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Lymphomagenesis predictors and related pathogenesis

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ABSTRACT

Sjögren's syndrome (SS) is a systemic autoimmune disease characterised by a wide range of clinical manifestations and complications, including B-cell lymphoma.

This study aims to describe the predictors associated with lymphomagenesis in patients with Sjögren's syndrome, emphasising the pathophysiological bases that support this association. We performed a review of the literature published through a comprehensive search strategy in PubMed/MEDLINE, Scopus, and Web of science. Forty publications describing a total of 45,208 patients with SS were retrieved. The predictors were grouped according to their pathophysiological role in the lymphoproliferation process. Also, some new biomarkers such as MicroRNAs, P2X7 receptor-NLRP3 inflammasome, Thymic stromal lymphopoietin, and Three-prime repair exonuclease 1 (TREX1) were identified.

The knowledge of the pathophysiology allows the discrimination of markers that participate in the initial stages. Considering that the lymphoproliferation process includes the progression of lymphoma towards more aggressive subtypes, it is essential to recognise biomarkers associated with a worse prognosis.

1. Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that predominantly affects postmenopausal women, with an estimated prevalence of 43.03 per 100,000 persons [1]. One of the most severe complications of SS is B-cell lymphoma, mainly non-Hodgkin's lymphoma (NHL), which occurs in approximately 3%–10% of patients with primary SS (pSS) [2]. The most prevalent histological types include mucosa-associated lymphoid tissue (MALT) lymphoma, followed by marginal zone lymphoma (MZL) and diffuse large B-cell lymphoma (DLBCL) [3].

The association between lymphoma and SS was first described by Kassan et al. who reported a 44-fold risk compared to the general population, and identified some factors associated with this outcome, including splenomegaly, parotid gland enlargement (PGE) and lymphadenopathy [4].

SS is considered as the prototype of a pathology involving both lymphoproliferation and autoimmunity. Lately, it has been possible to elucidate the pathophysiological components in this context and to better understand the lymphocyte proliferation process, allowing to identify new predictors of lymphoma and promoting a timely diagnostic and therapeutic approach.

The present review aims to describe the predictors associated with lymphomagenesis in SS patients, emphasising their usefulness and the pathophysiological bases that support this association.

2. Methods

We performed a review of literature published between 1978 and 2020.

The following databases were screened: PubMed/MEDLINE, Scopus and Web of science, using the Medical Subject Headings (MeSH) terms: 'Sjögren's syndrome', 'lymphoma', 'non-Hodgkin's lymphoma', 'Biomarkers', 'biologic markers', 'predictors' and 'prediction'. The non-MeSH terms were also used, including 'lymphomagenesis' and 'lymphoproliferation'. These terms were linked using the Boolean connector 'AND' and 'OR'. We included only articles published in Spanish or English. The exclusion criteria were case reports and articles without access to the

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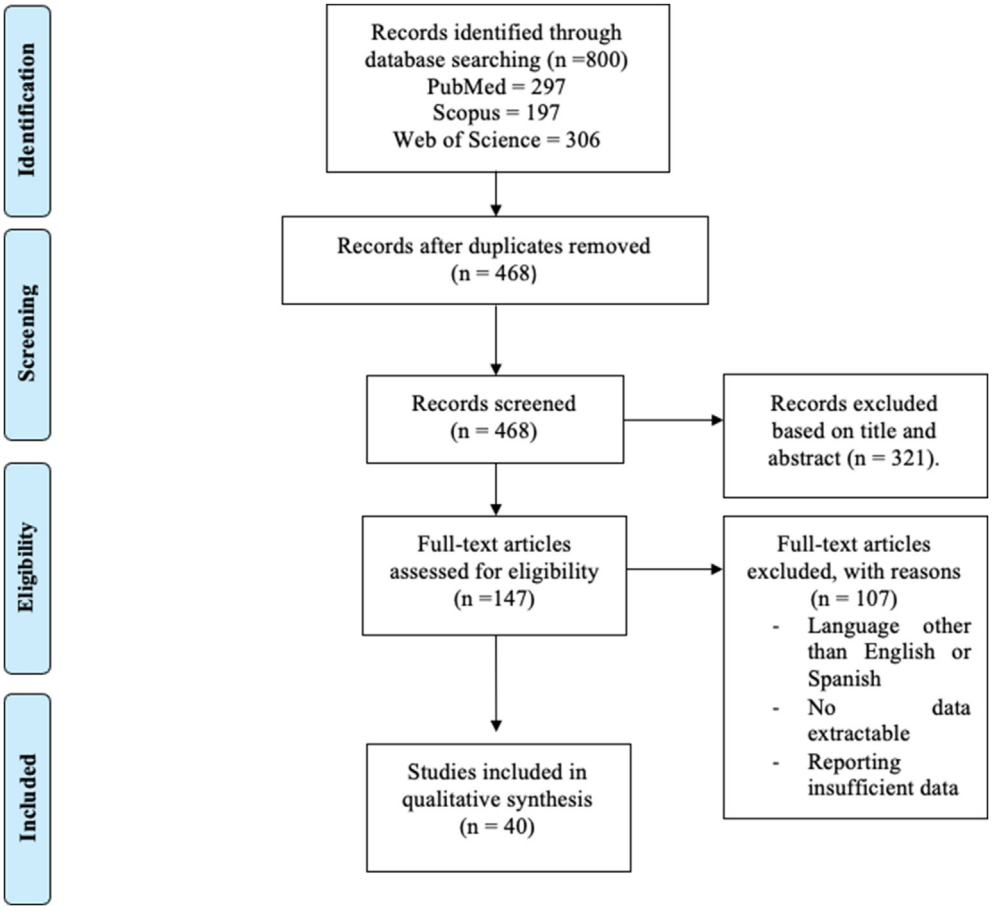

Fig. 1. PRISMA flow chart of study selection.

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The Preferred Reporting Items for Systematic Reviews and Meta-Analyses was implemented to organise the results of the databases [5]. All potentially relevant citations identified by the literature search were imported into the reference management software (Mendeley Desktop Software), where duplicates were removed. Afterward, two reviewers independently screened the abstracts, titles and keywords of the identified citations. After the studies were screened, data was extracted from each paper. This process was done using a data extraction form developed by the authors. Then, data were analysed and compiled.

3. Results

During the study selection (Fig. 1), we identified 800 studies, and 332 duplicates were removed. Of the 468 abstracts and titles screened for relevance, 147 studies were considered potentially relevant, and the data were retrieved and reviewed; of these, 107 were excluded. Finally, 40 primary research papers, defined as original papers in which the authors generated and reported their own data, were selected [6]. These studies provided data from 45,208 patients for analysis. Most of them used observational study designs, of which 50% (20/40) were retrospective and 30% (12/40) were prospective.

The general characteristics of the articles included are described in Table 1, as well as the independent predictive markers of lymphoproliferation found in each article.

4. Discussion

4.1. *Lymphoproliferation in SS*

SS appears to be a crossroad between autoimmunity and malignancy. It is the autoimmune disease conferring the highest risk of lymphoma development, estimated in 320 cases of NHL per 100.000 patient-years [7,8]. Patients with evidence of B-cell clonal expansion in their salivary glands have a high risk of developing a lymphoma [9,10]. This process also involves the progression of lymphomas [11]. Gorodetsky et al. reported the clonal relationship between MZL and DLBCL, supporting the fact that low-grade MZL may transform into high-grade DLBCL in the course of the disease [12].

Lymphoproliferation in SS is a multistate process. Consecutive steps could involve the following five mechanisms: **1)** monoclonal expansion of lymphocytes; **2)** chronic antigenic stimulation; **3)** apoptosis inhibition; **4)** *In situ* cytokines production and **5)** oncogenic mutations.

B-cell clonal expansion is an early event in the course of SS [13]. However, lymphoma development involves the progression from polyclonal to monoclonal. Auto-reactive B cells are activated and proliferate within salivary glands, probably triggered by **chronic antigenic stimulation** [14]. This notion is strongly supported by the observation of B-cell clones in pSS that express a unique pattern of immunoglobulin genes and cross-reactive idiotypes of rheumatoid factor (RF) in pSS patients, such as 17.109 encoded by vKIIIb gene [15] and G6 (VH1-related) [16].

Table 1
Characteristics of studies of lymphoma predictors in Sjögren's syndrome.

First author	Year	Country	No of lymphoma-SS related/ patients	Study design	SS selection criteria	Biomarker
Kassan [4]	1978	US	7/136	Retrospective	Clinical, laboratory and histologic evidence of keratoconjunctivitis sicca and xerostomia. All patients had typical lymphocytes infiltrate.	• Parotid swelling • Splenomegaly • Lymphadenopathy
Tzioufas [86]	1996	Greece	7/103	Prospective	1993 European criteria [128]	• Monoclonal cryoglobulinemia
Sutcliffe [35]	1998	UK	5/72	Retrospective	1993 European criteria	• Parotid swelling • Lymphadenopathy
Davidson [99]	1999	UK	4/100	Retrospective	Fox criteria (1986) [129]	• Parotid swelling • Lymphadenopathy
Pertovaara [93]	2001	Finland	3/110	Retrospective	Fox criteria (1986)	• B2M
Ioannidis [34]	2002	Greece	38/723	Retrospective	1993 European criteria	• Palpable purpura • Low C4 levels
Theander [36]	2006	Sweden	12/507	Prospective: Swedish cancer register	Copenhagen criteria (1986) [130] 1993 European criteria American-European consensus criteria (AECC) [131]	• Purpura/skin vasculitis • Low C3 levels • $CD4^+$ T lymphocytopenia • Low CD4+/CD8+ T cell ratio
Barone [56]	2006	UK	20/36	Cross-sectional	American-European criteria (AECG) (2002) [131]	• CXCL13, CCL21, and CXCL12 expression in SG biopsy
Brito-Zerón [33]	2007	Spain	9/266	Prospective	1993 European criteria	• Low C3 levels
Baimpa [90]	2009	Greece	40/536	Prospective	AECG criteria (2002)	• Neutropenia • Cryoglobulinemia • Splenomegaly • Lymphadenopathy • Low C4 levels
Zhang [132]	2010	China	29/1320	Retrospective/ Shanghai registry	AECG criteria (2002)	• Lymphadenopathy • Enlargement of parotid glands • Monoclonal immunoglobulins
Ramos-Casals [133]	2010	Spain	450	Retrospective	1993 European criteria	• Class 4 in parotid scintigraphy
Solans-Laqué [92]	2011	Spain	11/244	Prospective	1993 European criteria	• hypocomplementaemia • Lymphocytopenia
Theander [47]	2011	Sweden	7/175	Retrospective	1993 AECC	• GC-like structures
Baldini [91]	2012	Italy	12/563	Prospective	AECG criteria (2002)	• SGE • Low C4 levels • Disease duration
Ismail [134]	2013	Egypt	8/58	Retrospective	AECG criteria (2002)	• $CD4^+$ T lymphocytopenia
Tobón [27]	2013	France	18/369	Cross-sectional	AECG criteria (2002)	• Flt-3L
Nocturne [72]	2013	France	44/574	Prospective	AECG criteria (2002)	• TNFAIP3
Risselada [94]	2013	Netherlands	21/195	Retrospective	AECG criteria (2002)	• IgM-kappa clonal components
Johnsen [135]	2013	Norway	7/443	Population based	AECG criteria (2002)	• High focus score • Longer pSS duration • Younger age at pSS diagnosis
Quartuccio [38]	2014	Italy	40/661	Retrospective, multicentre	AECG criteria (2002)	• Anti-La/SSB • Leukopenia • Low C4 levels • Serum cryoglobulins
Abrol [136]	2014	UK	43/152	Retrospective	AECG criteria (2002)	• Vasculitis • Glandular manifestations
Rissselada [68]	2014	Netherlands	16/174	Retrospective	AECG criteria (2002)	• FS $\geq$ 3 on MSGB
Papageorgiou [76]	2015	Greece	70/177	Retrospective	AECG criteria (2002)	• BAFF-R His159Tyr mutation
Nishishinya [37]	2015	Spain	15,000	Systematic review	Various	• Lymphadenopathy • Parotid enlargement • Palpable purpura • Low c4 serum levels • Lymphopenia
Nocturne [57]	2015	France	385	Prospective	AECG criteria (2002)	• Serum CXCL13 • Serum CCL11
Nezos [40]	2015	Greece	13/70	Retrospective	AECG criteria (2002)	• IFNγ/IFNα mRNA ratio in MSGB
Ciccia [66]	2015	Italy	17/30	Retrospective	AECG criteria (2002)	• IL-22 receptor 1 (IL-22R1)
Fragkioudaki [39]	2016	Greece	92/473	Retrospective	AECG criteria (2002)	• SGE • Lymphadenopathy • Raynaud phenomenon • Anti-Ro/SSA and Anti-La/SSB • Rheumatoid factor positivity • Monoclonal gammopathy • C4 hypocomplementemia
Brito-Zerón [137]	2017	Spain	46/1300	Prospective	AECG criteria (2002)	• ESSDAI • Cryoglobulins • Cytopenia • Low C3 and C4 levels

(*continued on next page*)

Table 1 (*continued*)

First author	Year	Country	No of lymphoma-SS related/ patients	Study design	SS selection criteria	Biomarker
Chiu [138]	2017	Taiwan	36/16,396	Population-based	AECG criteria (2002)	• Monoclonal gammopathy • Age
Baldini [116]	2017	Italy	5/147	Prospective	AECG criteria (2002)	• P2X7 receptor-NLRP3
De vita [100]	2018	Italy	30/255	Prospective	AECG criteria (2002)	• SGE • Cryoglobulinemia
Sène [49]	2018	France	8/115	Retrospective	AECG criteria (2002)	• GC-like structures • Cryoglobulin • Male gender • Sensorimotor neuropathy • Splenomegaly
Nezos [126]	2018	Greece	89/318	Retrospective	AECG criteria (2002)	• TREX-1 variants
Kapsogeorgou [111]	2018	Greece	52/79	Cross-sectional	AECG criteria (2002)	• miR200b-5p
Schenone [139]	2019	Argentina	16/681	Restrospective, multicentre	American-European criteria (2002) ACR/EULAR criteria (2016) [140]	• ESSDAI
Delli [88]	2019	US, Netherlands	1418	Systematic review	Various	• Parotid swelling • Mixed monoclonal cryoglobulins • Low C4 levels
Gandolfo [122]	2019	Italy	21/275	Prospective	ACR/EULAR criteria (2016)	• TSLP
Traianos [141]	2020	UK	38/359	(UKPSSR) Registry	AECG criteria (2002)	• Serum CXCL13 levels

ACR: The American College of Rheumatology, B2M: Beta-2 microglobulin; ESSDAI: The European League Against Rheumatism (EULAR) Sjögren's syndrome (SS) disease activity index (ESSDAI); Flt3-L: Fms-like Tyrosine Kinase 3 Ligand; FS: Focus score; GC: Germinal center; MSGB: Minor salivary gland biopsy; SG: Salivary gland; SGE: Salivary gland enlargement; UKPSSR: United Kingdom Primary Sjögren's Syndrome Registry; TSLP: thymic stromal lymphopoietin.
* Note: The biomarkers reported in the table correspond to independent risk factors associated to lymphoma development found in each study, mostly extracted from the multivariate analysis.

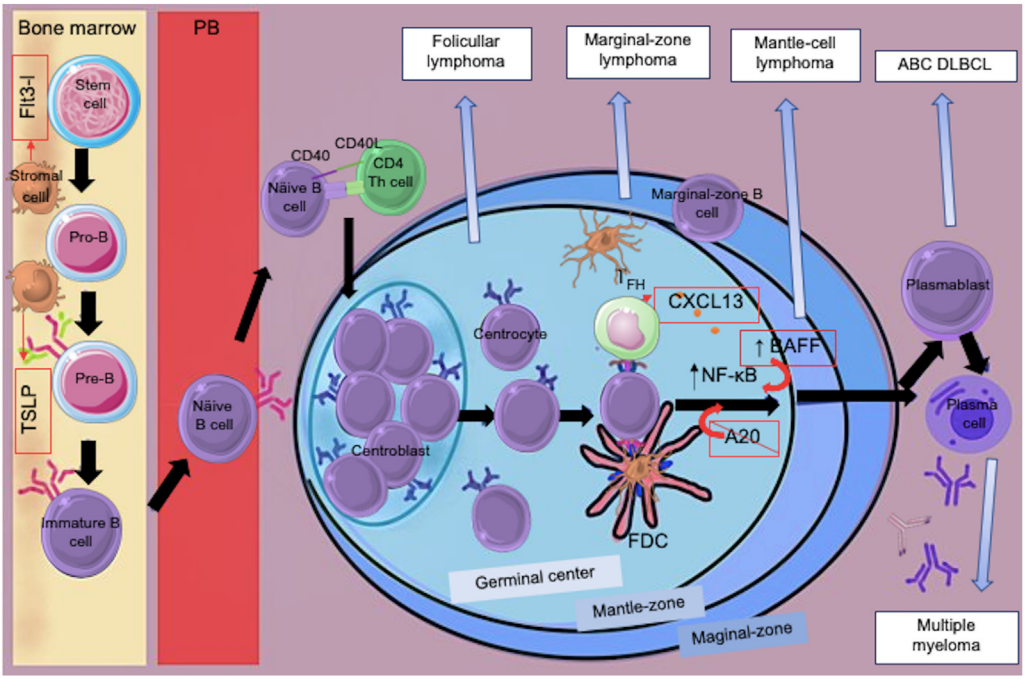

Fig. 2. Stages of B cell maturation and activation. Also, some lymphoma predictors and germinal center derived lymphomas according to their order of appearance or progression in the pathophysiological process. Activated B cell-like diffuse large B-cell lymphomas (ABC DLBCL); BAFF, B cell activation factor; CXCL13, Chemokine (C-X-C motif) ligand 13; FDC: Follicular dendritic cell; Flt3-l, protein-ligand FMS-like tyrosine kinase 3; T_{FH}, T follicular helper cells; TSLP, Thymic stromal lymphopoietin.

Upon exposure to an antigen in the secondary lymphoid organs, B cells enter the secondary follicle to form the germinal center (GC), where they undergo several biological processes. Under normal conditions, the GC formation is regulated by the transcriptional factor B-cell lymphoma 6 (BCL6) by silencing the anti-apoptotic BCL2 during the somatic hypermutation (SHM) process [17]. Translocations affecting BCL2 occur early during B-cell development, but its dysregulation contributes to lymphomagenesis at later stages during the GC reaction [18]. It promotes the scope of BCL2 from BCL-6-mediated repression and its ectopic expression with consequent **apoptosis inhibition** [19].

Salivary gland (SG) immunohistochemistry studies have shown T cells infiltration comprising mild lesions, whereas B cells are found at advanced SS stages. Several cytokines and chemokines associated with the B lymphocytes are expressed in minor SG (MSGs) (***in situ* cytokines production**), contributing to GC-like structures formation [20]. The SHM process occurring in the dark zone of the GC is a crucial contributor to the development of lymphoid neoplasm by increasing the **oncogenes' translocation** risk [21,22]. The accumulation of genetic alterations frequently results in the activation of the nuclear factor kappa-B (NF-κB) pathway, promoting lymphoma development [23].

The mechanisms involved in the lymphoproliferation process can include epigenetic, genetic, immunological and histological factors that

intervene in the B lymphocyte's continuous activation. An approach for lymphoma predictors will be made according to their appearance order in the pathophysiological process.

4.2. B-cell development

B-cell lineage commitment is initiated from haematopoietic stem cells (HSCs) in the bone marrow (Fig. 2). Maturation of HSCs is regulated by a large number of haematopoietic growth factors or cytokines, such as the protein-ligand **FMS-like tyrosine kinase 3 (Flt-3L)**.

The Flt-3L is an important regulator of lymphopoiesis. Its receptor is expressed on multipotent progenitors and sustained on the earliest B-cell and T-cell progenitors [24,25]. **Flt-3L** is found as membrane-bound and soluble forms. It has been observed that **Flt-3L** enhances the reconstitution of the B-cell compartment after myeloablation and bone marrow transplantation [26], appearing to be essential for B lymphopoiesis. The first evidence of **Flt-3L** as a marker of lymphoproliferation was provided by Tobón et al. [27] who demonstrated that increased serum levels above 175 pg/mL were associated with lymphoma in SS patients. Another interesting finding of this study was that in six patients with pSS whose serum samples were available prior to the development of lymphoma, the serum levels of Flt-3L were found to be elevated up to 94 months before the diagnosis of NHL, highlighting the possible utility of Flt-3L as a predictive factor for lymphoma development.

B-cell development is a regulated process during which several transcription factors, modulators and extrinsic signals participate in the immunoglobulin (Ig) loci rearrangement [28]. If it occurs within the reading frame, it will produce a κ chain associated with the previously synthesised μ chain, which will form a complete IgM protein giving rise naïve B cells (16,27). After successful V(D)J recombination and expression of functional B-cell receptors, naïve B cells leave the bone marrow and migrate to peripheral lymphoid tissues.

4.3. Antigen chronic stimulation

The antigen chronic stimulation has been proposed as a cardinal mechanism in the pathophysiology of SS associated to lymphoma, where the first step in this process is the formation of an immunocomplex (IC) [29,30].

Increased epithelial cell apoptosis and exosome release lead to the immunogenic exposure of autoantigens [31]. Later in pSS, the formation of IC containing mainly ribonucleoproteins can stimulate Toll-like receptors (TLR7 or TLR9) of plasmacytoid dendritic cells, favouring the production of type I interferon (IFN-a) [31,32], an important characteristic of SS.

On the other hand, regarding the most useful markers for the diagnosis of SS, including anti-SSA/Ro and anti-SSB/La, there is little evidence in favour of its predictive value related to the development of lymphoma [33–39].

4.3.1. The IFN-γ/IFN-α mRNA ratio

An IFN-I signature usually predominates in pSS. However, in the context of lymphomagenesis, an increase in IFN-γ transcripts has been observed in minor salivary gland biopsies (MSGB), concomitantly with a low expression of IFN-α. After this evidence, Nezos et al. [40] proposed an IFN-γ/IFN-α mRNA ratio as a histopathological marker for the prediction of lymphoma in the context of SS. They also performed the same analysis (real time-PCR for interferon-inducible genes) on peripheral blood without significant differences between SS with or without lymphoma. However, as a limitation, they used independent peripheral blood and MSGB cohorts.

Historically, IFN-γ has been recognised for its leading role in antitumour immunity. However, it also exerts a pro-tumoral function. For example, the IFN pathway's target genes have been shown to be involved in immunosuppressive and immune-evasive mechanisms aimed at suppressing the antitumour immune response mediated by cytotoxic T lymphocytes and natural killer (NK) cells [41].

4.3.2. B-cell activating factor (BAFF)

On the other hand, it has been observed that the stimulation of IFN-α and IFN-γ in epithelial cells of the SG favours the expression of the BAFF belonging to the tumour necrosis factor (TNF) family [42], which in turn stimulates the activation of B lymphocytes.

As mentioned above, B lymphocyte activation is essential in the lymphoproliferation process. BAFF mediates different molecular events that intervene in the function and survival of the B lymphocyte and, therefore, in this offspring's pathogenesis. Polymorphisms linked to BAFF will be described further. However, it has been described that the increase in serum levels and the subsequent clonal expansion of B lymphocytes in SG tissue is characteristic of SS and it is more pronounced in SS patients with a B cell lymphoproliferative disorder [43].

4.4. Germinal centers

The presence of GC-like structures supports the continuous activation of B cells. GC are transitory structures where different events occur, such as affinity maturation and class switching [28]. The SHM is a necessary process for affinity maturation; however, it confers a high risk of lymphoma by favouring different oncogenes' translocation [44–46].

GC themselves have been identified as markers of lymphoproliferation. Theander and Sène are some of the authors who have described the evidence in favour. Theander et al. [47] evaluated the presence of these structures in MSGB during the follow-up of 175 patients with pSS. Six out of seven patients with lymphoma were found to have structures similar to the GC at the diagnosis of pSS, with a median of seven years before malignancy development.

It is important to note that, in general, the low number of events limits the interpretation in favour of the associations found between biomarkers and lymphoma development. Nevertheless, although the risk of lymphoma in patients with pSS is high in comparison with healthy people, the estimated frequency of this event is approximately 5% [11].

Subsequently, Sène et al. evaluated this risk factor through a multicentre study, identifying that the presence of GC-like structures was associated with a 7.8-fold risk of lymphoma occurrence (95% CI: 1.73–34.86, $P = 0.0075$) [48]. The greatest criticism that has been raised against this marker is that the presence of GC is dependent on the activity of the disease and maybe a surrogate of it. Additionally, the marking of GC is usually performed on MSGB and not in the sites where MALT lymphoma preferentially develops [49].

4.4.1. Formation of GC

The entry of B lymphocytes into the follicles is favoured mainly by the expression of CXCL13 by follicular dendritic cells (fDC). In SS, epithelial cells play an active role in the disease pathogenesis by expressing CXCL13 (28). This chemokine has been widely implicated in the development of lymphoproliferative disorders due to CXCL13 overexpression that favours the formation of ectopic GCs [20,50].

Another crucial cell for GC is the T follicular helper cell (Tfh cells), which characteristically produces IL-21 and express the ligand for CD40 (CD40L) [51]. The interaction between CD40 on GC B cells with CD40L on Tfh cells helps maintain GC responses, high-affinity bone marrow plasma cells, and memory B cell production [52]. Also, IL-21 maintains BCL6 expression in GC B cells, controlling the maintenance and optimal affinity maturation of the GC response [53,54]. It has been suggested that Tfh cell infiltrates may influence the growth and survival of certain lymphoid tumours. T cells with phenotypic features of Tfh cells secreting abundant IL-4, TNF, IFN-γ, and lymphotoxin-α typically infiltrate follicular lymphomas, and their number appears to be a significant predictor of outcome, with worse prognosis when they are localized to neoplastic follicles [55].

4.4.2. Chemokine (C-X-C motif) ligand 13 (CXL13)

The clinical utility of CXCL13 as a biomarker in lymphoproliferation has been demonstrated. Barone et al. [56] found that the ectopic expression of CXCL13 and chemokine (CC motif) ligand 21 (CCL21) were involved in the formation of the GC, thereby infiltrating lymphoepithelial lesions (lymphoepithelial sialadenitis or LESA). They included a small number of patients (n = 12) and compared the expression of the chemokines in the salivary glands of SS patients with LESA and patients with SS-associated MALT lymphoma. However, they were diagnosed with lymphoma before the inclusion in the cohort. Therefore, this supports and association between SS and lymphoma, rather than its value as a predictive marker.

Besides, Nocturne et al. [57] found that high serum levels of CXCL13 and CCL11 (eotaxin 1) correlated with lymphoma occurrence. This finding is important considering that the MSGB is invasive and has a variable performance [58].

4.4.3. Interleukin 22 and 18 (IL-22 and IL-18)

In the process of lymphomagenesis, other molecules have been identified to intervene in the formation of ectopic GC or tertiary lymphoid structures. Among these molecules, **IL-22 and IL-18** are described as lymphoproliferation markers.

IL-22 belongs to the IL-10 family. It is produced mainly by CD4 Th17 T lymphocytes and, a lesser extent, by other subtypes of T lymphocytes, NK cells and DC [59]. It has been involved in malignant epithelial proliferation, and it has been proposed that it plays a role in the development of tertiary lymphoid structures by influencing the production of CXCL12 and CXCL13 [60].

IL-22 activates IL-10R2 and IL-22R1 subunits' heterodimeric receptors, the latter confined to the epithelial cell compartment. Hence, it can act as a messenger between this compartment and the lymphocytes [61].

IL-18 is produced by monocytes, macrophages and epithelial cells. It facilitates IFNγ production by Th1 T lymphocytes, particularly in conjunction with IL-12 [62], IL-18 and IL-12. In turn, interleukins are pleiotropic pro-inflammatory cytokines [63].

IL-18 and IL-22 exert a positive regulation between them, and the counter-regulation depends on antagonistic variants, consisting of soluble receptors such as the binding protein of IL-18 (IL-18BP) and IL-22 (IL-22BP), respectively [64]. In patients with pSS, the infiltration of MSGB by macrophages and DC with the expression of IL-18 and IL-12 was demonstrated with a possible role in the development of chronic inflammatory lesions. Additionally, a correlation was observed between IL-18 and other predictors of lymphoma, such as C4 hypocomplementaemia and enlargement of the SGs [65].

Ciccia et al. [66] identified an increase in the expression of IL-22 and IL-18 in the MSGB of patients with SSp and NHL and aberrant IL-22R infiltration in macrophages and infiltrating myeloid cells. They also demonstrated the specific aberrant activation IL-18-driven, of the IL-22R1/STAT-3 pathway.

4.4.4. High focus score (FS)

The histological diagnostic approach of SS includes the observation of at least one focus in the MSGB, defined as the presence of lymphocytic infiltrates with >50 lymphocytes/4 mm^2 [67]. The FS reveals the severity of the autoimmune inflammatory process. Risselada et al. demonstrated that the FS $\geq$ 3 was associated with an increased risk of lymphoma with a positive predictive value of 16%, and a negative predictive value of 98% [68].

4.5. Disruption of signalling pathways

4.5.1. NF-kB pathway

Several aberrantly activated pathways are involved in lymphomagenesis, such as the NF-kB and B cell receptor (BCR) pathways [69]. Mutations in molecules that regulate or alternatively activate this signalling pathway have been identified as markers of lymphomagenesis.

Briefly, the NF-kB is a major transcription factor critical for several physiologic cellular functions [70]. Its constitutive activation is a feature of most types of B-cell lymphomas, particularly the extranodal marginal zone B-cell lymphoma. NF-kB signalling is categorised into canonical and non-canonical pathways. The canonical pathway is activated by the BCR, Toll-like receptors and TNF family receptors, while the non-canonical pathway is activated by other receptors, such as the B cell activating factor receptor (BAFF-R) and CD40 [71]. The dysregulation of the NF-kB via chromosomal translocations, mutations or somatic deletions may influence the survival and proliferation of lymphoma cells [70].

4.5.2. TNF α-induced protein 3 (TNFAIP3)

The TNFAIP gene encodes the A20 protein, which exerts negative NF-kB regulation and plays a significant role as a tumour suppressor gene by controlling B lymphocytes' stimulation.

A20 restricts NF-kB activities through inactivation of several critical proteins, such as receptor-interacting serine/threonine-protein kinase 1/2 (RIP1/2), TNFR-associated factor-6 (TRAF6), NF-κB essential modulator (NEMO) and transforming growth factor beta-activated kinase (TAK) [70].

Nocturne et al. [72] reported that 77% of patients with pSS and MALT lymphoma had functional abnormalities of the A20 protein in the lymphomatous tissue. Particularly, the rs2230926 exonic variant enhances the risk of lymphoma in pSS patients. In two genome-wide association studies carried out in a population with European ancestors and the Han ethnic group's Chinese population with pSS, the presence of polymorphisms of the TNFAIP gene was identified [73,74].

4.5.3. B cell activation factor (BAFF)

Polymorphisms (SNPs) of the BAFF have been associated with pSS-related lymphomagenesis. Nezos et al. [75] found a high risk of lymphoma in the pSS group, characterised by an increased frequency of the minor T allele of rs9514828 compared to the healthy controls.

Moreover, an increased prevalence of the BAFF-R His159Tyr mutation was detected, conferring the risk of lymphoma through the non-canonical NF-κβ pathway [76].

4.6. Biological reflex of lymphoproliferation

4.6.1. Cryoglobulinaemia

The RF corresponds to an IgM directed against the Fc portion of immunoglobulin G. It is frequently associated with mixed cryoglobulinaemia, corresponding to precipitable immunoglobulins under temperatures below 37° [77].

This process is pathophysiologically explained as follows: chronic stimulation by autoantigens in the GC can lead to the formation of immune complexes and the subsequent stimulation of RF + B lymphocyte clones in the marginal zone, precipitating monoclonal expansion and promoting the lymphomatous escape [78–81]. Monoclonal RF can form complexes with polyclonal IgG and cryoprecipitates [82].

The transformation of clones from polyclonal to monoclonal conditions a decreasing in RF with respect to baseline values [83], which constitutes a marker of lymphoproliferation, together with monoclonal gammopathy and cryoglobulinemia.

The presence of cryoglobulins is considered an important factor in the development of lymphoma, in the same way, it is correlated with the greater systemic activity of the disease [11,84]. Its frequency of presentation is approximately 3%–4% of patients with SS [38,85,86].

4.6.2. C4 hypocomplementaemia

As we described above, lymphoproliferation's pathogenesis involves the formation of IC at the level of the ectopic-germinal-like centers in salivary glands. Therefore, these IC may activate the complement via the classical pathway, resulting in low C4 and C3 levels, mainly the first one mentioned [87].

Table 2
Prediction models or scores of lymphomagenesis.

First author	Predictors of lymphomagenesis	Risk of lymphomagenesis
Ioannidis	6. Parotid enlargement 7. Palpable purpura 8. Low C4 levels	Presence of ≥1 predictor confers a 9.08-fold risk of developing lymphomagenesis.
Baimpa	9. Cryoglobulinemia 10. Neutropenia 11. Low C4 levels 12. Lymphadenopathy 13. Splenomegaly Group A (low risk) none of lymphoma predictors. Group B (high risk) at least one predictor.	Group B had a probability of 20.6% for lymphoma developing compared with 3.6% for a group A patient.
Quartuccio	14. Cryoglobulins 15. Low C4 16. Anti-La/SSB 17. Leukopenia	Presence of ≥2 biomarkers confers 10-fold risk of lymphoma (AUC: 0.82 CI 0.76–0.87).
Fragkioudaki	- SGE - Lymphadenopathy - Raynaud phenomenon - anti-Ro/SSA - anti-La/SSB autoantibodies - RF positivity - Monoclonal gammopathy - Low C4 levels	Patients presenting with 2 risk factors had a 3.8% probability of NHL development, those with 3–6 risk factors 39.9%, while in the presence of all 7 risk factors the corresponding probability reached 100%.
Pzoulas	- Low C4 levels - RF - Lymphadenopathy	Decision tree model based on the presence of the biomarkers mentioned above with an accuracy of 87.1% and AUC of 88 ± 6%.

AUC: Area under the curve; RF: Rheumatoid factor; SGE: Salivary gland enlargement.

Several studies, including a systematic review [88], associate this finding with the risk of lymphoma development. Ioannidis et al. [34], Theander et al. [89], Baimpa et al. [90], Baldini et al. [91] and Quartuccio et al. [38] through a multivariate model found that C4 hypocomplementaemia was an independent factor for the development of lymphoma and a factor related to the increase in mortality (Table 2).

Although low C3 serum levels have been revealed as independent risk factors in some studies [33,36,92], others have been unable to demonstrate this association [34,37,90,93,94].

4.6.3. Increased levels of serum Beta-2 microglobulin (B2M)

The high levels of B2M are also associated with lymphoma. B2M forms the light subunit of the major histocompatibility complex (MHC) class I antigen, and it binds non-covalently to MHC class I molecules [95,96]. The biological mechanism underlying the predictive value of B2M is not fully understood. Thus far, its usefulness as a prognostic factor has been demonstrated, hypothesised by the direct relation with the tumour burden when released from the cell membrane or cytoplasm, correlating with the cell turnover rate [97].

As a predictive factor, B2M reflects the degree of activation of the immune system. Pertovaara et al. found that patients with pSS and subsequent lymphoma had higher baselines levels of B2M [93].

4.7. Clinical reflex of lymphoproliferation

The constant activation of B lymphocytes, and the clinical evolution towards lymphoproliferation, can manifest clinically with lymphadenopathy, splenomegaly, PGE, etc. The evidence is shown below:

4.7.1. Lymphadenopathy and splenomegaly

Kassan et al. were the first to document the presence of clinical and paraclinical signs that conferred an increased risk of developing lymphoma in pSS. Among the markers of lymphoproliferation, the presence of parotid enlargement, splenomegaly and lymphadenopathy stood out [4]. The main clinical features include reflex aberrant lymphocytic activation.

To date, only Baimpa et al. confirmed the association between the presence of splenomegaly and the development of lymphoma [90]. In the meta-analysis performed by Nishishinia et al., splenomegaly failed to reach statistical significance [98]. Nevertheless, lymphadenopathy predicts lymphoma in patients with pSS according to several reports [4,34,35,88,90,99].

4.7.2. Persistent SG swelling

SG swelling defined as a swelling lasting for at least two months reflects the biologic background of pSS and it is closely linked to the lymphoma evolution [13,98,100–102]. Approximately two third of pSS patients with MALT lymphomas involve the parotid gland with a slow rate of progression [11]. A strong relationship between lymphoproliferation in pSS patients and parotid enlargement has been reported in the literature [4,33–35,37,38,94].

4.7.3. Cutaneous vasculitis

Vasculitic involvement, particularly palpable purpura, has been commonly reported as an independent predictive marker of NHL development [11,34,36,39,103,104].

Nevertheless, some studies, such as the one by Risselada et al. [94], proposed that this manifestation may be a paraneoplastic phenomenon, supported by the lack of prospective studies to delimit the time interval between the presence of palpable purpura and the development of lymphoma.

4.7.4. Peripheral neuropathy

Peripheral neuropathy, particularly sensorimotor, is considered a significant marker of pSS disease activity and drives a risk excess of lymphomas [48,94,105]. For example, patients with pSS sensorimotor neuropathy more frequently have positive serum markers of monoclonal B-cell proliferation, such as monoclonal gammopathy and cryoglobulins [105]. In addition, peripheral neuropathy is related to a cryoglobulin-mediated-Vasculitic process [106,107].

4.7.5. The European League Against Rheumatism Sjögren's syndrome (SS) disease activity index (ESSDAI)

The ESSDAI is a validated clinical index designed to measure systemic disease activity in patients with pSS. It includes 12 domains: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, haematological, glandular, constitutional, lymphadenopathic and biological; each one is divided into 3–4 levels of activity [108].

The ESSDAI is an essential tool for assessing patients with a higher risk of developing lymphoma. Retamozo et al. [11] found a more significant relationship with the cutaneous, glandular and lymphadenopathy domains, as well as De vita et al. [100].

4.8. Novel biomarkers

4.8.1. miR200b-5p

MicroRNAs (miRNAs) are a large family of small non-coding RNA molecules that negatively regulate post-transcriptional protein-coding gene expression [109]. Prior studies have noted the importance of miR200 in inhibiting malignant cell transformation, thus preventing tumour initiation [110]. Specifically, the miR200b-5p is considered an essential regulator of epithelial-to-mesenchymal transition, a necessary process for cell acquisition of migratory and invasive properties [111].

Kapsogeorgou et al. [111] examined the expression of miR200b-3p and miR200b-5p in the MSGs of SS patients and sicca controls. They found that the miR200b-5p levels were significantly lower in the MSGs of high-risk patients with SS who were diagnosed with NHL during follow-up, in contrast with low-risk patients who did not develop lymphoma, and correlated with adverse prognostic markers. Also, its expression was impaired years before lymphoma development. Indeed,

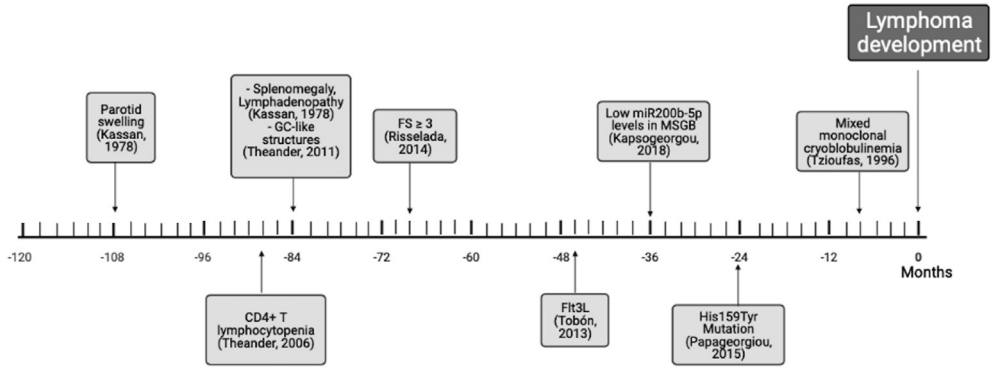

Fig. 3. Biomarker timeline prior to lymphoma development. Shown are chronologically organized the biomarkers when detected before lymphoma development. The dates correspond to the median or mean time reported in the different studies.

this miR constitutes a novel predictive marker for NHL in SS patients. The median follow-up time to NHL diagnosis was 3.67 (IQR: 0.42–8.5) years, and this downregulation long before the clinical onset of lymphoma supports its potential as a predictive biomarker.

4.8.2. P2X7 receptor-NLRP3 inflammasome

The $P2X_7$ receptor ($P2X_7R$) is an ATP-gated ion channel that plays an essential role in the innate immune response, mediating several inflammatory pathways [112]. $P2X_7R$ mediates the activation of the NOD-like receptor family py rin domain containing 3 (NLRP3). The latter stimulates caspase-1 activation and the subsequent release of the mature forms of IL-1b and IL-18 [112]. These cytokines are involved in a chronic state of inflammation and tissue damage [113]. Moreover, the expression of $P2X_7R$ and the inflammasome components in MSGs have been correlated with the FS [112].

Both IL-1b and IL-18 participates in the orchestration of the formation of GC-like structures in the salivary glands [112,114,115]. Baldini et al. [116] found an increased expression of the axis $P2X_7R$-inflammasome in glandular biopsies taken at diagnosis of the SS, years before the development of MALT-NHL, suggesting that this axis could represent a potential biomarker useful for patients with a high risk of lymphoma. It is worth highlighting the strength of the evidence provided by this study, in which 147 patients with SS were followed up for a period of 52 months, five of them developed MALT-NHL lymphoma. Additionally, the increase in expression of the P2X7R-inflammasome axis was confirmed by different techniques at different levels. That is, an increase in gene expression was found through RNA extraction and RT-PCR, at the protein level through Western blot, and in tissue by immunohistochemistry. Integrating the role of the innate immune response in the pathophysiology of lymphoproliferation and in which temporality and follow-up allow it to be constituted within the framework of lymphoproliferation biomarkers.

4.8.3. Thymic stromal lymphopoietin

Thymic stromal lymphopoietin (TSLP) is a member of the interleukin (IL) 2 family and a distant paralog of IL-7, essential for lymphoid development [117–119]. TSLP mediates signalling through TSLPR, a type I cytokine receptor, and IL-7Rα. TSLP and IL-7 are united by common features involving the structure and cross-utilisation of IL-7Rα [120]. TSLP has been found in the induction and progression of various tumours, including haematological tumours such as B-cell acute lymphocytic leukaemia (B-ALL) [121].

Gandolfo et al. [122] provided evidence of an increase in the serum TSLP levels from myoepithelial sialadenitis (MESA) to NHL in prospective sera from single patients. Furthermore, in SG biopsies, TSLP-positive B lymphocytes increased with lymphoproliferation, maximally in NHL. This study presents the first evidence of the possible pathogenic role of TSLP in SS patients, and significantly it was reproduced on salivary gland biopsy and serum. It has a few patients. However, the number of SS patients and controls according to the lesions found on salivary gland biopsy is proportional.

4.8.4. Three-prime repair exonuclease 1 (TREX1)

The TREX1 encodes an exonuclease for the DNA repairing, replication and recombination pathways. The most important role is to maintain host innate immune tolerance to cytosolic self-DNA [123,124]. Persistence of the ssDNA species substrate of TREX1 triggers autoimmunity by chronic activation of checkpoint signalling and GMP–AMP synthase (cGAS) and its downstream signalling effector stimulator of interferon genes (STING) (cGAS-STING)-mediated IFN-I response [123,125].

Nezos et al. [126] found that in the setting of SS, decreased prevalence of rs11797 was associated with high type I IFN-related transcript levels in MSGs tissues, implying a potential mechanism of TREX1-related lymphomagenesis in the context of SS.

It should be noted that no statistically significant differences were detected in the frequency of the three TREX-1 gene variants evaluated (rs11797, rs3135941, rs3135945) between SS patients with or without lymphoma and healthy controls. Additionally, the finding of the decreased prevalence of rs11797 was detected in a subset of SS patients complicated with non-MALT lymphomas, which were the smallest group of patients (19 patients) compared with healthy controls ($n = 240$), limiting the statistical power. The contribution of the TREX1 rs11797 variant seems to play a role in the pathogenesis of SS-related lymphomas more than a lymphomagenesis biomarker.

5. Conclusion

The ongoing investigation on the pathogenesis of pSS and lymphomagenesis has led to the identification of novel prognostic markers. However, many studies on SS-lymphoma-related biomarkers have been limited to small sample sizes, cross-sectional studies, and differing primary SS classification criteria. Also, the low number of lymphoma cases implies low precision in the statistical analysis.

Additionally, the pathogenesis of lymphoma development is not well understood, and it is a heterogeneous and complex process. Moreover, lymphoma predictors related to the single hypothesis mechanism would not accurately predict the risk of lymphoma development in most cases.

The predictive biomarkers for assessing the lymphoma risk may help clinicians ameliorate the management of SS patients and provide information on the pathophysiological mechanism. However, only a minority have been adopted in clinical use; this is probably due to the lack of validation data [127]. Some of the biomarkers have not been subsequently tested on separate patient sample cohorts as the following: BAFF-R His159Tyr mutation, Serum CCL11, IFNγ/IFNα mRNA ratio in MSGB, IL-22 receptor 1 (IL-22R1), P2X7 receptor-NLRP3, TREX-1 variants, miR200b-5p, and Flt-3L.

Although many of these studies included internal validation techniques in which cohorts were separated into multiple samples, external validation is considered the most effective way to validate a biomarker. More studies are needed in this regard.

Another critical aspect to keep in mind is that very few studies documented the time span between the measurement of the biomarker and the onset of lymphoma. Most of the studies made a comparison based on the presence or absence of lymphoma and subsequently determined the biomarker in question. We made an approximation through a timeline considering the time in months in which the presence of the biomarker was verified before lymphoma development (Fig. 3). For example, Kassan and et al. argued that the clinical findings were not a paraneoplastic manifestation since they preceded the development of lymphoma for many years. For example, parotid swelling was found on average nine years before the diagnosis of lymphoma, while cryoglobulinemia was documented by Tzioufas et al. eight months earlier. It means that considering the temporality, clinical signs may offer good performance in terms of prediction.

Further studies with prospective cohort designs are needed to determine the timing between pSS diagnosis and the development of lymphoma, in order to recognise early predictive markers. Perhaps the knowledge of the pathophysiology allows the discrimination of markers that participate in the initial stages.

Likewise, it is necessary to consider that the lymphoproliferation process includes the progression of lymphoma towards more aggressive subtypes. Therefore, it is essential to recognise biomarkers associated with a worse prognosis.

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Declaration of competing interest

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