provide a closer follow-up for those patients at high risk for malignant progression [8]. Thus, the aim of our study was to examine and review the available evidence regarding the identification of lymphoma predictors in pSS patients.

Methods

We performed a systematic review and meta-analysis to summarize and evaluate the existing empirical evidence regarding factors predictive of lymphoma onset among pSS patients.

Search strategy

The studies were identified using comprehensive search strategies of major bibliographic databases (Tables 1, 2, 3). Searches were reviewed and approved by an expert librarian. Also, experts from the Systemic Autoimmune Disease working group SER provided the main questions for this review.

The following bibliographic databases were searched: Medline and Embase from 1961 through January 2014, and the Cochrane Central register of Controlled Trials (CENTRAL) up to January 2014. The search conducted on January 2014 was limited to studies written in English or Spanish, all retrieved references were managed in EndNote X5.

Finally, we reviewed the reference lists of all the studies manually to retrieve any relevant article missed by the automated search. The search strategy methodology is described in further detail in a supplemental file.

Selection criteria

Studies were included if they met the following preestablished criteria: sample included pSS patients aged 18 years or older who were followed and assessed for lymphoma or LPD-independent risk factors such as: (a) sex, parotid enlargement, splenomegaly, lymphadenopathy, palpable purpura, skin ulcers or arthralgia; or (b) immunological and hematological outcomes such as the presence of anti-Ro/anti-La antibodies, C3 and C4 serum levels, cryoglobulinemia, lymphocytopenia (particularly CD4 and CD3 T cells), neutropenia, anemia, positive antinuclear antibodies (ANA), positive rheumatoid factor (RF) and hypergammaglobulinemia. In addition, results of minor salivary gland biopsies performed at the time of pSS diagnosis were also taken into account. Finally, all types of lymphoma or LPD disease were considered as possible outcomes. Regarding statistical estimates, relative risk (RR), odds ratio (OR), hazard ratio (HR), standardized incidence rate (SIR) and incidence rate, with their corresponding 95 % confidence intervals (CI), were utilized. In terms of study design, we considered meta-analyses, systematic literature reviews, randomized controlled trials, cohort studies with a control group and case–control studies. Studies examining secondary SS as well as basic science and animal studies were excluded.

Screening of studies, data collection and analyses

Based on these selection criteria, two reviewers (MBN and CAP) screened the articles' titles and abstracts independently. Data were collected from the selected studies using ad hoc standard forms. Discrepancies between reviewers were resolved by a third researcher (EL) when necessary. Also, articles not fulfilling all inclusion criteria or reporting insufficient data were excluded. Based on the "The Oxford 2011 Levels of Evidence," [11] we evaluated the methodological quality of selected trials and produced evidence tables.

Table 1 Main characteristics of studies of lymphoma predictors in patients with primary Sjögren's syndrome

Study, country, design, follow-up	Population	pSS diagnostic criteria	Outcome	Quality[a]
Baimpa 2009 [13] (Greece) Cohort, median follow-up 31 months	$n = 536$ (92.3 % women, mean age 53 years)	AECC	Lymphoma: *n*, risk of development, predictors	Oxford 2c
Brito-Zerón 2007 [14] (Spain) Cohort, mean follow-up 8.66 years	$n = 266$ (93 % women, mean age 56 years)	European Criteria 1993	B-cell lymphoma: *n*, predictors	Oxford 4
Davidson 1999 [15] (UK) Cohort, median follow-up 10 years	$n = 100$ (97 % women, mean age 48 years)	Fox Criteria or -European Criteria 1993	NHL: *n*, SIR	Oxford 2c
Ioannidis 2002 [16] (Greece) Cohort, mean follow-up 6.06 years	$n = 723$ (94.2 % women, mean age 52 years)	European Criteria 1993	LPD: *n*, risk of development, predictors	Oxford 2c
Kassan 1978 [2] (USA) Cohort, mean follow-up 8.1 years	$n = 142$ (95.8 % women, mean age: na)	Clinical, laboratory, and histologic evidence of keratoconjunctivitis sicca + xerostomia	Lymphoma: *n*, SIR	Oxford 2c
Kauppi 1997 [17] (Finland) Cohort, follow-up 5,336 persons-years	$n = 676$ (proportion women and age: na)	Not defined	Lymphoma: *n*, SIR	Oxford 4
Lazarus 2006 [18] (UK) Cohort, mean follow-up 10.8 years	$n = 112$ (94.6 % women, mean age 53 years)	European Criteria 1993	Lymphoma: *n*, SIR	Oxford 2c
Martel 2011 [19] (France) Cohort, mean follow-up 76 ± 51 months	$n = 445$ (89.8 % women, mean age 54 years)	AECC	Lymphoma: *n*, predictors	Oxford 2c
Pertovaara 2001 [20] (Finland) Cohort	$n = 110$ (97.2 % women, mean age 62 years)	Modified Californian criteria for pSS	NHL: *n*, predictors, SIR	Oxford 2c
Skopoulis 2000 [21] (Greece) Cohort, mean follow-up 3.6 years	$n = 261$ (96.0 % women, mean age 51 years)	European Criteria 1993	LPD: *n*, incidence rate, predictors	Oxford 2c
Smedby 2008 [26] (Sweden) Pooled analysis (8 case–control studies)	$n = 18{,}721$ (cases = 8,178; controls = 10,543)	Self-reported and many physician-diagnosed	NHL: prevalence, risk of development, predictors	Oxford 3a
Solans-Laqué 2011 [27] (Spain) Cohort, median follow-up 8.6 years	$n = 244$ (96.3 % women, mean age 57)	European Criteria 1993	NHL: *n*, risk of development, predictors, SIR	Oxford 2c
Sutcliffe 1998 [22] (UK) Retrospective, follow-up (up to 10 years)	$n = 72$ (94.4 % women, mean age 50 years)	European Criteria 1993	MALT lymphoma: *n*, prevalence, risk of development, predictors	Oxford 2c
Theander 2006 [23] (Sweeden) Cohort, median follow-up 8 years	$n = 286$ (90 % women, median age 56 years)	Copenhagen criteria set or -1993 European Criteria or -AECC	NHL: *n*, predictors, SIR	Oxford 2c
Valesini 1997 [24] (Italy) Retrospective, mean follow-up 5.95 years	$n = 295$ (90 % women, mean age 50 years)	European Criteria 1993	NHL: *n*, SIR	Oxford 2c
Zhang 2010 [25] (China) Retrospective, mean follow-up 4.2 years	$n = 1{,}320$ (91 % women, mean age 39 years)	AECC	Lymphoma: *n*, predictors, SIR	Oxford 4
Risselada 2013 [35] (Netherlands) Retrospective, mean follow-up 7.6 years	$n = 195$ (81 % women, mean age 59 years)	AECC	NHL: prevalence, risk of development, predictors	Oxford 2c
Quartuccio 2013 [36] (Italy) Retrospective, cross-sectional, multicentre, review	$n = 661$ (95,3 % women, mean age 50 years)	AECC	Lymphoma: predictors, risk of development	Oxford 2b

pSS primary Sjögren syndrome, *UK* United Kingdom, *USA* United States of America, *AECC* American-European Consensus Classification, *NHL* non-Hodgkin's lymphoma, *SIR* standardized incidence ratio, *LPD* lymphoproliferative disease, *Na* not available

[a] Study quality was assessed using the Oxford 2011 Levels of Evidence [11]

Table 2 Clinical risk factors of lymphoma or lymphoproliferative disease development

Study	Parotid enlargement	Splenomegaly	Lymphadenopathy	Palpable purpura	Skin ulcers	Arthralgia	Men	P. neuropathy
Baimpa [13]	NS	HR 3.97 (1.49–10.60)	HR 2.62 (1.15–5.94)	NS	–	–	–	–
Brito-Zerón [14]	HR 3.16 (0.60–16.70)	–	–	NS	–	–	–	–
Ioannidis [16][a]	HR 5.56 (1.89–16.40)	NS	HR 2.62 (1.14–6.00)	HR 5.05 (2.09–12.70)	–	–	NS	–
Kassan [2]	RR = 9.2	NS	RR = 3.7	–	–	–	–	–
Skopouli [21][a]	–	–	–	HR 5 (1.4–18.40)	–	–	–	–
Solans-Laque [27]	NS	–	–	NS	–	–	–	–
Sutcliffe [22]	OR 15.1 (1.60–146.40)	–	OR 9.7 (1.40–66.10)	NS	OR 21.7 (2–211)	NS	–	–
Theander [23][b]	NS	–	–	HR 4.64 (1.13–16.50)	–	–	–	–
Risselada [35]	OR 2.84	–	–	NS	–	OR 3.25	–	$p = 0.0003$
Quartuccio [36][c]	OR = 10.20	–	–	–	–	–	–	–

Results from the multivariate analyses are expressed as RR, HR or OR (95 % confidence interval) unless otherwise is indicated

NS no statistically significant, *RR* relative risk, *HR* hazard ratio *OR* odds ratio

(–) No data available

[a] Lymphoproliferative disease

[b] Only adjusted for age

[c] Plus at least the presence of two biomarkers

Meta-analysis

We estimated the pooled ln(SIR) using the inverse of the square root of the observed number of cases as a weighted factor. To calculate the 95 % CI of the pooled SIR, we took the exponential of the 95 % limits of the ln(SIR). The pooled ln(SIR) was calculated using both fixed-effects and random-effects models (DerSimonian-Laird method). The heterogeneity between studies was tested using the Q statistic, which is a weighted sum of squares of the deviations of individual-study ln (SIR) estimates from the overall estimate. Heterogeneity was considered statistically significant if $p < 0.10$. Heterogeneity was also quantified with the I^2 metric, which is independent of the number of studies in the meta-analysis. Values of I^2 of 25, 50 and 75 % were considered low, moderate and high heterogeneity, respectively. Analyses were performed using Stata 12.0 statistical software (Stata Corp., College Station, TX, USA).

Results

The electronic search identified 900 potentially eligible studies (Fig. 1), of which 18 were included and analyzed in the current systematic literature review [2, 13–27, 35, 36]. Table 1 shows the main characteristics of these studies. Most of them were cohort studies of moderate quality, comprising over 15,000 patients, (90 % women) with mean ages ranging from 39 to 67 years. Patients fulfilled criteria for pSS diagnosis based on at least one of the following: the Preliminary European Classification Criteria of 1993 [28], the American-European Consensus Group [29], Fox Classification Criteria [30], The Copenhagen Criteria [31] or the recent American College of Rheumatology Classification Criteria for Sjögren syndrome [32]. In most studies, the assessment of lymphoma/LPD was based on histological findings obtained from clinical records or cancer registries. NHL was the cancer reported most frequently.

Risk and predictors of lymphoma or LPD

The risk of developing lymphoma or LPD was examined in seven studies [13, 16, 21, 26, 27, 33–36]. According to these reports, the risk of lymphoma or LPD development was about 4 % during the first 5 years, 10 % at 15 years and 18 % after 20 years post-diagnosis. Patients with more than one risk factor also had an increased risk of a malignant outcome. Tables 2 and 3 show the results of the multivariate analyses modeling the predictors of lymphoma or LPD development.

Parotid enlargement was considered a predictive factor in six studies [2, 14, 16, 22, 35, 36], but failed to reach significance in 3 [13, 27, 37]. Kassan and colleagues [12] considered this symptom as an identifier of a pSS subgroup

Table 3 Serological and hematological risk factors for lymphoma or lymphoproliferative disease development

Study	Anti-ro	Anti-La	↓ C3	↓ C4	Cryoglobulinemia	Lymphocyto-penia	Neutropenia	Anemia	ANA+	RF+	Hypergammaglob	Leukope-nia
Baimpa [13]	–	–	NS	HR 3.31 (1.35–8.12)	HR 2.91 (1.15–6.44)	NS	HR 8.97 (1.10–73.00)	NS	–	–	–	–
Brito-Zerón [14]	NS	NS	HR 7.54 (1.46–39.00)	NS	NS	–	–	–	NS	NS	–	
Ioannidis [16][a]	HR 3.17 (1.25–8.03)	HR = 2.47 (1.09–5.60)	NS	HR 3.11 (1.32–7.31)	–	–	–	–	NS	NS	–	
Kassan [2]	–	–	–	–	–	NS	NS	NS	NS	>In controls	–	
Martel [19]	NS	NS	–	–	OR 1.9 (1.10–3.50)	–	–	–	NS	NS	NS	
Pertovaara [20]	–	–	NS	–	–	–	NS	NS	NS	NS	–	
Skopoulis [21][a]	–	–	–	HR 7.5 (2.10–26.00)	HR 7.9 (2.30–27.00)	–	–	–	–	–	–	
Solans-Laqué [27]	–	–	$p < 0.050$	$p < 0.050$	NS	$p < 0.050$		NS	–	–	NS	
Sutcliffe [22]	NS	NS	–	–	NS	–	–	–	NS	NS	NS	
Theander [23][b]	NS	NS	HR = 6.18 (1.57–24.00)	HR = 9.49 (1.94–46.00)	–	HR = 8.14 (2.10–31.50)	–	–		NS	–	
Risselada [35]				OR 7.71 ($p = 0.001$)			NS	NS		NS	NS	
Quartuccio [36]	–	RR = 5,2 (2,3–11,9)	–	RR = 8.3 (3.6–19,2)	RR = 6.8 (2,1–22,1)	–	–	–	–	–	–	RR = 3,3 (1,5–7,0)

Results from the multivariate analyses are expressed as RR, HR or OR (95 % confidence interval) otherwise is indicated

ANA antinuclear antibodies, *Hypergammaglob* hypergammaglobulinemia, *HR* hazard ratio, *NS* no statistically significant, *OR* odds ratio, *RR* relative risk, *RF* rheumatoid factor

(–) No data available

[a] Lymphoproliferative disease

[b] Only adjusted for age

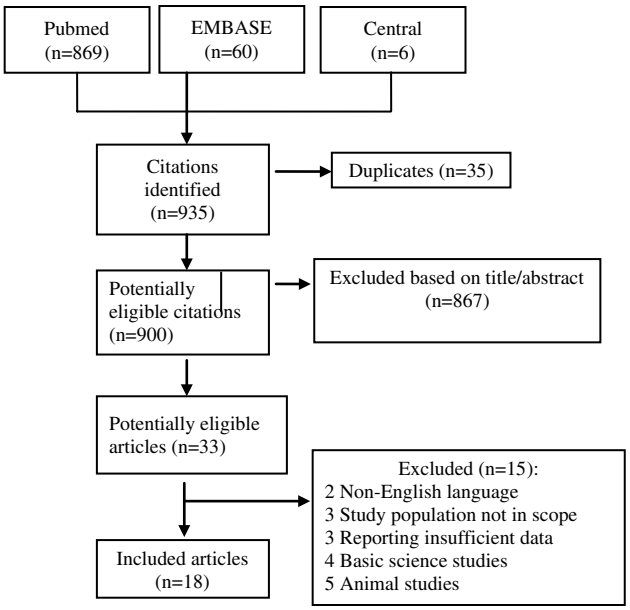

Fig. 1 Lymphoma predictors in patients with primary Sjögren's syndrome—literature flow

with marked lymphoid reactivity, as well as an independent predictor. Further evidence confirmed this marker's ability to predict almost all lymphoproliferative diseases regardless of their grade and aggressiveness [16]. Supporting this association, parotid scintigraphy was postulated not only as an independent prognostic factor, but also as a valuable tool for identifying pSS patients at high risk of developing extra-glandular manifestations [14].

Three articles studied s*plenomegaly* [2, 13, 16] but only in one of them [13] was this sign deemed an independent risk factor (HR 3.97, 95 % CI 1.49–10.60), despite its association with increased mortality in another study [16]. In contrast, *lymphadenopathy's* potential as a valid predictor of malignancy was confirmed in four studies [2, 13, 16, 22], though it was not observed in one [35].

Though *Palpable purpura* was significantly associated with LDP [4, 21, 27], only one study [23] out of six [13, 14, 22, 27, 35] found it statistically significant as an independent risk factor. Similarly, one small study [22] found an association between skin ulcers and LPD with an OR 21.7, 95 % CI 2.2–211, and also with regard to arthralgia [35] (OR 3.25), peripheral neuropathy, sensory axonal neuropathy and sensorimotor neuropathy ($p = 0.003$) [35]. On the other hand, male sex was not found to be associated with lymphoma or LPD development [16, 22].

Regarding serological and immunological factors, six studies evaluated anti-Ro/anti-La antibodies [14, 16, 19, 22, 23, 36], but only one study showed a significant association with LPD development [16]. Although *low C3 serum levels* (<0.82 g/l) were revealed as an independent risk factor in three studies [14, 23, 27], there were still four other studies that failed to find an association [13, 16, 20, 35]. In contrast, *low C4 serum levels* were identified as a strong predictor of lymphoma or LPD. Seven of the eight studies [13, 14, 16, 21, 23, 27, 35, 36] examining this predictor confirmed a significant association. Further, one of the studies found that low C4 serum levels were also a strong predictor of different lymphoma subtypes [13]. In addition, low complement levels emerged not only as an immunological predictor but also as a prognostic factor of overall survival [27].

Cryoglobulins were examined in eight studies, finding statistical association with malignancy in four of them [13, 19, 21, 36]. Brito-Zeron and colleagues concluded that both cryoglobulins and low complement serum levels, particularly of C4, were substantially correlated with lymphoma progression, either independently or in combination [13]. However, this association failed to be supported by the four other studies [14, 22, 27, 35].

Lymphopenia was shown as an independent risk factor in half of the papers evaluating this outcome [23, 27]. Particularly, there was a statistically significant association between CD4+ T lymphopenia and NHL ($p = 0.001$) [13, 38]. Neutropenia was also identified as a significant predictor by one study [13], but failed to reach significance in another three [2, 20, 35]. In fact, a CD4+/CD8+ T cell ratio <0.8 increased the HR of 10.20 (95 % Cl 2.80–41.83) and was suggested as a potential risk factor for malignancy. Quartuccio et al. [36] considered leukopenia as risk factor. Finally, anemia, the presence of ANA or rheumatoid factor and hypergammaglobulinemia were not associated with lymphoma or LPD in adjusted analyses [2, 13, 14, 16, 19, 20, 22, 23, 27, 35].

Standardized incidence ratio of lymphoma

We also collected data regarding the SIR of lymphoma (Table 4), which was reported in ten studies [2, 15, 17, 18, 20, 23–25, 27, 34]. Most of these studies analyzed data from local and/or national cancer registries to estimate the expected number of lymphomas at the population level. SIR ranged from 8.7 (95 % CI 4.3–15.5) [17] to 48.1 (95 % CI 20.7–94.8) [25]. We detected moderate heterogeneity between studies in both fixed-effects and random-effects models ($I^2 = 47.50$ %).

Discussion

Recent studies proposed that the switch from pSS to lymphoma respond to a multi-step process [39], set off by environmental and hormonal factors, together with an appropriate genetic background. Consecutive steps could involve

Table 4 Standardized incidence ratio of lymphomas

Study	Expected number of lymphomas source	Number of lymphomas	SIR (95 % CI)
Davidson [15]	Cancer registry statistic	3	14.40 (4.70–44.70)
Kassan [2]	Connecticut cancer register	4	44.40 (16.70–118.40)
Kauppi [17]	Finnish cancer registry	11	8.70 (4.30–15.50)
Lazarus [18]	Thames cancer registry	11	37.50 (20.70–67.60)
Pertovaara [20]	Finnish cancer registry	3	13.00 (2.70–38.00)
Solans-Laqué [27]	GLOBOCAN database	11	15.60 (8.70–28.20)
Theander [23]	National and local registers	11	15.57 (7.80–27.90)
Valesini [24]	Local cancer registers	9	33.30 (17.30–64.00)
Zhang [25]	Local cancer register	8	48.10 (20.70–94.80)
Johnsen [34]	Cancer registry of Norway	7	9.00 (7.10–26.3)

LPD lymphoproliferative disease, *SIR* standardized incidence ratio, *CI* confidence interval

liberalization of salivary gland epithelial cells, aberrant homing of auto reactive B and T-cells, activation of epithelial cells by cytokines and TNF, necrosis and release of autoantigens. Hence, stimulation of B cell activating factor production, (BAFF—member of TNF super family), is supposed to contribute to B-cell survival, aggregation, altered differentiation and possibly lymphoma development [40].

Early investigations suggested that the clinical and serological profile prevailing in each pSS patient at the time of diagnosis might be of substantial prognostic value [41]. Based on this preliminary work, we analyzed the present information currently available on potential lymphoproliferative markers. As expected, our systematic review confirmed a higher incidence of lymphoma/LPD development in pSS patients, compared to the general population [7, 12, 42]. Lymphadenopathy, parotid enlargement and palpable purpura remained the clinical variables most frequently associated with lymphoma/LPD, along with the serological markers cryoglobulinemia and low serum C4 levels. Moreover, the presence of more than one clinical or serological risk factor further raised the probability of malignancy progress [13, 22]. This assertion was supported in a recent multicentre study [36], analyzing salivary gland swelling, and cryoglobulinemic vasculitis as possible prelymphomatous stages of pSS-related lymphoprolipheration, each one separately. Among patients with salivary gland swelling presenting at least two positive biomarkers (cryoglobulinemia, low C4, anti-SSB/anti-La antibodies or leukopenia), there was an increased risk of lymphoma evolution, while the association with one or no biomarker at all resulted in negative predictive value. Yet, Ioannidis and colleagues among other authors support classifying SS patients into type 1 and 2, according to the risk of developing lymphoma [4, 19, 41]. The majority of pSS cases (80 %) do not present low C4 levels and/or palpable purpura main predictors of malignancy and thus could be classified as type 1 (i.e., low risk of malignancy). The remaining 20 % with one or both risk factors would be classified as type 2. Voulgarelis and colleagues [8] not only considered most previous markers as indicators of lymphoproliferation, but inferred that pSS might have higher levels of B cell activating factor (BAFF) and/or present inactivation of tumor suppression genes. In this line, Nezos et al. [43] suggested an interaction of pSS-related BAFF gene haplotypes together with distinct BAFF genetic variants as possible contributors to lymphoma. Among cytokines, high levels of Fms-like tyrosine Kinase 3 ligand were also linked to lymphoproliferative disorders in pSS [44]. Additional paths like deregulation in the mechanisms leading to apoptosis, overregulation of B-1 cells and infectious agents have also been proposed [9]. A similar model has been advocated in a number of articles [9, 10, 24, 45], but others like Zufferey et al. [46] did not find any statistical association between parotid enlargement and lymphoma development. Interestingly, lymphadenopathy was the only risk factor that remained as significant predictor of malignancy in all the studies that examined this marker, followed by parotid enlargement and palpable purpura which reached statistical significance in almost 50 % of the relevant studies. In contrast, splenomegaly failed to reach statistical significance in any fully adjusted analyses. As expected, based on the literature, low serum C4 levels and cryoglobulinemia were strong predictors of lymphoma/LPD development in 80 and 50 % of the articles reviewing these markers, respectively. Lymphopenia and especially CD4+ T cells have yielded interesting results. Two studies [27, 38] found a significantly lower ratio CD4+/CD8+ in those patients who eventually developed lymphoma/LPD. In addition, a recent report revealed a positive correlation between CD4+ lymphocytopenia with B-NHL and also CD4+ lymphocytopenia with other risk factors such as parotid enlargement, low serum C3 levels and cryoglobulinemia in patients with lymphoma [47]. Conversely, male sex, arthralgia, anemia, positive ANA, rheumatoid factor and hypergammaglobulinemia failed to reach the statistical significance required to be considered potential independent risk factors.

The results of this systematic review should be interpreted in the context of the reviews' limitations. First, the most important limitation is that the studies reviewed applied different pSS classification criteria (Table 1). For instance, the American-European Consensus Group (AECC) criteria [29] consider salivary gland biopsy as an essential classification tool, but only four of the studies reviewed here included it. This is relevant, because we have examined a wide spectrum of clinical, serological and hematological potential risk factors. Moreover, a recent study by Theander and colleagues [42] concluded that the presence of germinal center-like lesions (GC+) in labial salivary gland biopsies obtained at pSS diagnosis reached a significant predictive value of 16 % for NHL [38], while the predictive value of the absence of lesions achieved almost 99 %. These authors advised that patients not fulfilling the AECC criteria did not display any increased lymphoma risk. Despite more than ten SS classification criteria considered during the past decades, their performance targets were not met. None of them could differentiate between the patients who could only be classified as having pSS during the follow-up, from those who would develop another systemic autoimmune disease. Yet, this review exposed the heterogeneity of the included studies, due not only to the different criteria sets proposed for SS classification, but also to the complexity of pSS pathogenesis and lymphomagenesis yet poorly understood [48].

The diversity in lymphoproliferative evolution in pSS include several lymphoma subtypes, such as diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and in particular mucosa-associated lymphoid tissue (MALT) lymphoma [8, 12, 13, 22, 45]. The risk for malignancy appears to augment with disease duration, since cumulative risk of developing lymphoma might reach 3.4 % in the first 5 years and 9.8 % after 15 years, since the initial pSS diagnosis [27]. Also, Ioannidis and colleagues reported an increased probability of LPD of 2.6 and 3.9 % at 5 and 10 years, respectively [4]. When compared to systemic lupus erythematosus and rheumatoid arthritis (RA), lymphoid malignancies development remained elevated in pSS, possibly, due to higher levels of serum B-cell activating factor [7]. However, only two studies included patients with LPD [16, 21]. Correlation between pSS and other malignant tumors, despite remaining out of the scope of this systematic review, will also require further investigation [25, 33, 49].

Another limitation directly relates to the absence of available data in pSS, on biological or DMARD therapy, and its consequences on NHL/LPD evolution. Yet, this analysis was evaluated previously by Zintzaras and colleagues [7], but the information on the role of biological or immunomodulatory agents was limited.

In summary, according to the present review, the number of identified clinical and immunological risk predictors is broadening. All these elements could facilitate the identification of those patients at elevated risk, at the time of pSS diagnosis, which, consequently, would require closer supervision in order to anticipate lymphoma onset. The identification of lymphoma predictors does not allow the precise determination of the time of lymphoma onset. For this reason, we recommend that patients categorized as high-risk group should undergo periodical clinical assessment and complete laboratory tests including serum cryoglobulins, complete blood count, biochemical profile, protein electrophoresis and complement assays. We also consider necessary to simplify the various pSS diagnostic criteria presented, and for studies to include minor salivary gland biopsy as an essential part of pSS diagnosis.

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