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# Risk Predictors for Lymphoma Development in Sjogren Syndrome - A Systematic Review

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## ABSTRACT

**Introduction:** *Sjogren* syndrome is a systemic autoimmune disease characterized by lymphocytic infiltrates of salivary and tears glands, leading to oral and ocular dryness and by autoantibody secretion. The association between primary *Sjogren* syndrome and lymphoma, mostly non-Hodgkin's lymphoma or lymphoproliferative disease, has been documented for the past 40 years. The aim of our systematic review was to evaluate the available evidence regarding the identification of serological and hematological predictors for lymphoma in *Sjogren* syndrome patients.

**Materials and Methods:** Articles were searched and selected through PubMed. Hand search from the relevant journals was also performed. Articles were reviewed and analyzed. The articles were reviewed based on serological and hematological risk predictors such as Anti-Ro antibodies, Anti-La, C3 levels, C4 levels, Cryoglobulins, Lymphopenia, anemia, antinuclear antibodies (ANA), and Rheumatoid Factor positivity.

**Results:** Review of these articles showed significant associations of prognostic factors with development of lymphoma. Within the limitations, Identification of a high-risk phenotype for lymphoma development at the time of *Sjogren* Syndrome diagnosis has been a major diagnostic challenge over years.

**Conclusion:** All these factors act as a guide to identify patients with high risk at the time of diagnosis leading to an increase in disease free survival rate.

**Key Words:** Sjogren syndrome, Lymphoma, Risk Predictors, Autoantibody, Antinuclear antibodies, Rheumatoid Factor

## INTRODUCTION

*Sjogren* syndrome (SS) is a systemic autoimmune disease characterized by lymphocytic infiltrates of salivary and lacrimal glands, leading to oral and ocular dryness.<sup>1</sup> It can be encountered either alone (primary *Sjogren's* syndrome) or in the presence of other systemic autoimmune diseases (secondary *Sjogren's* syndrome), such as rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory myositis or systemic sclerosis.<sup>2</sup> Its estimated prevalence ranges from 0.6 to 6 per 1000. The association between primary *Sjogren* syndrome (pSS) and lymphoma, mostly non-Hodgkin's lymphoma (NHL) or lymphoproliferative disease (LPD), has been documented for the past 40 years.<sup>3</sup>

1 in 5 patients of pSS patients die due to lymphoma<sup>4</sup> Increased incidence rate of NHL among these patients is 40 times more compared to the general population. The most

common histological lymphoma type among primary SS patients is mucosa associated lymphoid tissue (MALT), which is found mostly in the salivary glands.<sup>5</sup> Lymphoma in patients with SS is considered a multifactorial process. Chronic antigenic stimulation, chromosomal translocations and polymorphisms of molecules with regulatory role in both innate and adaptive immune activation pathways<sup>6,7</sup> have been so far implicated.

Generally, patients with *Sjogren* syndrome of all ages are affected, but common among menopausal women in the fourth and fifth decades of life. The female: male ratio of SS patients 9:1<sup>8</sup> Various studies have showed clinical and laboratory features associated with increasing risks of developing NHL in patients with SS; such features include major salivary gland enlargement, splenomegaly, lymphadenopathy, purpura, low complement level, especially C4, monoclonal gammopathy,

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cryoglobulinemia, neutropenia, and lymphopenia<sup>9</sup> Germinal centre formation<sup>10</sup> has been established as an unfavourable predictor of SS-related NHL development in minor salivary gland biopsies. Thus, the aim of our systematic review was to evaluate the available evidence regarding the identification of serological and hematological predictors for lymphoma in *Sjogren* syndrome patients.

## MATERIALS AND METHODS

We carried out a systematic review according to the Cochrane guidelines to summarize the serological and hematological risk predictors associated with development of lymphoma in *Sjogren* syndrome patients.

### Search methodology:

The search methodology in PUBMED was using the following MESH terms from Jan 2015- 2020 were considered.

(((*Sjogren's* syndrome) OR (Sicca syndrome)) AND (lymphoma)) AND (risk development)

We also carried out google internet search using keywords *Sjogren* syndrome and risk indicators for lymphoma and articles meeting the inclusion criteria were considered for the review.

### Selection criteria:

#### Inclusion criteria:

Studies with hematological and serological risk predictors for *Sjogren* syndrome

Studies on *Sjogren's* syndrome associated with development of lymphoma

### Studies conducted in English language

#### Exclusion criteria:

Review articles not included

Studies using gene, single nucleotide polymorphism (SNP) in development of *Sjogren* syndrome

Studies showing association of *Sjogren* syndrome with other abnormalities

Studies on therapeutic interventions

### Methods of review:

The selection and exclusion of the reviewed studies are summarized in [Figure 1]. The search strategy identified 4 studies that evaluated the risk predictors of lymphoma in *Sjogren* syndrome patients. The description of the individual studies is shown in [Table 1].

## Data extraction and outcome:

Articles to be reviewed were finalised, data were extracted from each article, tabulated and verified and interpreted. The outcome assessed in this review evaluated the serological and hematological risk predictors for development of lymphoma in *Sjogren* syndrome.

## RESULTS

The electronic search showed overall 36 articles relevant to the search strategy from PUBMED and MEDLINE. Based on inclusion and exclusion criteria 4 articles were included in this review.

All the studies are based on a set of serological and hematological prediction categories, which are Anti-ro antibodies, Anti-La, low C3 levels, low C4 levels, Cryoglobulins, Lymphopenia, anemia, antinuclear antibodies (ANA), and Rheumatoid Factor positivity. Prediction score for SS and Lymphoma development was examined in four studies. All the studies show patients with *Sjogren* syndrome, with follow up at least 5 years. Disease free Survival with 5, 10, 20, and 30 years was 93.9, 87.9, 76.9, and 70.3%, respectively.<sup>9</sup>

Anti-Ro/SSA showed statistical significance in Sofia Fragkioudaki et al. study in the year 2016<sup>11</sup> Another study showed no statistical significance with HR=1.07<sup>12</sup> Mean value of 33.5% and 68.6% of Anti-Ro was present in a study done by G. Nocturne et al. and C. Baldini et al. Respectively<sup>13,14</sup>

Anti-La/SSB was studied in all four articles with odds ratio 4.4 which was statistically significant in a study done by Sofia Fragkioudaki et al. study in the year 2016. Another study showed no statistical significance with HR=0.66<sup>12</sup> Mean value of 59.2% and 29.2% for Anti -La/SSB was present in patients with lymphoma in *Sjogren* syndrome<sup>13,14</sup>

C3 hypocomplementemia values studied in three articles, of which two studies show low C3 levels with statistical significance in solid cancers<sup>12,11</sup> Low C3 levels were presented with odds ratio 1.9, HR value = 3.25 and mean of 18.3% in Sofia Fragkioudaki et al., Pilar Brito Zeron et al., C. Baldini et al. studies respectively.

C4 hypocomplementemia values studied in all four articles shows odds ratio of 4.6, HR=1.76,  $6.66 \times 10^{-4}$ . Multivariate analysis showed statistical significance of low C4 and had a strong association with development of lymphoma ( $P=0.0175$ ), could be a consequence of cryoglobulin levels.<sup>13</sup>

Cryoglobulin analysis done in all four studies revealed that, odds ratio of 6.9, HR=6.32 with statistical significance,<sup>12</sup>  $P=0.031$  in univariate analysis and  $P=0.01$  in multivariate analysis showed significant association with development of lymphoma.<sup>13</sup> Both cryoglobulins and low complement serum levels, particularly of C4, substantially correlated

with lymphoma progression, either independently or in combination.

Anemia and Lymphocytopenia was studied only in 2 out of 4 studies. Prediction scores of lymphopenia showing odds ratio 3.0 in a study showing significant association with development of lymphoma.<sup>11</sup> Lymphocytopenia, HR=2.12 showed no statistical significance, odds ratio of 1.80 in solid cancers and 1.43 in hematological cancers. Anaemia HR=0.89 with significant association in development of lymphoma (P = 0.047)<sup>12</sup>

Antinuclear antibodies (ANA) were studied in 2 out of 4 articles. HR=1.15 in B-cell MALT, HR=0.86 in B-cell non-MALT<sup>12</sup> and mean value shown 92%<sup>14</sup> Rheumatoid factor positivity was studied in all the 4 articles. In a study done by Sofia Fragkioudaki et al., odds ratio of 5.3 with significant association with development of lymphoma was present<sup>11</sup> Pilar Brito Zeron et al. HR=1.16 and 0.94 in B-cell non-MALT and B-cell MALT respectively, no statistical significance related SS development was noted.<sup>12</sup>

## DISCUSSION

Lymphoid malignancy is an unwelcome complication that affects a large proportion of SS patients, who are at a higher risk than individuals with other systemic autoimmune disorders.<sup>1,12</sup> Various prognostic criteria have been used for prediction of development of lymphoma in *Sjogren* syndrome patients. A predictive score for lymphoma development was formulated based on the number of independent risk factors. Recent studies used predictive criteria, like salivary gland enlargement, Raynaud's phenomenon, lymphadenopathy.<sup>15</sup> Risk factors in patients with *Sjogren* syndrome associated with B-cell non-MALT lymphomas include cryoglobulins and low C3 levels, while for B-cell non-MALT lymphomas, risk factors are anemia, monoclonal gammopathy, cryoglobulins and low C4 levels. Comparatively non-B-cell hematological cancers have prognostic factors such as anemia, neutropenia, thrombocytopenia, and cryoglobulins which show significant association.

Our findings are similar with earlier research that has identified a number of clinical and laboratory factors as potential predictors of lymphoma development in *Sjogren* syndrome patients<sup>11,16</sup> Based on the number of independent risk factors, a predictive score for lymphoma development was developed, like Anti-ro/SSA, Anti-La/SSB, C3 levels, C4 levels, Cryoglobulins, Lymphocytopenia, anemia, antinuclear antibodies (ANA), and Rheumatoid Factor positivity.

Analysis of Anti-ro/SSA and Anti-La/SSB shows significant association with development of lymphoma, which was in concordance with previous literature. Literature reveals that Anti-ro/SSA and Anti-La/SSB antibodies against these ri-

bonucleoprotein complexes are an independent predictor in development of lymphoma in patients with *Sjogren* syndrome.<sup>11</sup>

Analysis of C3 and C4 hypocomplementemia in present study shows significant association with development of lymphoma found among two different studies. Literatures show patients with systemic activity, positive cryoglobulins, and low C3 levels at diagnosis had a greater risk of non-MALT lymphoma, although the risk of non-MALT B-cell lymphomas was independent to systemic activity. Analysis of rheumatoid factor positivity shows significance association among the studies reviewed. Previous studies show subsets of malignant B-cells secrete monoclonal RF, derived by clonally expanded B cells exhibiting RF activity. Rheumatoid Factor is a new predictive factor of lymphoma occurrence in SS patients<sup>11,13,17</sup>

The probability of lymphoma development shows high risk of 100% in the presence of all 7 risk factors comparatively lesser with patients showing 3 to 6 risk factors,<sup>11</sup> and much more lesser for patients presenting with 2 risk factors. According to the present review, the number of identified serological and hematological risk predictors is broadening. All of these factors would make it easier to identify individuals who are at a higher risk for lymphoma at the time of their pSS diagnosis, necessitating better monitoring to prevent lymphoma from development. The identification of lymphoma predictors does not allow the precise determination of the time of lymphoma onset. Patients categorized as high-risk groups should undergo periodical clinical assessment and complete laboratory tests including serum cryoglobulins, complete blood count, biochemical profile, protein electrophoresis and complement assays.

Limitations of the study is the restricted clinical information available on the individual patients, variations in subtype analysis and evaluation of risk factors were not possible. Also, patients with subclinical symptoms and signs were not evaluated. Efforts should be taken, to focus on risk stratification and prognostic assessment for predicting the appropriate treatment plans.

## CONCLUSION

Identification of a high-risk phenotype for lymphoma development at the time of *Sjogren* syndrome diagnosis has been a major diagnostic challenge over years. The available literature establishes the role of risk determinants for development of lymphoma in patients with *Sjogren* syndrome. All these risk predictors act as a guide to identify patients with high risk at the time of diagnosis leading to an increase in disease free survival rate.

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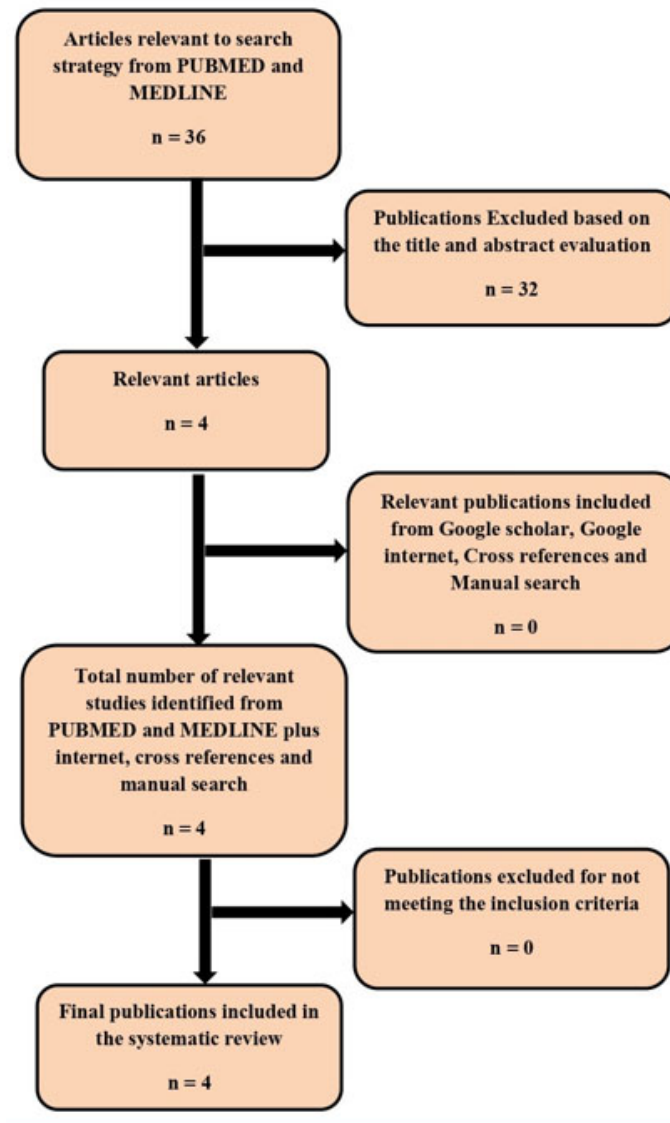
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**Authors' Contribution:** Monica. K, Conceived and designed, collected the data for this review, wrote the paper.

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**Figure 1:** PRISMA Flow chart showing selection and exclusion of the reviewed studies.

**Table 1:** Serological and hematological risk factors for lymphoma development in *Sjogren* syndrome.

Study	Anti-ro/SSA	Anti-La/SSB	Low C <sub>3</sub> levels	Low C <sub>4</sub> levels	Cryoglobulin	Lymphopenia	Anemia	ANA	RF
G. Nocturne et al -2015	Mean = 59.2%	Mean = 33.5%	-	6.66 x 10 <sup>-4</sup>	P = 0.031	-	-	-	-
Sofia Fragkioudaki et al - 2016	OR = 4.4	OR = 4.4	OR = 1.9	OR = 4.6	OR = 6.9	OR = 3.0	OR = 2.8	-	OR = 5.3
Pilar Brito Zeron et al -2017	HR = 1.07	HR = 0.66	HR = 3.25	HR = 1.76	HR = 6.32	HR = 2.12	HR = 0.89	HR = 1.15	HR = 0.94
C. Baldini et al - 2018	Mean = 68.6%	Mean = 29.2%	Mean = 18.3%	Mean = 12%	Mean = 2.8%	-	-	Mean = 92%	Mean = 48.2%

Results from the multivariate analyses are expressed as HR or OR. ANA antinuclear antibodies, HR hazard ratio, OR odds ratio, RF rheumatoid factor, (-) No data available