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# Lymphoma in Sjögren's Syndrome

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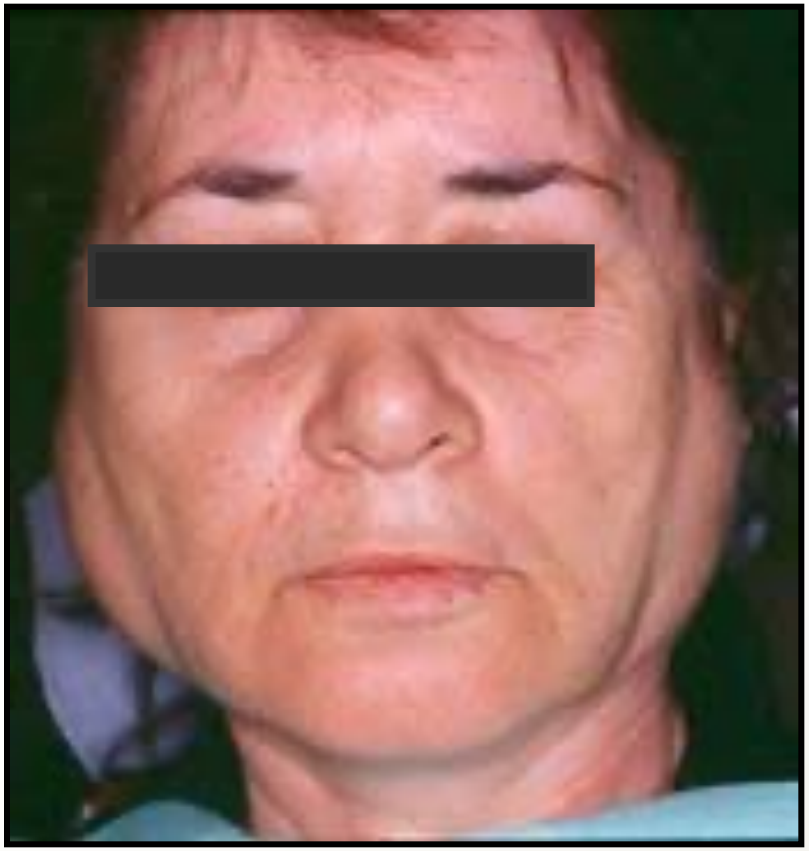
# Sjögren's Syndrome
## Epidemiology

- Prevalence
  - ~0.1% of general population
- Incidence (annual)
  - ~3/100.000 person-years
- Sex
  - ♀/♂ > 15/1
- $4^{th}$-$5^{th}$ decade of life
- Slowly progressive



*Goules et al. Autoimmun Rev 2016*
*Chatzis et al. J Clin Med 2020*
*Hammit et al. Clin Exp Rheumatol 2020*

*Gabriel et al. Arthritis Res Ther 2009*
*Izmilrt et al Arthrits Care Res 2019*

# Sjögren's Syndrome
## General Features

- Systemic autoimmunity
  - Isolated (primary)
  - Accompany other diseases (secondary)
  - Humoral
  - Cellular

- Wide clinical spectrum
  - organ-specific
  - systemic
  - **lymphoma**

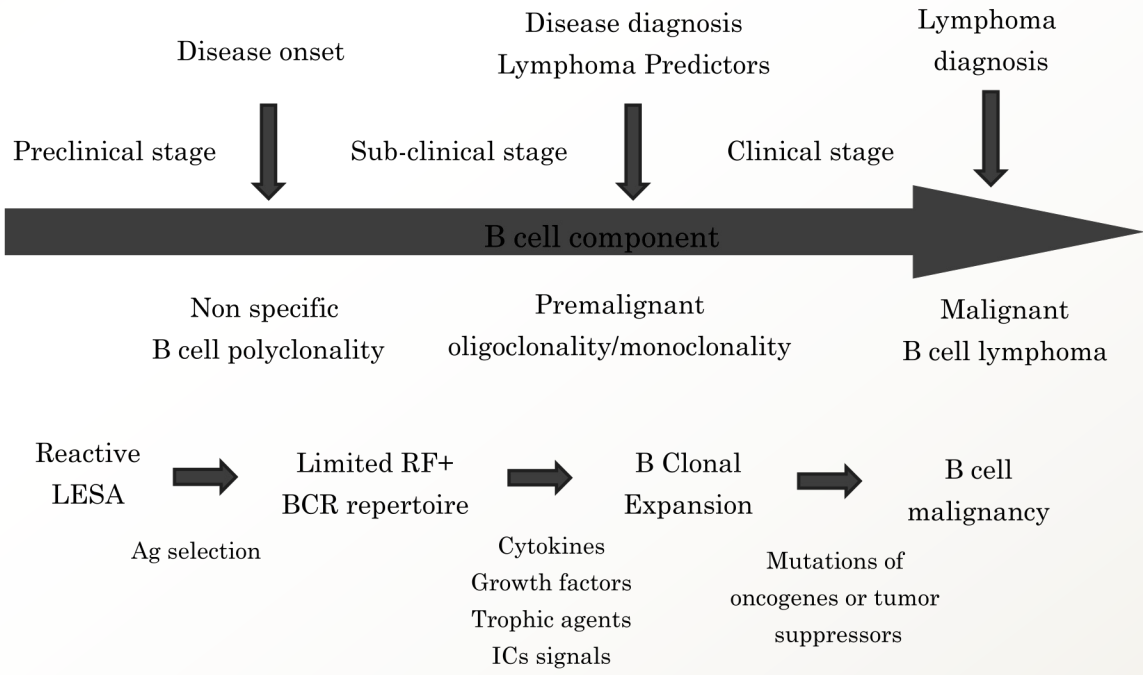
- Accessibility to tissue injury with low morbidity (MLSGB)

*Goules et al. Autoimmun Rev 2016*

# Sjögren's Syndrome
## Lymphomagenesis

## Proposed Model

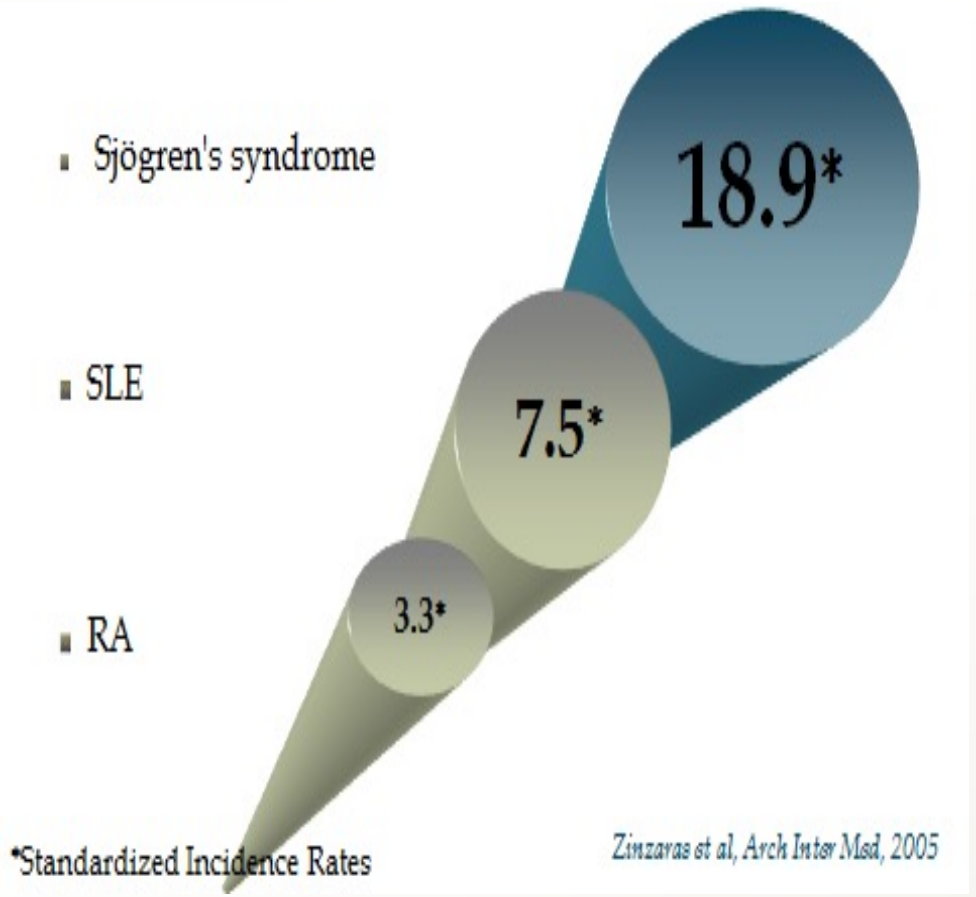
- Multistep
- Antigen dependent process
- MZ RF+ B cells
- Ectopic germinal centres
- Germline mutations




*Goules et al. J Autoimmunity 2018*

# Sjögren's Syndrome
## Lymphoma Risk

- SIR: 14-19
- ↑ risk compared to other autoimmune diseases (meta-analysis)
- 2.2% increase per year of age
- 1000-fold increased risk of parotid gland MALT lymphoma




*Zinzaras et al. Arch Inter Med 2005*
*Liang et al Ann Rehum Dis 2014*
*Chiu et al Oncotarget 2017*

# Sjögren's Syndrome
## Lymphoma-prevalence

| Study | Type of study | Subjects (n) | Lymphoma [n (%)] |
|---|---|---|---|
| Pertovaara et al. Ann Rheum Dis 2001 | Retrospective | 111 | 3 (2.7) |
| Lazarus et al. *Rheumatology* 2006 | Retrospective | 112 | 11 (9.8) |
| ***Zinzaras et al Arch Intern Med 2005*** | ***Metanalysis*** | ***1323*** | ***30 (2.3)*** |
| Theader et al. Ann Rheum Dis 2006 | Retrospective | 286 | 11 (3.8) |
| Baimpa et al. Medicine 2009 | Retrospective | 536 | 40 (7.4) |
| Martel et al. J Clin Immunol 2011 | Retrospective | 445 | 18 (4) |
| Solans-Laque et al. Sem Arthritis Rheum 2011 | Retrospective | 244 | 11 (4.5) |
| Theander et al Ann Rheum Dis 2011 | Retrospective | 175 | 7 (4) |
| Voulgarelis et al Medicine 2012 | Retrospective | 584 | 53 (9) |
| Weng et al Ann Rheum Dis 2012 | Retrospective | | |
| Johnsen et al Arthritis care Res 2013 | Retrospective | 443 | 7 (1.6) |
| Baldini et al Rheumatology 2014 | Retrospective | 1115 | 50 (4.5) |
| ***Liang et al Ann Rheum Dis 2014*** | ***Metanalysis*** | ***14.523*** | - |
| **Chiu et al Oncotarget 2017** | **Retrospective population based** | **16.396** | **66 (4)** |
| Chatzis et al Rheumatology 2022 | Retrospective | 878 | 121 (13) |

*Chiu et al. Oncotarget 2017*

# Sjögren's Syndrome

## Lymphoma-Mortality

| Study | Year | Location | Patients (n) | SMR (CI) |
|---|---|---|---|---|
| **Skopouli** | **2000** | **Greece** | **261** | **2.07 (95%CI 1.03-3.71)** |
| Petrovaara | 2001 | Finland | 110 | 1.2 (95%CI 0.64-2.29) |
| Ioannidis | 2002 | Greece | 723 | 1.15 (95%CI 0.86-1.73) |
| **Thomas** | **2003** | **Scotland** | **834** | **1.97 (85%CI 1.74-2.23)** |
| Theander | 2004 | Sweden | 484 | 1.17 (95%CI 0.81-1.63) |
| Alamanos | 2006 | Greece | 422 | 1.02 (95%CI 0.4-2.0) |
| Brito-Zeron | 2007 | Spain | 266 | 1.22 (95%CI 0.74-2.01) |
| Weng | 2011 | China | 3352 | 1.12 (95%CI 0.86-1.43) |
| **Voulgarelis** | **2012** | **Greece** | **53** | **3.25 (95%CI 1.32-6.76)** |
| Nannini | 2013 | USA | 105 | 0.92 (95%CI 0.57-1.41) |
| Horvath | 2014 | Hungary | 547 | 1.32 (95%CI 0.96-1.82) |
| **Brito-Zeron** | **2016** | **Spain** | **1045** | **4.66 (95%CI 3.85-5.60)** |
| **Kim** | **2017** | **Korea** | **5891** | **1.47 (95%CI 1.21-1.77)** |
| Maciel | 2017 | USA | 172 | 1.15 (95%CI 0.86-1.50) |
| **Yazisiz** | **2019** | **Turkey** | **372** | **2.11 (95%CI 1.39-2.83)** |
| **Overall** | | | | **1.46 (95%CI 1.1-1.93)** |

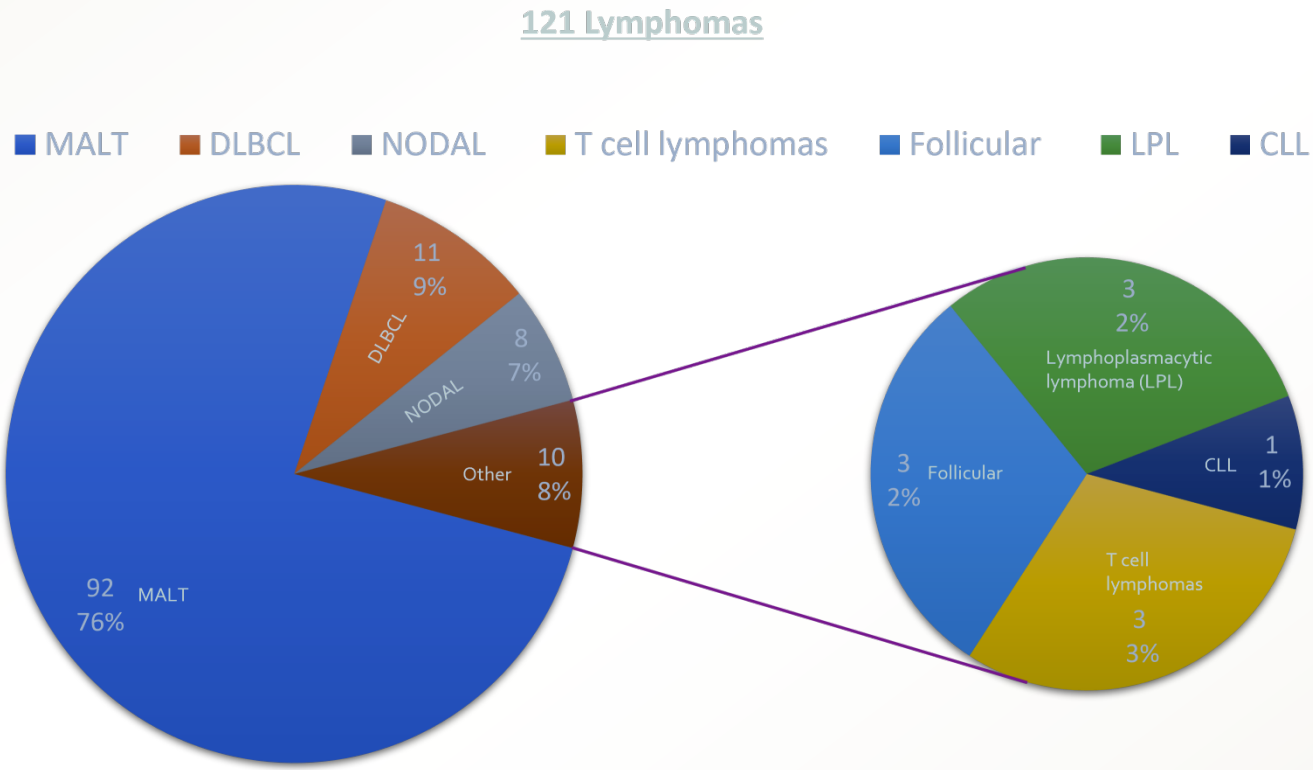
*Huang et al. Rheumatology 2021*

# Sjögren's Syndrome
## Mortality in SS with or without lymphoma

| Outcome | SS patients with Lymphoma (53) | SS patients without Lymphoma (531) |
|---|---|---|
| **Observed/Expected deaths** | 6/1.84 | 41/37.89 |
| **SMR (exact 95% CI)** | 3.25 (1.32 to 6.76) | 1.08 (0.79 to 1.45) |
| **Follow up, person years** | 556 | 1912 |
| **Excess Deaths due to Lymphoma** | 1.58 /1000 person-years | |

*Voulgarelis M, et al. Medicine 2011*

# Sjögren's Syndrome
## Lymphoma-Clinical Features




*Chatzis et al. Rheumatology 2022*

# Sjögren's Syndrome
## Lymphoma Predictors

### Clinical

- Salivary gland enlargement
- Palpable purpura
- Glomerulopathy
- Peripharal neuropathy
- Lymphadenopathy
- Leukopenia
- Lymphopenia

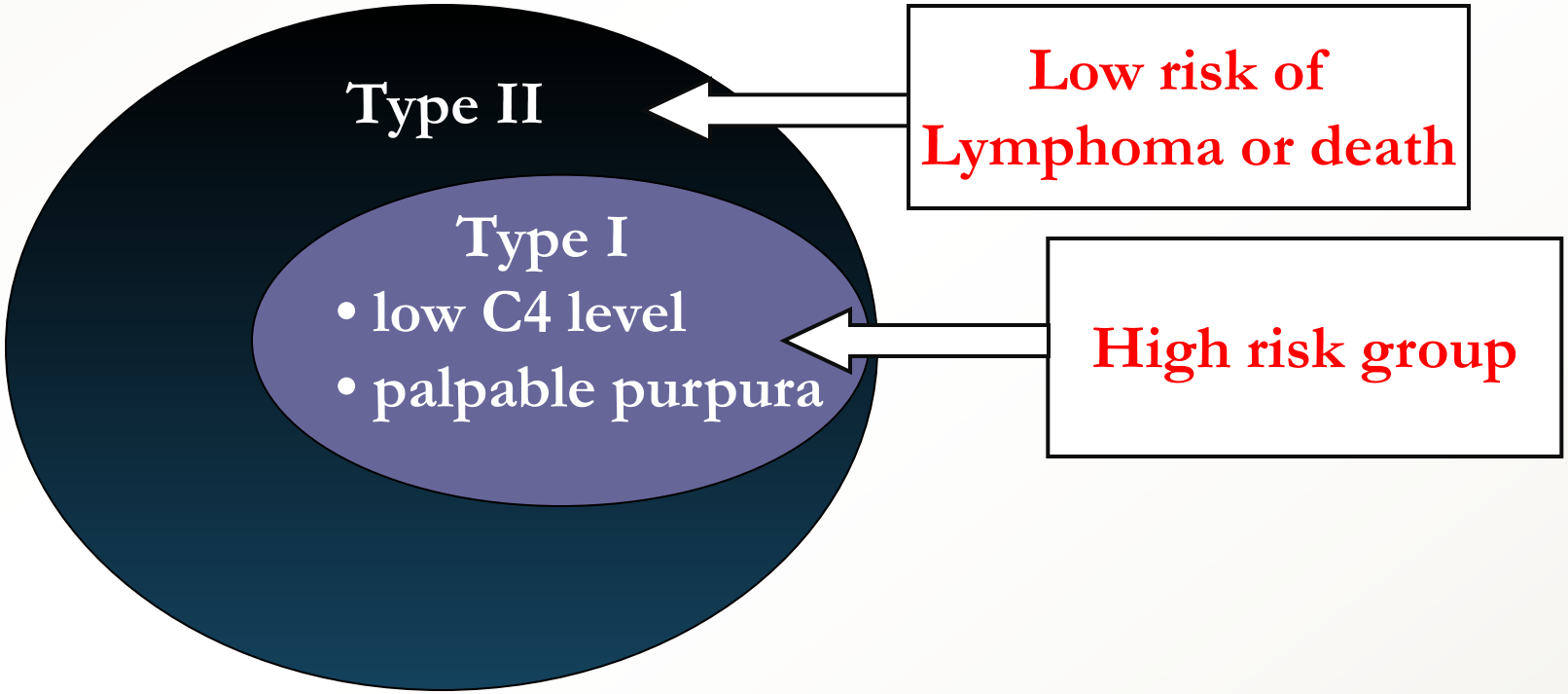
### Biologic

- Cryoglobulinemia
- Hypocomplementemia
- RFs
- Monoclonal component
- Germinal centers?
- High FS>3-4
- High ESSDAI at SS diagnosis

*Ruiz-Ordonez et al J Transl autoimmun 2021, Stergiou et al JCM 2021, Nocturne et al Rheumatology 2021*
*Kapsogeorgou et al J Autoimmun 2019, Goules et al. J Autoimmun Rev 2019*

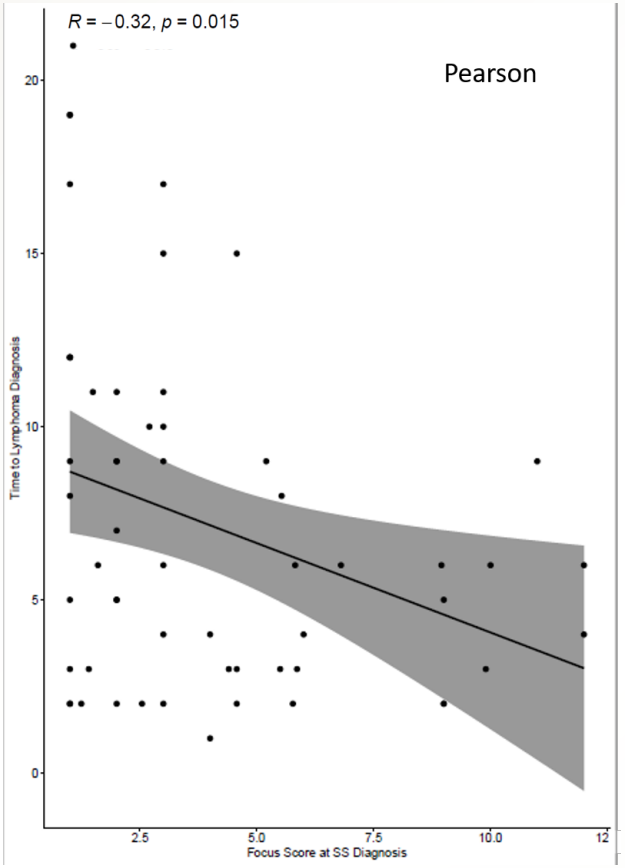
# Sjögren's syndrome

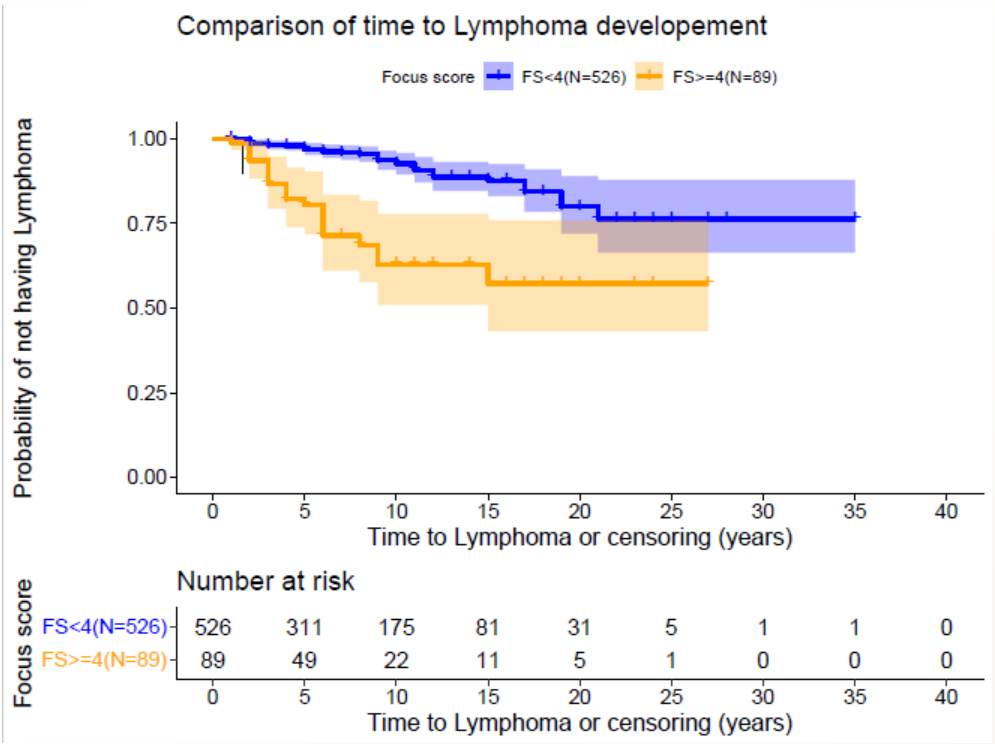
## Categorization according to risk for lymphoma development




*Ioannidis JP, et al. Arthritis Rheum 2002*

# Sjögren's Syndrome associated Lymphomas
## Focus score

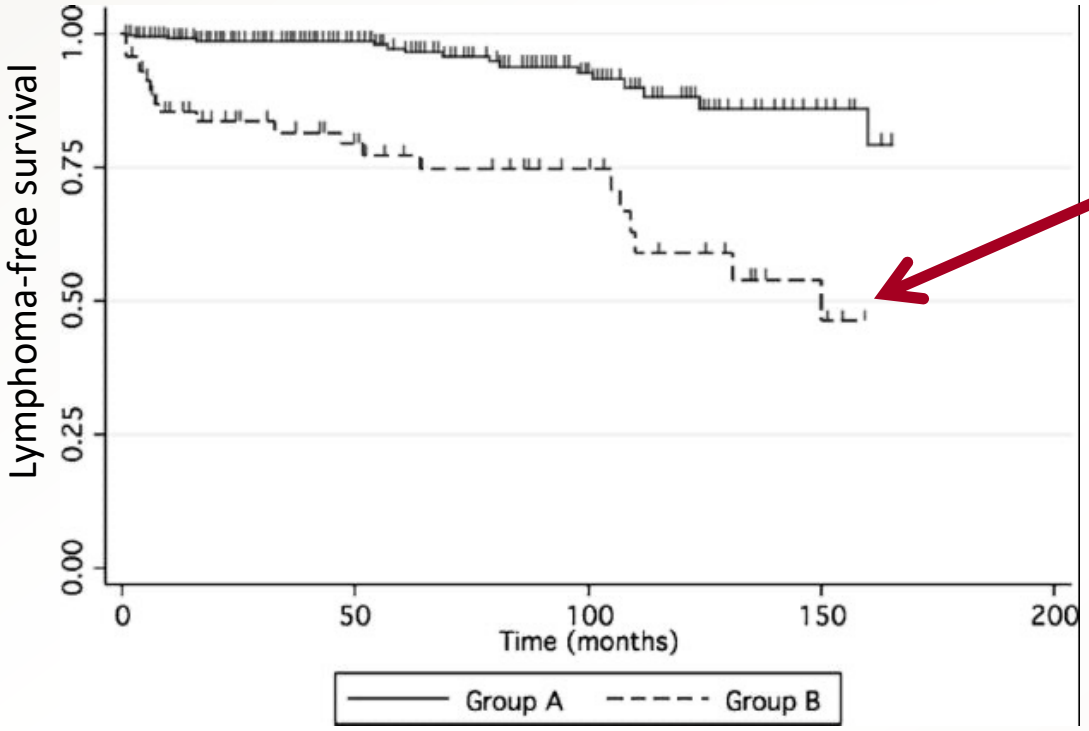



*Chatzis et al. J Autoimmun. 2021*

# Predictors of Lymphoma Development in SS

## Different risk factors for different types of lymphoma?




neutropenia (p = 0.041)
cryoglobulinemia (p = 0.008)
splenomegaly (p = 0.006)
lymphadenopathy (p = 0.021)
low C4 levels (p = 0.009)

**Marginal zone lymphomas**

Lymphocytopenia (p = 0.044)

**Diffuse large B cell lymphomas**

*Baimpa E, et al. Medicine 2009*

# Sjögren's Syndrome
## Lymphoma-General Features

| | ALL PATIENTS (n=121) | MALT (n=92) | DLBCL (n=11) | NMZL (n=8) |
|---|---|---|---|---|
| Females/Males | 113/8 | 7/83 | 11/0 | 7/1 |
| **Age at lymphoma diagnosis (median)** | **58 (29-82)** | **57 (29-82)** | **71 (43-81)** | **54 (36-79)** |
| **Disease duration from SS onset to lymphoma diagnosis (median)** | **8 (0-37)** | **7 (0-37)** | **14 (0-25)** | **13.5 (1-20)** |
| **Disease duration from SS diagnosis to lymphoma diagnosis (median)** | **4 (0-30)** | **3.5 (0-30)** | **8 (0-21)** | **6.5 (0-20)** |
| ECOG PS 1,0 % (no) | 96.6% (115/159) | 100 (92/92) | 100 (11/11) | 50% (4/8) |
| B symptoms | 6,8% (8/118) | 4,4% (4/92) | 9% (1/11) | 12,5% (1/8) |
| Nodal involvement | 35,9% (42/117) | 22,2% (20/92) | 91% (10/11) | 100% (8/8) |
| Extranodal involvement | 83,8% (98/117) | 100% (92/92) | 45,5% (5/11) | 0% (0/8) |
| **Bone marrow involvement** | **23,9% (28/117)** | **20% (19/91)** | **27,3% (3/11)** | **25% (2/8)** |
| Bulky disease | 0,8% (1/119) | 0% (0/92) | 18,2% (2/11) | 0% 0 |
| Splenomegaly | 11,8% (14/119) | 5,6% (5/92) | 18,2% (2/11) | 75% (6/8) |
| Ann Arbor stage | | | | |
| **I** | **54** | **52** | **2** | **0** |
| **II** | **23** | **18** | **4** | **0** |
| III | 10 | 0 | 2 | 6 |
| IV | 31 | 21 | 3 | 2 |

*Chatzis et al. Rheumatology 2022*

# Sjögren's Syndrome
## Lymphoma-Clinical Manifestations

SS cumulative clinical features of lymphoma patients

- Cutaneous vasculitis (35%)
- Peripheral neuropathy (10%)
- Glomerulonephritis (5%)
- Cryoglobulinemia (39%)
- Episodes of parotid swelling (30%)

Lymphoma related features-Nodal Involvement

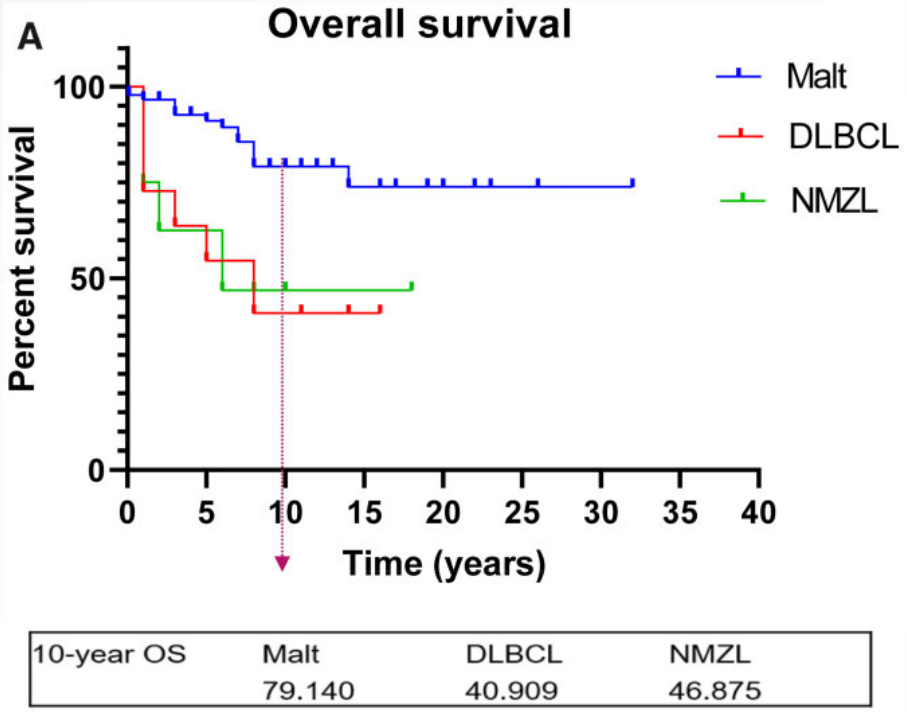
- Cervical (50%)
- Axillary (30%)
- Inguinal (10%)
- Supraclavicular (7%)
- Splenomegaly (12%)

Lymphoma related features - Extranodal Involvement

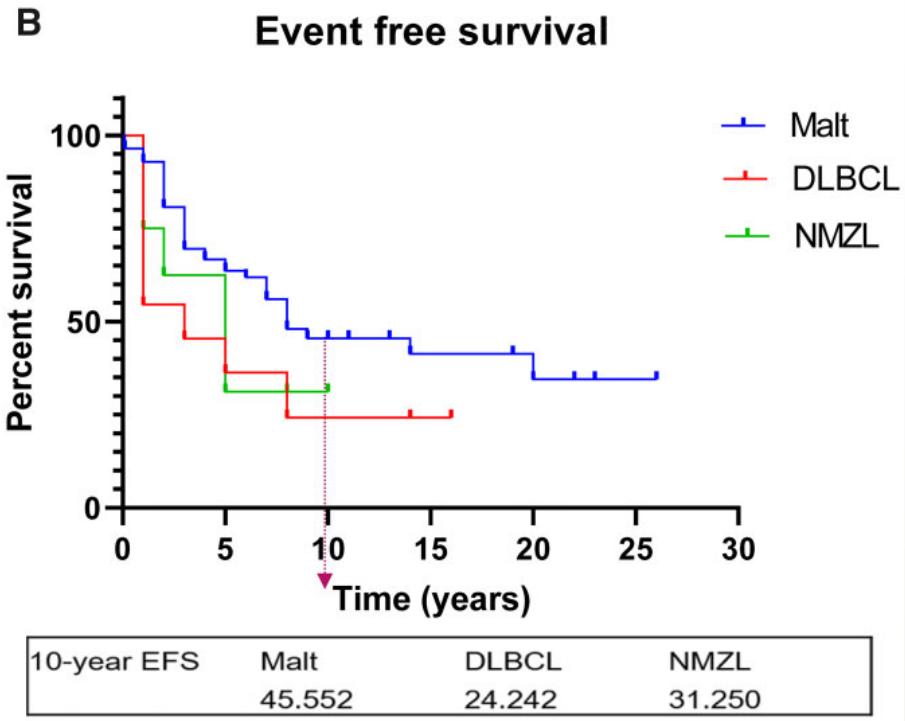
- Minor salivary glands (54%)
- Parotid enlargement (35%)
- Bone marrow (24%)

*Chatzis et al. Rheumatology 2022*

# Sjögren's Syndrome
## 10-yrs Lymphoma Outcome




| 10-year OS | Malt | DLBCL | NMZL |
|---|---|---|---|
| | 79.140 | 40.909 | 46.875 |




| 10-year EFS | Malt | DLBCL | NMZL |
|---|---|---|---|
| | 45.552 | 24.242 | 31.250 |

Event
- Disease progression
- Lymphoma relapse
- Histologic transformation
- Starting treatment after a watch and wait approach
- Death from any cause

*Chatzis et al. Rheumatology 2022*

# MALT Lymphoma Prognosis

## MALT-IPI 2017

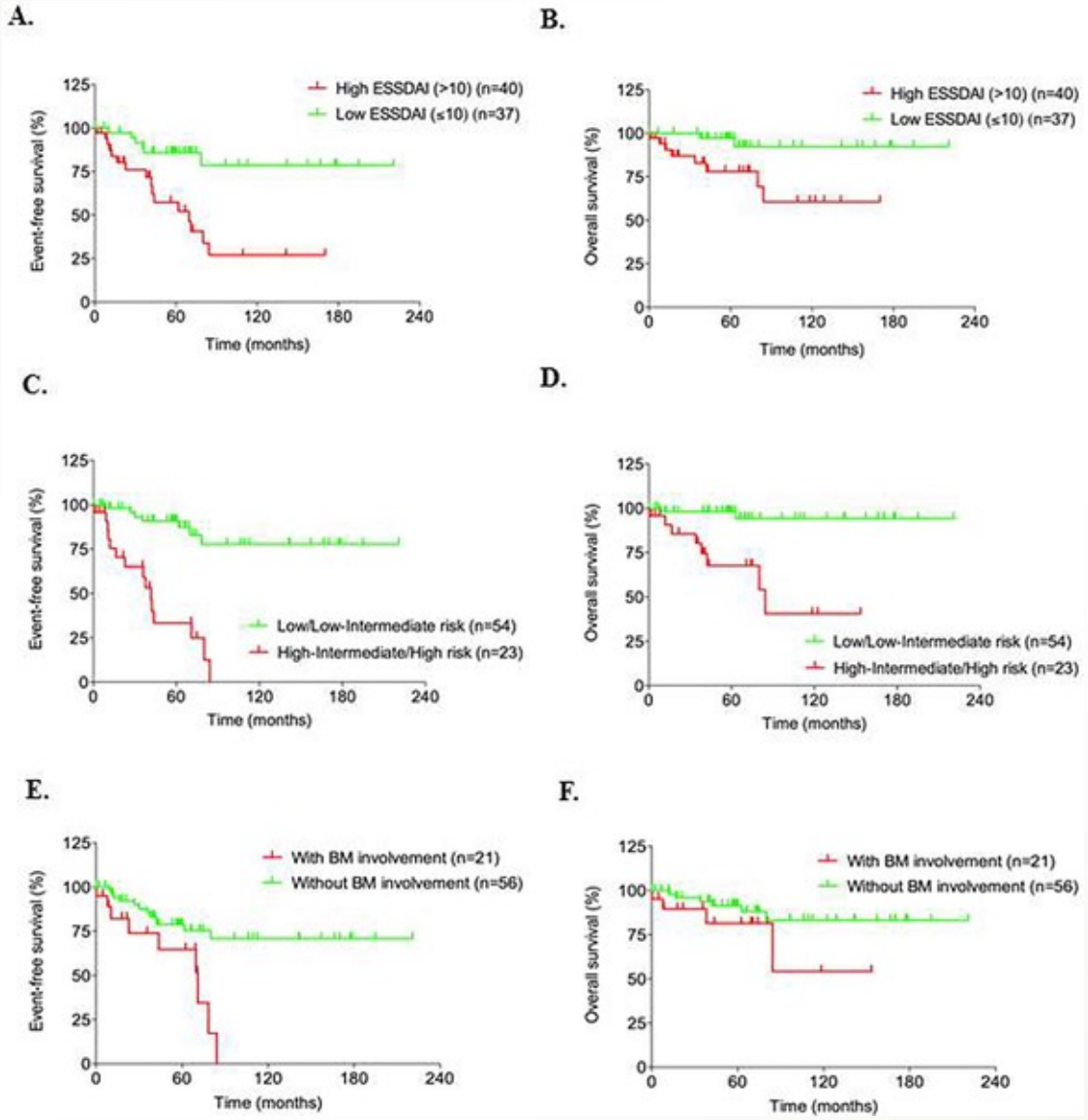
- Age ≥ 70 years old, ↑LDH, Ann-Arbor III or IV (1 point)
- Low (0) → 99% (5-year OS)
- Intermediate (1) → 93% (5-year OS)
- High (≥ 2) → 64% (5-year OS)

## Revised MALT-IPI 2022

- Age ≥ 60 years old, ↑LDH, Ann-Arbor III or IV (1 point) + MMS (multiple mucosal sites) (2)
- Low (0) → 93% (5-year OS)
- Low medium (1) → 87% (5-year OS)
- High medium (2) → 83% (5-year OS)
- High (≥ 3) → 64% (5-year OS)

*Thieblemont et al. Blood 2017*
*Alderuccio et al. Am J Hematol 2022*

# High SS disease activity, adverse IPI score and bone marrow involvement impair survival of lymphoma




*Papageorgiou A, et al. Plos One, 2015*

# Sjögren's Syndrome
## Lymphoma-Clinical Manifestations

**Alarm features for underlying lymphoma in SS**

- Persistent parotid swelling>3 months
- Persistent mass within the oral cavity
- Persistent swelling of submandibular or lachrymal glands
- Generalized lymphadenopathy and/or splenomegaly
- B symptoms
- Cryoglobulimenic Vasculitis
  - Glomerulonephritis
  - Palpable purpura
  - peripheral neuropathy
- Monoclonal component
- Persistent leukopenia and/or thrombocytopenia
- Hypogammaglobulinemia
- Pleurisy
- Rapidly progressive dyspnea with ILD component

# Sjögren's Syndrome
## Lymphoma-Clinical Manifestations

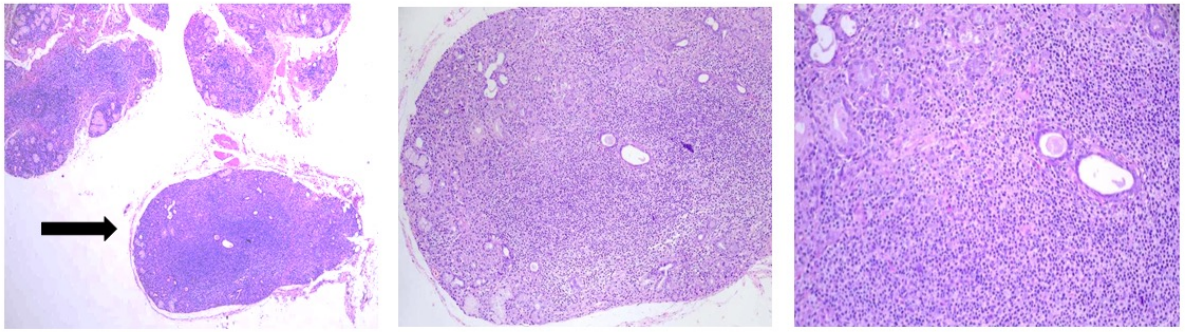
**Work-Up**

- History and thorough physical examination
- CBC, biochemistry panel, Urinalysis, ESR, CRP, SPEP, quantitative immunoglobulin analysis, serum immunofixation
- Cryoglobulins, RFs, C3 and C4 serum levels
- Serology for HIV, HBV, HCV
- ***Minor salivary labial biopsy or mass biopsy or parotid core needle biopsy u/s guided, lymph node biopsy***
- Further work up
  - Imaging (Neck, chest and abdomen CT)
  - Gastroscopy plus biopsy when needed
  - U/S thyroid plus FNA
  - Bone marrow biopsy and flow cytometry

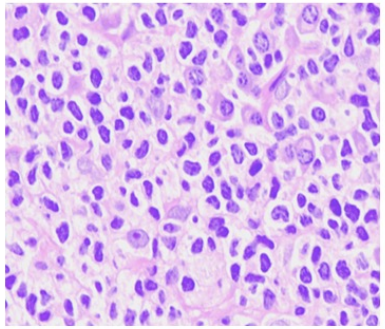
# Sjögren's Syndrome

## MALT Lymphoma - Histological Features

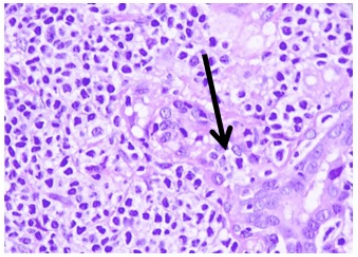
Loss of tissue architecture

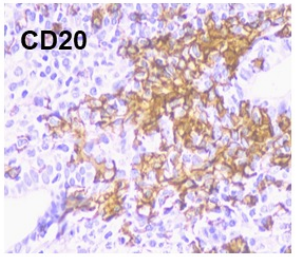


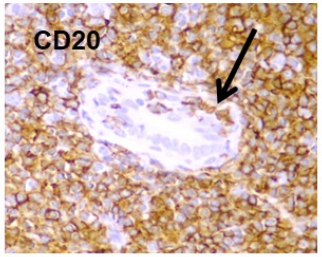
Centrocyte-like cells



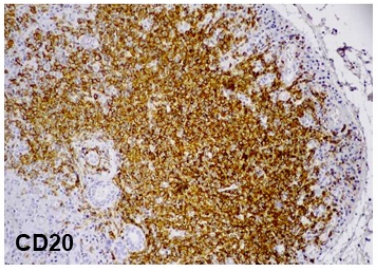
Lymphoepithelial lesions

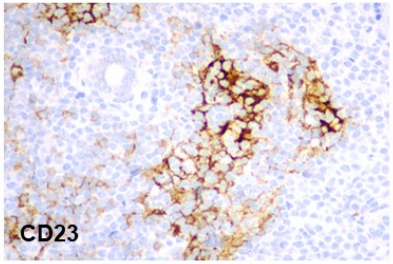




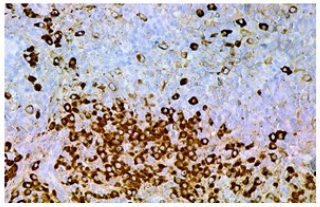



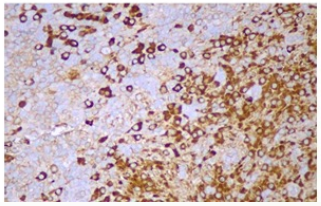

Resolution of follicular DC network




Clonality
CIgMκ





# Sjögren's Syndrome
## Lymphoma Management

### MALT Lymphomas

- When to treat: dessimination (bone marrow involvement, stomach, thyroid, kidney, lungs, generilizwd lymphadenopathy), cryoglobulinemic vasculitic manifestations
- Historical Approaches: irradiation, surgical removal
- Older regimens: rituximab, rituximab plus cyclophosphamide, rituximab plus fluadarabine
- Current Treatments: wait and see policy, rituximab plus bendamustine

### DLBCL

- R-CHOP
- ESHAP plus autologous transplanation

# Thank you for your attention