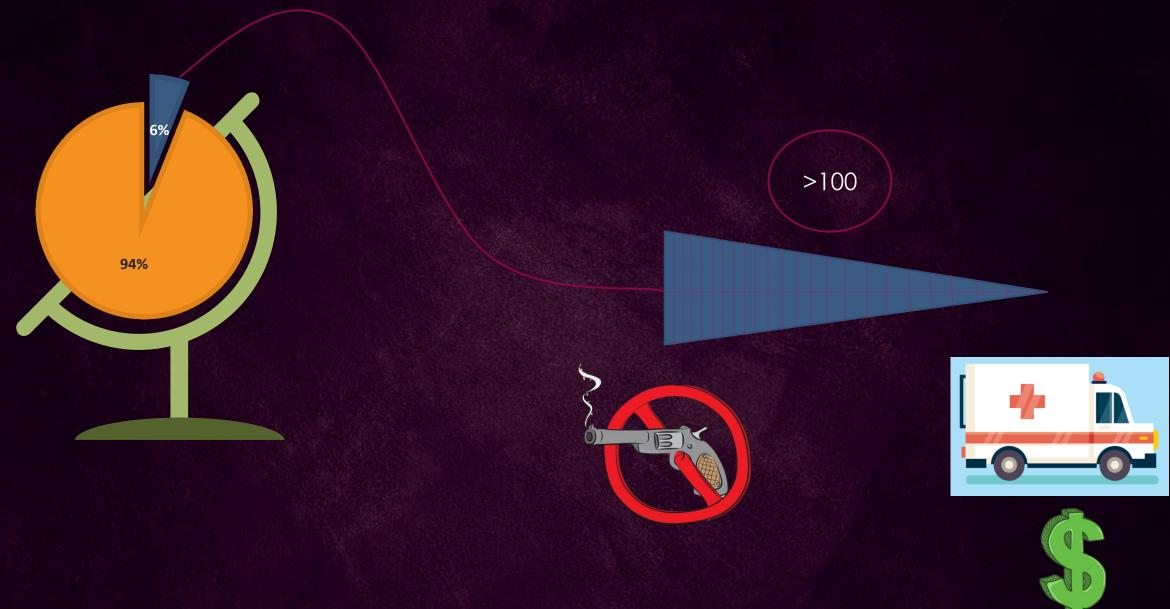**National & Kapodistrian University of Athens Greece**

CLINICAL PHENOTYPES IN SYSTEMIC AUTOIMMUNE DISEASES: THE SJOGREN'S SYNDROME PARADIGM

LOUKAS CHATZIS

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Pathophysiology Dept. School of Medicine

Systemic autoimmune diseases

6%

94%

>100

Moroni L et al. Geoepidemiology, gender and autoimmune disease. *Autoimmunity reviews*
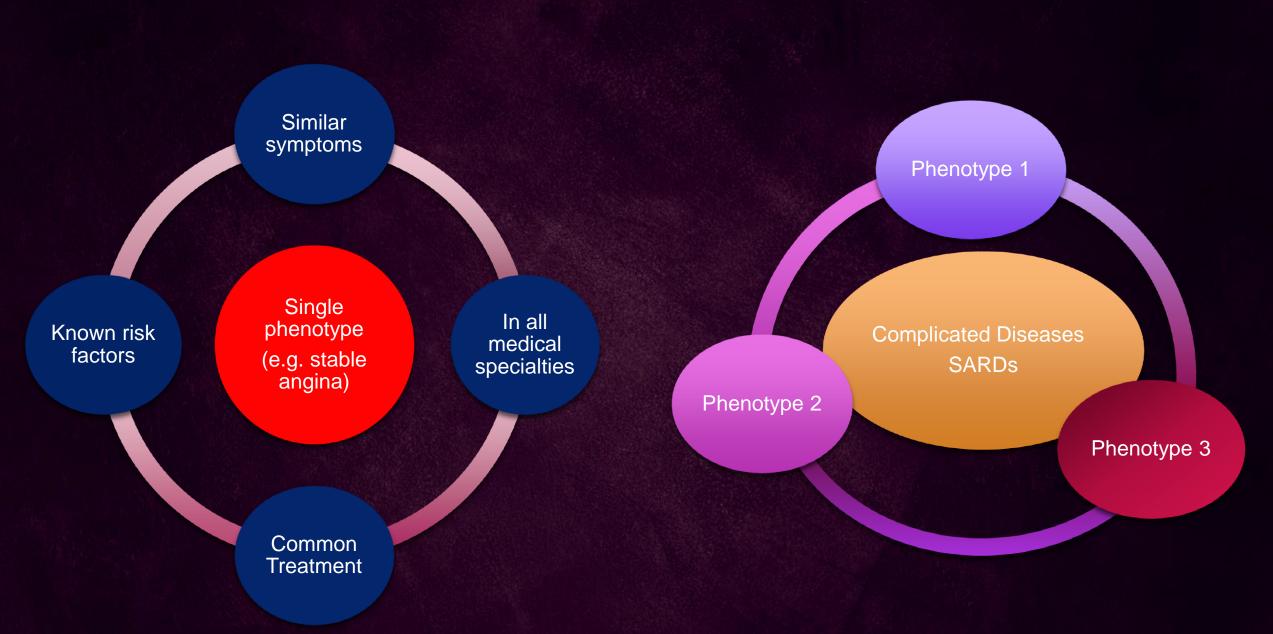
Systemic autoimmune diseases
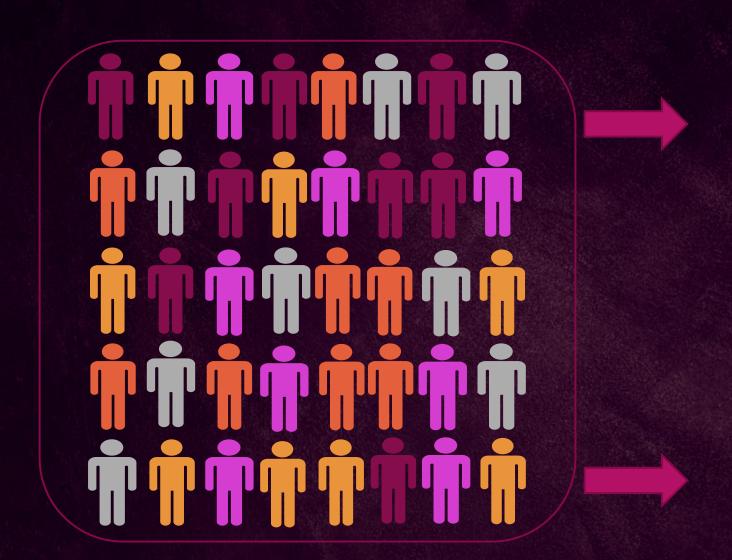
1. Challenging to diagnose

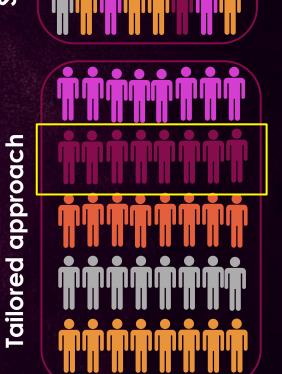2. Challenging to treat

Heterogeneity of the clinical phenotype
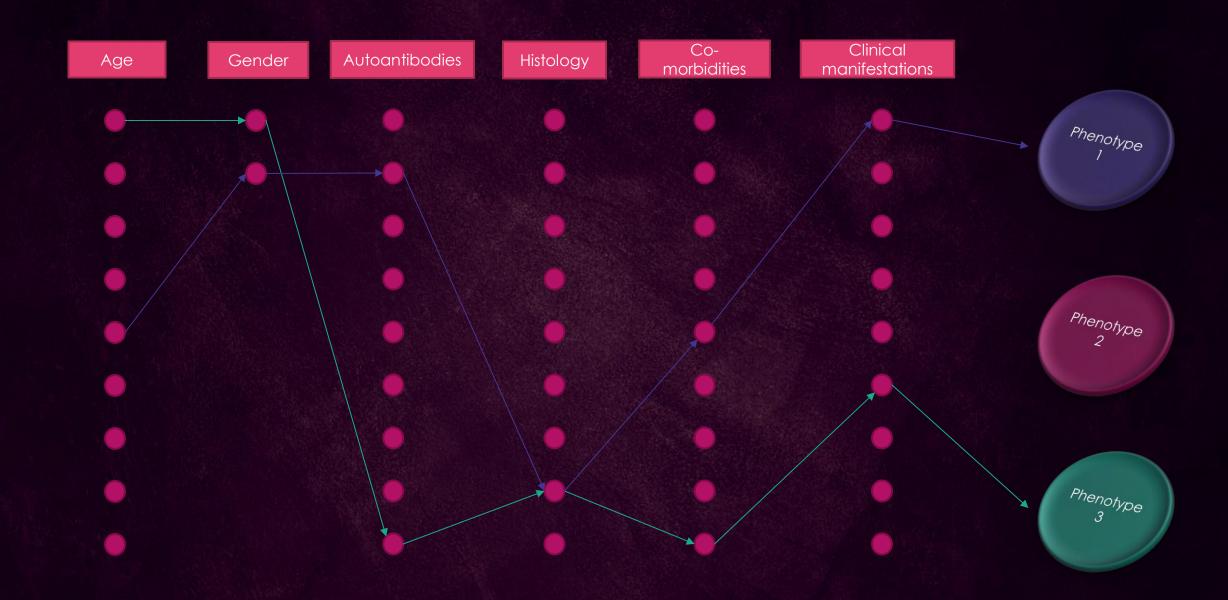
Systemic autoimmune diseases
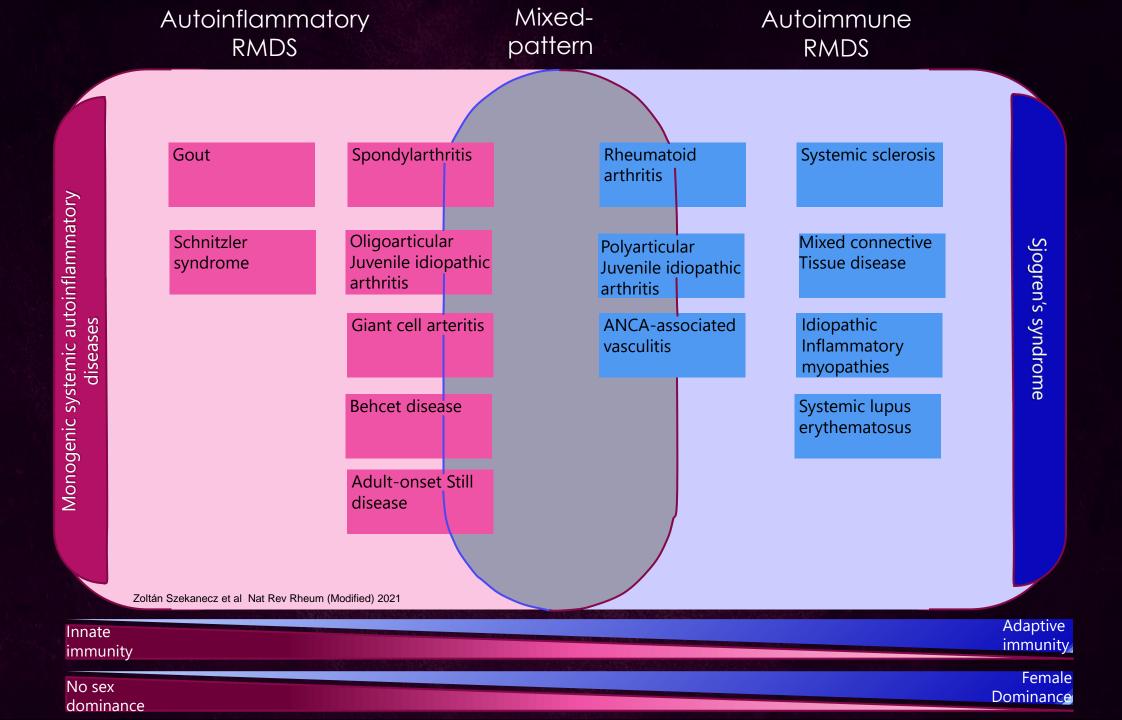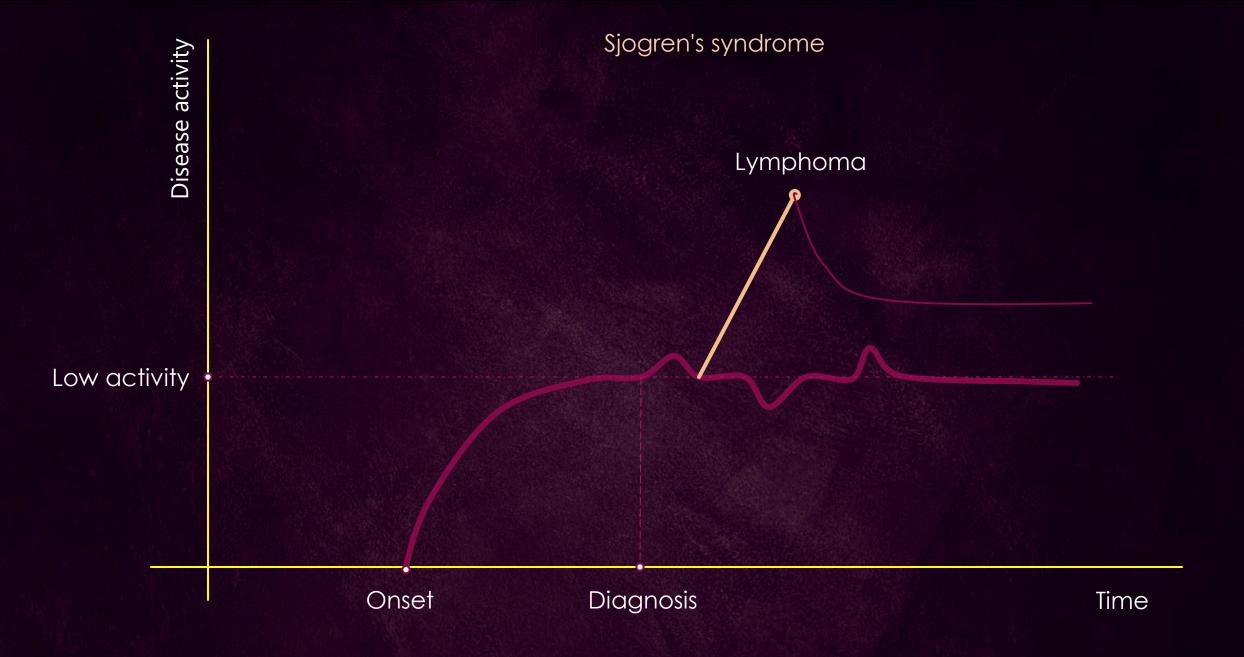
Connecting the dots

Connecting the dots

Autoinflammatory RMDS

Mixed-pattern

Autoimmune RMDS

Monogenic systemic autoinflammatory diseases

Sjogren's syndrome

Gout

Schnitzler syndrome

Spondylarthritis

Oligoarticular Juvenile idiopathic arthritis

Giant cell arteritis

Behcet disease

Adult-onset Still disease

Rheumatoid arthritis

Polyarticular Juvenile idiopathic arthritis

ANCA-associated vasculitis

Systemic sclerosis

Mixed connective Tissue disease

Idiopathic Inflammatory myopathies

Systemic lupus erythematosus

Zoltán Szekanecz et al Nat Rev Rheum (Modified) 2021

Innate immunity → Adaptive immunity

No sex dominance → Female Dominance

Sjogren's syndrome
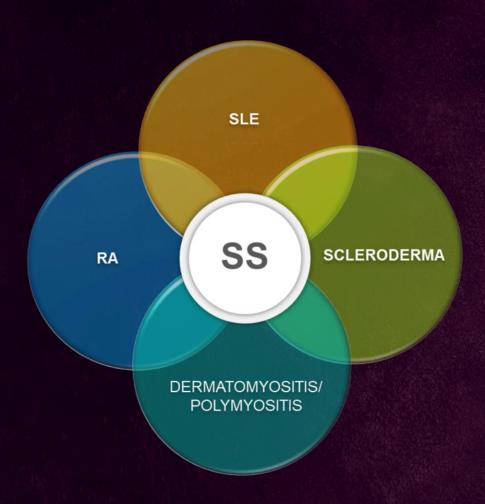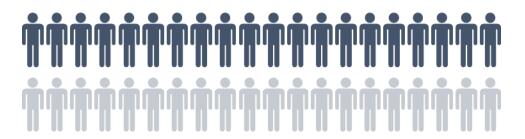
Why Sjogren's Syndrome

SS can present either alone (primary) or in the context of another systemic autoimmune disorder (secondary)
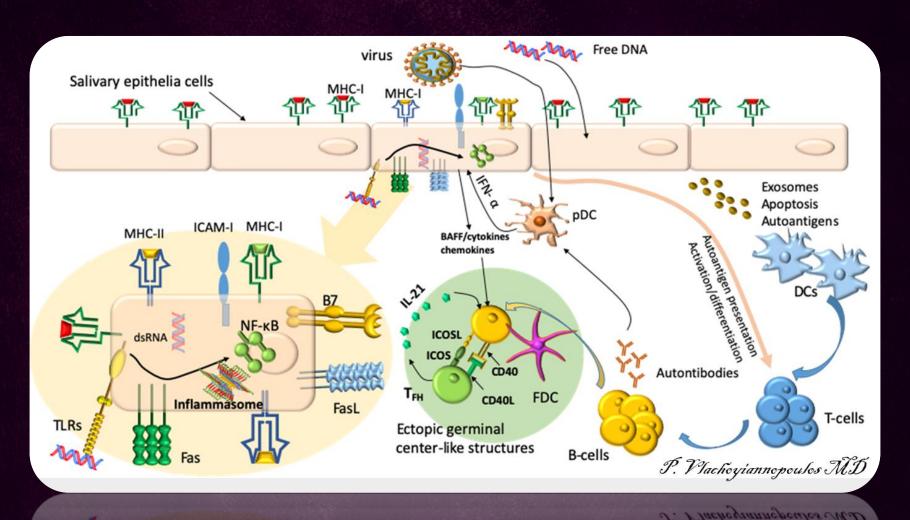
The pathophysiology of SS is complicated and not well understood

ABSTRACT NUMBER: 1904

IL-6 Receptor Inhibition in Primary Sjögren Syndrome : Results from a Randomized Multicenter Academic Double Blind Placebo-controlled Trial of Tocilizumab in 110 Patients

Interleukin-1 Inhibition and Fatigue in Primary Sjögren's Syndrome – A Double Blind, Randomised Clinical Trial

Inefficacy of Infliximab in Primary Sjögren's Syndrome

Etanercept in Sjögren's Syndrome

Efficacy and safety of abatacept in active primary Sjögren's syndrome: results of a phase III, randomised, placebo-controlled trial

Randomized Controlled Trial of Rituximab and Cost-Effectiveness Analysis in Treating Fatigue and Oral Dryness in Primary Sjögren's Syndrome

Rituximab Effectiveness and Safety for Treating Primary Sjögren's Syndrome (pSS): Systematic Review and Meta-Analysis

TREATMENT IS CHALLENGING

A variety of Systemic Clinical Manifestations

Non-specific (e.g Raynaud, fatigue, arthralgias)

Peri-epithelial (sialadenitis, interstitial renal disease, PBC, small airways disease)

Extra-epithelial (Immune-complex mediated)

B-cell lymphomas

F N Skopouli et al Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. *Semin Arthritis Rheum. 2000*

SS ← | → LYMPHOMA

Sjogren 18.8*

Lupus 7.4*

RA 3.9*

*Standardized Incidence Ratios

Zinzaras E, et al. Arch Inter Med 2005

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	
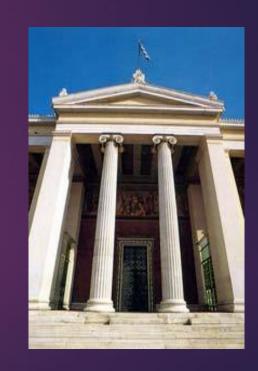
✓ Sjogren's unmet needs

❑ To stratify patients according to their basic characteristics

    ❑ Development of lymphoma

    ❑ Gender

    ❑ Age

    ❑ Histologic features

    ❑ Presence of autoantibodies

✓ **The consortium**

Cohorts

HarmonicSS Services and Tools
- ► Cloud infrastructure
- ► Semantic interlinking
- ► Harmonization
- ► Data Governance
- ► External information source retrieval
- ► Text mining
- ► Big data mining
- ► Genetics analytics
- ► Social media analytics
- ► Health policy impact assessment
- ► Visual analytics
- ► Clinical trial patient selection
- ► Segmentation of imaging tests
- ► Training/Education

Outcomes
- • Network of partners
- • Legal and privacy report on data sharing
- • Integrative harmonized cohort
- • Improved stratification for patient management
- • Validation of existing biomarkers
- • Identification of novel biomarkers
- • Shared health policy
- • Sustainability and expandability plan

How it was achieved

✓ Sjogren's unmet needs

❑ To stratify patients according to their basic characteristics

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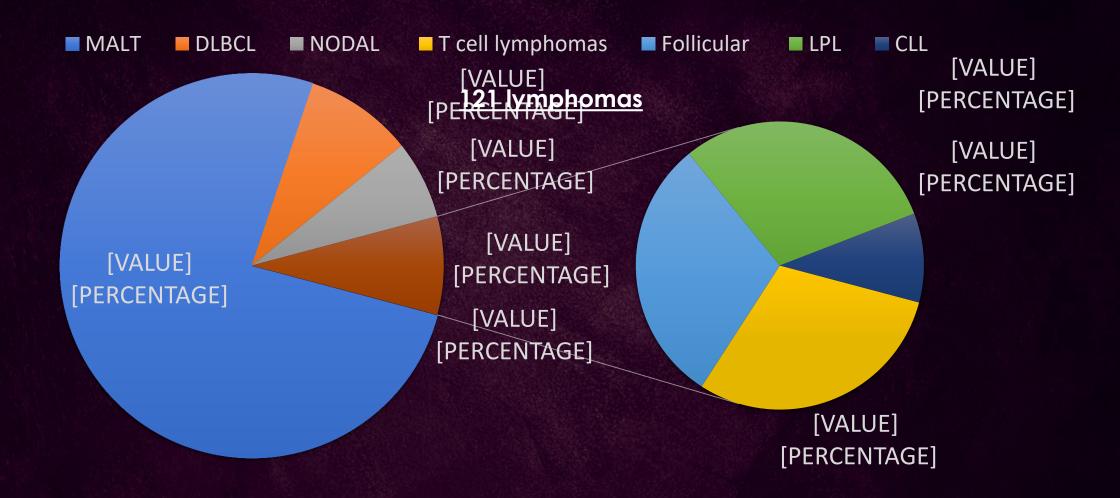
❑ Presence of autoantibodies

1st wave/level

Sjögren's Syndrome associated lymphoma patients: histologic subtypes

121 lymphomas

Chatzis LG et al manuscript under preparation
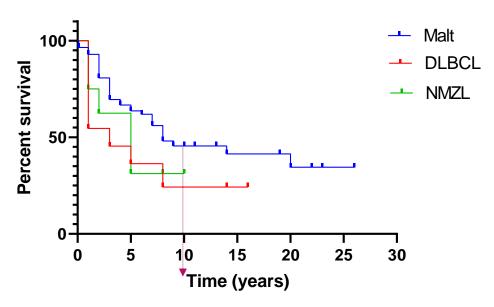
	ALL PATIENTS (n=121)	MALT (n=92)	DLBCL (n=11)	NMZL (n=8)
Females/Males	8/113	7/83	11/0	7/1
Age at lymphoma diagnosis (median)	58 (29-82)	57 (29-82)	71 (43-81)	54 (36-79)
Disease duration from SS onset to lymphoma diagnosis (median)	8 (0-37)	7 (0-37)	14 (0-25)	13.5 (1-20)
Disease duration from SS diagnosis 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 LG et al manuscript under preparation

SURVIVAL ANALYSIS

Chatzis LG et al manuscript under preparation

✓ **Sjogren's unmet needs**

❑ To stratify patients according to their basic characteristics

   ❑ Development of lymphoma

   ❑ Gender

   ❑ Age

   ❑ Histologic features

   ❑ Presence of autoantibodies
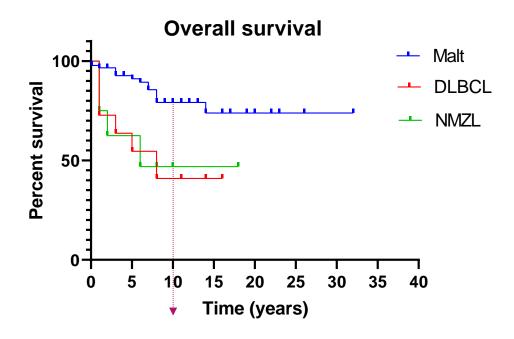
2nd **wave/level**

Sjögren Syndrome
does not respect
gender equality

Sjögren Syndrome
does not respect
gender equality

THE   SAME

Sjögren's Syndrome: Clinical and serological associations according to gender (UPAHI)

1987 PATIENTS / 96 MALES
Female : Male ratio = 20:1

Percentage of patients %

- Xerostomia: P= 0,026
- Xerophthalmia: P= 0,074
- SGE: P= 0,19
- Lymphadenopathy: P= 0,09
- Palpable purpura: P= 0,830
- Lymphoma: P= 0,001
- Anti-La: P= 0,01
- RF(+): P= 0,727
- Low C4: P= 0,165

■ Women ■ Men

Chatzis LG et al Sjögren's Syndrome: The Clinical Spectrum of Male Patients. J Clin Med. 2020

Anti La antibodies

50%

Male

VS

P=0.01

Female

34%

Chatzis LG et al Sjögren's Syndrome: The Clinical Spectrum of Male Patients. J Clin Med. 2020

LYMPHOMA

17/96 Male

18%

VS

P=0.001

10/191 Female

5%

Chatzis LG et al Sjögren's Syndrome: The Clinical Spectrum of Male Patients. J Clin Med. 2020

Sjögren's Syndrome: Clinical and serological associations according to gender (UPAHI)

Prominent feature	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Lymphadenopathy	1.869	6.549	0.0003*	2.456	17.482
SGE	0.689	2.006	0.129	0.853	4.724
Anti-La	0.682	1.989	0.11	0.884	4.477
Female Gender	-1.119	0.332	0.011*	0.148	0.742
Low C4 (< 20mg/dl)	0.465	1.599	0.337	0.629	4.069
Monoclonal gammopathy	0.537	1.728	0.512	0.353	8.592
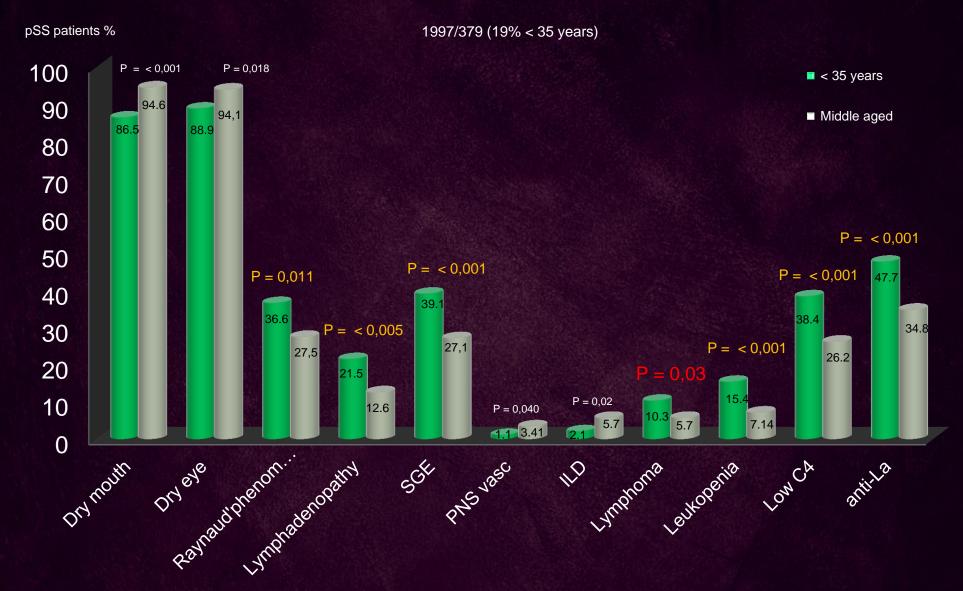
Chatzis LG et al Sjögren's Syndrome: The Clinical Spectrum of Male Patients. J Clin Med. 2020

✓ Sjogren's unmet needs

❑ To stratify patients according to their basic characteristics

    ❑ Development of lymphoma

    ❑ Gender

    ❑ Age

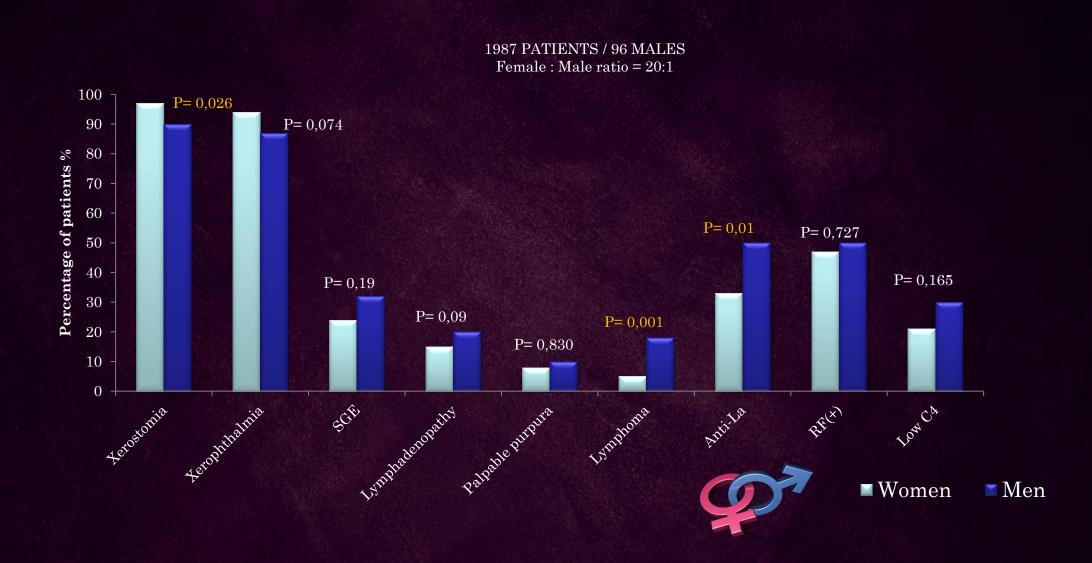   ❑ Histologic features

    ❑ Presence of autoantibodies
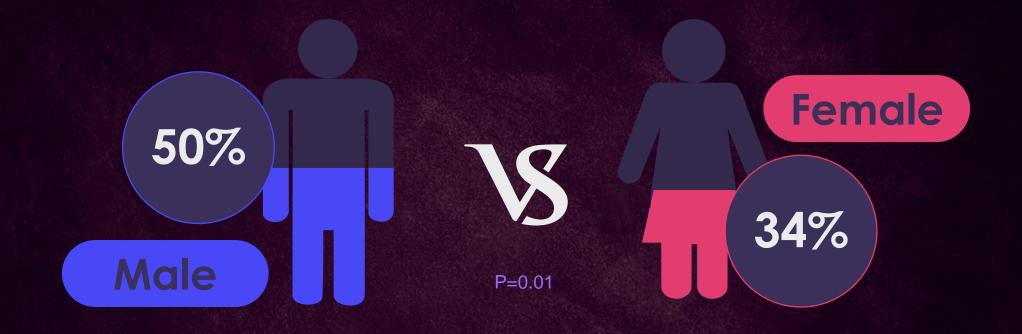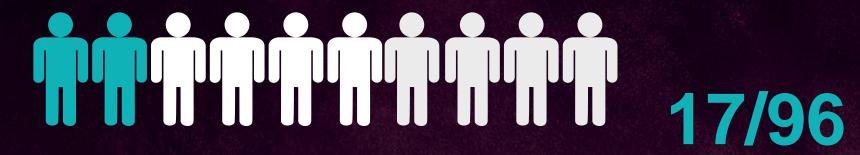
2nd **wave/level**

✓ *Sjögren's Syndrome: patients with early or late disease onset (UPAHI)*

1997 pSS patients

- ■ < 35 years
- ■ > 65 years
- ■ 36 - 64 years

19%
n = 379

14,7%
n = 293

66,3%
n = 1324

Goules A et al. Primary Sjögren's Syndrome of Early and Late Onset: Distinct Clinical Phenotypes and Lymphoma Development Front Immunol. 2020

Sjögren's Syndrome: patients with early or late disease onset (UPAHI)

Goules A et al. Primary Sjögren's Syndrome of Early and Late Onset: Distinct Clinical Phenotypes and Lymphoma Development Front Immunol. 2020

Sjögren's Syndrome: patients with early or late disease onset (UPAHI)

pSS patients %

Legend:
- > 65 years (blue)
- Middle aged (pink)

Dry mouth: 96.9 / 92.9 — P = 0,044
Arthritis: 10.2 / 17.2 — P = 0,037
ILD: 7.9 / 2.5 — P = 0,005
Lymphoma: 6.8 / 2.1 — P = 0,011
anti-R0: 68 / 79.2 — P = 0,002
anti-Ro/La: 70.3 / 80.1 — P = 0,008

Clinical & laboratory features

Goules A et al. Primary Sjögren's Syndrome of Early and Late Onset: Distinct Clinical Phenotypes and Lymphoma Development Front Immunol. 2020

Sjogren's unmet needs

- To stratify patients according to their basic characteristics

    - Development of lymphoma

    - Gender

    - Age

    - Histologic features
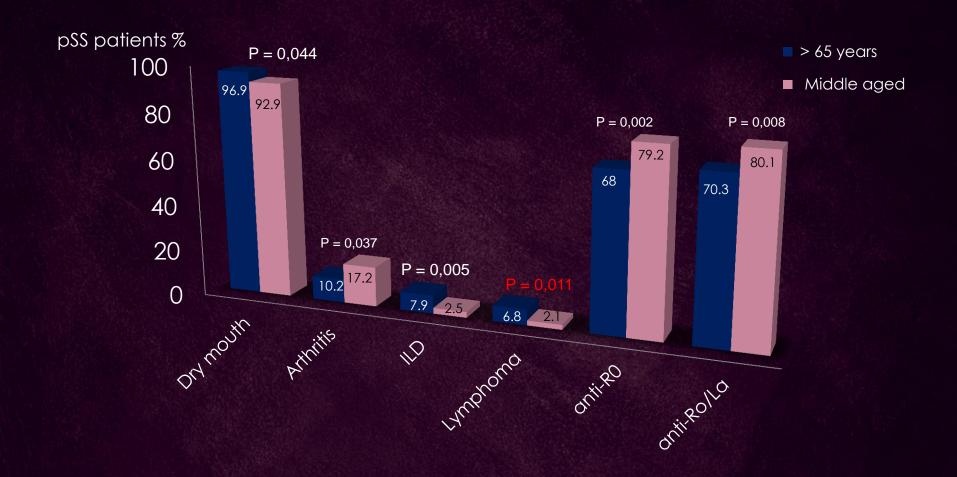
    - Autoantibodies profile

2nd **wave/level**

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

PATIENTS FOCUS SCORE ALLOCATION

- 1≤FS<2
- 2≤FS<3
- 3≤FS<4
- 4≤FS<5
- 5≤FS<6
- 6≤FS<7
- FS ≥7

Lymphoma prevalence per focus score group

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

Focus score as a continuous variable correlated independently with lymphoma development

FCBF-based multivariable logistic regression analysis results with lymphoma as an outcome in 618 SS patients with FS≥1.
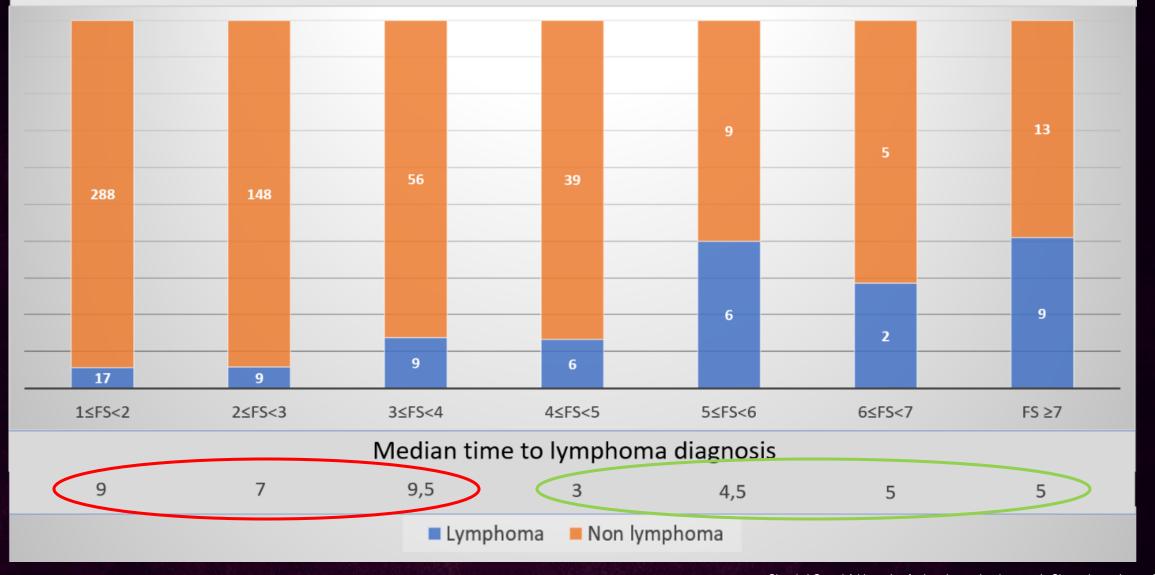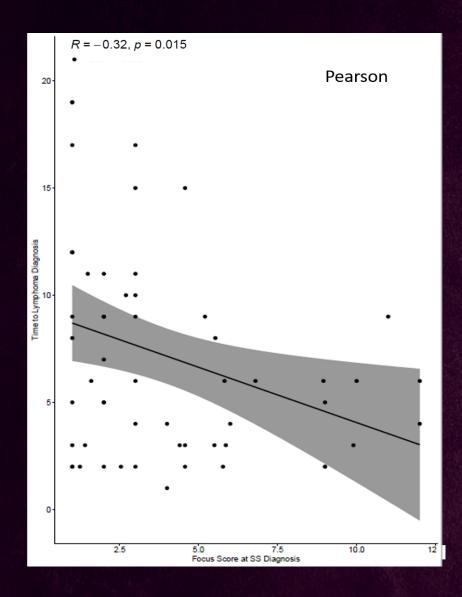
Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	1.73	5.928	0.021 **	1.457	24.558
SGE	1.577	5.078	0.008 **	1.849	13.975
Focus Score	0.27	1.316	0.049 **	1.034	1.677
Lymphadenopathy	0.739	2.239	0.29	0.661	7.713
Age at SS diagnosis	-0.033,	0.967	0.146	0.935	1.0
Autoimmune thyroiditis	-0.046	0.995	0.701	0.323	3.081
Dry mouth	0.387	0.995	0.654	0.258	9.679

* The strongest potentially independent variables identified by the FCBF algorithm to construct the logistic regression model, after analysing initially the following features included in the unified dataset: Gender, Age at SS, Dry mouth, Dry eyes, Anti-Ro, Anti-La, ANA, Focus Score, history of SGE, history of generalized Lymphadenopathy, Rheumatoid Factor, monoclonal gammopathy, Low C4(<20), Arthralgia-myalgia, Arthritis, Raynaud, Palpable purpura, Myositis, PNS-vasculitic, CNS involvement, Liver involvement – autoimmune hepatitis, Liver involvement- PBC, Lung involvement – interstitial disease, Lung involvement – small airway disease, Interstitial renal disease, Kidney involvement -GN-biopsy, Autoimmune thyroiditis, Cryoglobulinemia.

**< 0.05 (95% confidence interval): final independent lymphoma associated factors

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

NUMBER OF LYMPHOMAS/NON-LYMPHOMAS AND MEDIAN TIME TO LYMPHOMA DIAGNOSIS PER FOCUS SCORE GROUP

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

R = −0.32, p = 0.015

Pearson

Time to Lymphoma Diagnosis (y-axis), *Focus Score at SS Diagnosis* (x-axis)

Sequential algorithm for time interval from SS until lymphoma diagnosis for each FS threshold

FS range	P Value*
FS≥2 vs FS<2	0,0795
FS≥3 vs FS<3	0,0956
FS≥4 vs FS<4	**0,0080**
FS≥5 vs FS<5	0,0857
FS≥6 vs FS<6	0,1820
FS≥7 vs FS<7	0,2004
FS≥8 vs FS<8	0,2004
FS≥9 vs FS<9	0,1716
FS≥10 vs FS<10	0,9005
FS≥11 vs FS<11	0,9146

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

KAPLAN MEIER ANALYSIS: TIME TO LYMPHOMA DIAGNOSIS BETWEEN PATIENTS WITH FS<4 COMPARED TO PATIENTS WITH FS≥4

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

Lymphoma associated risk factors in high (≥4) and low (<4) LMSG FS subgroups of SS patients

FS< 4

FCBF-based multivariable logistic regression analysis results with lymphoma as an outcome in low Focus Score group.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	1.325	3.92	0.147	0.69	23.134
SGE	3.92	5.213	0.02 **	1.541	17.779
Lymphadenopathy	0.788	2.32	0.35	0.493	11.281
Age at SS diagnosis	-0.037	0.964	0.236	0.92	1.01
Gender	0.4	1.603	0.748	0.149	20.147
Autoimmune thyroiditis	0.008	1.051	0.736	0.283	3.956

**< 0.05 (95% confidence interval): final independent lymphoma associated factors
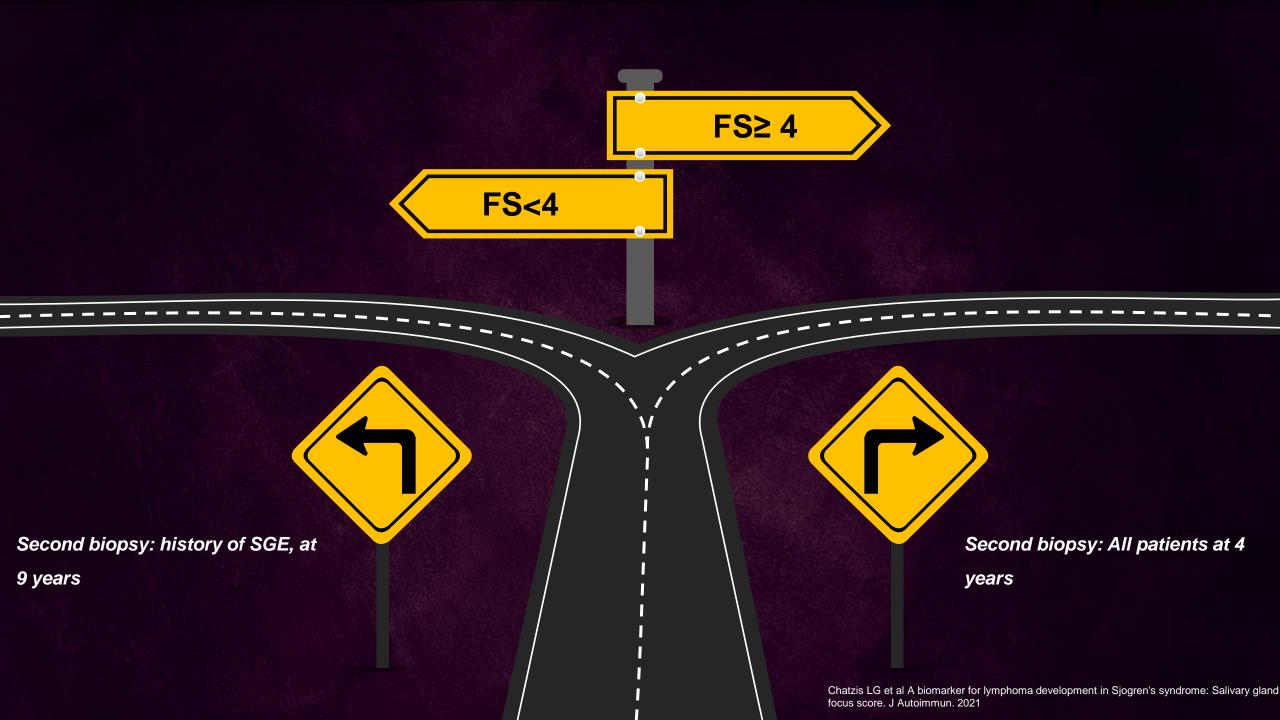
SGE

FS≥ 4

FCBF-based multivariable logistic regression analysis results with lymphoma as outcome in high Focus Score group.

Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	0.917	2.571	0.421	0.288	24.681
Low serum C4	1.306	3.836	0.147	0.701	21.575
Rheumatoid Factor	1.027	2.877	0.282	0.484	17.654
Salivary gland enlargement	0.815	2.34	0.345	0.47	11.777
Focus score	0.333	1.409	0.035**	1.104	1.803
Monoclonal gammopathy	0.298	1.399	0.779	0.142	15.134
Raynaud's phenomenon	0.517	1.75	0.561	0.321	9.746

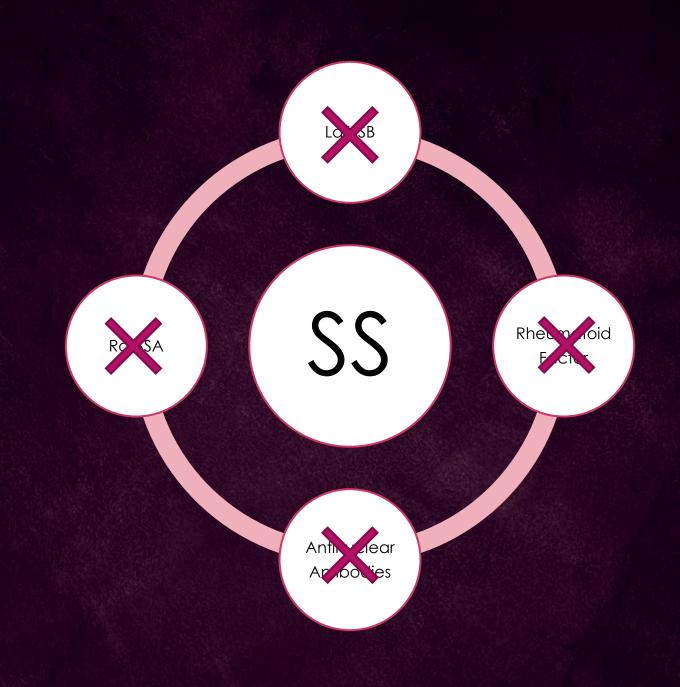**< 0.05 (95% confidence interval): final independent lymphoma associated factors

Focus score

FS≥ 4

FS<4

Second biopsy: history of SGE, at 9 years

Second biopsy: All patients at 4 years

Chatzis LG et al A biomarker for lymphoma development in Sjogren's syndrome: Salivary gland focus score. J Autoimmun. 2021

✓ **Sjogren's unmet needs**

❑ To stratify patients according to their basic characteristics

    ❑ Development of lymphoma

    ❑ Gender

    ❑ Age

    ❑ Histologic features

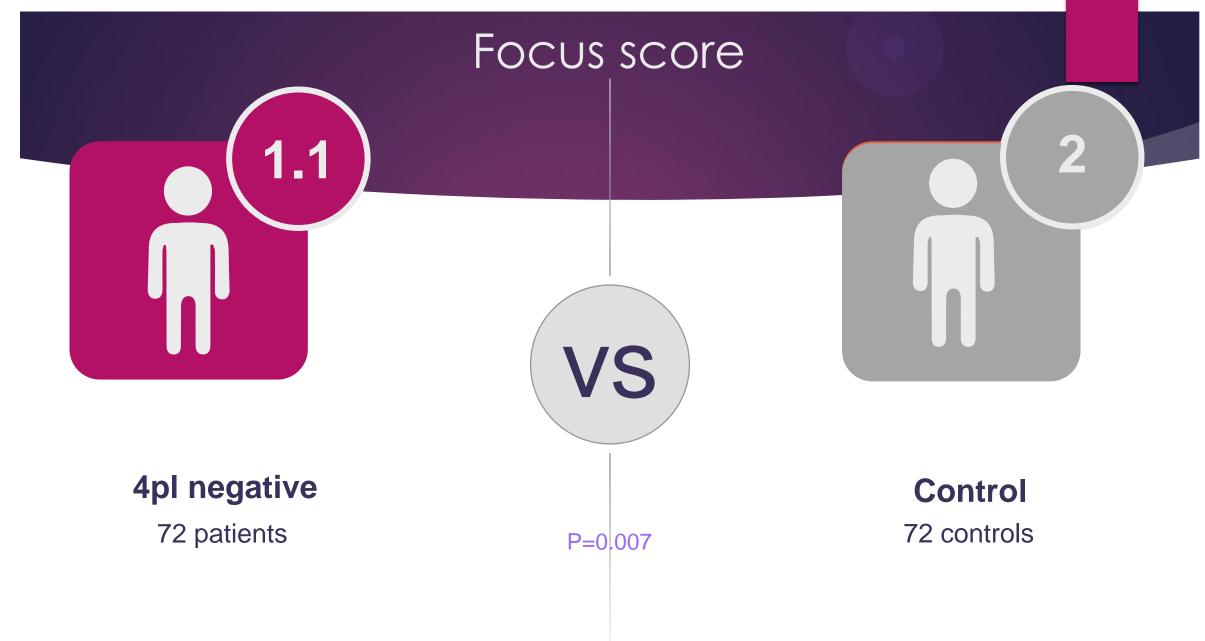   ❑ Autoantibodies profile

2nd **wave/level**
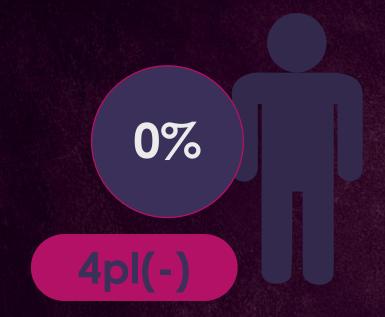
Peripheral nervous involvement

0%

3pI(-)

VS

Control

7%

P=0.002

Ro(-), La(-), Rf(-), **Ana(+)**

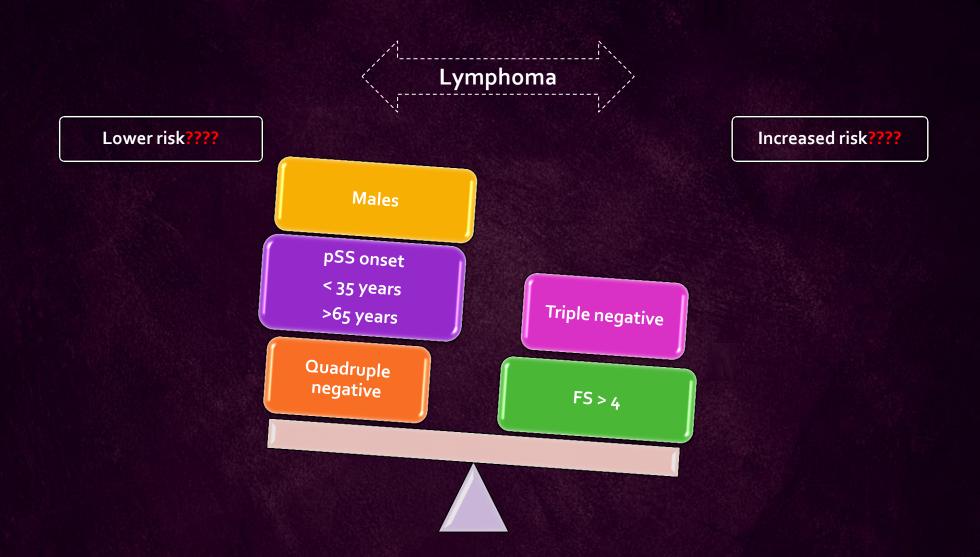Chatzis LG et Combined seronegativity in Sjögren's Syndrome Under review

Peripheral nervous involvement

1.5%

4pI(-)

VS

Control

16 %

P=0.004

Ro(-), La(-), Rf(-), Ana(-)

Focus score

1.1

4pl negative

72 patients

VS

P=0.007

2

Control

72 controls

Ro(-), La(-), Rf(-), **Ana(-)**
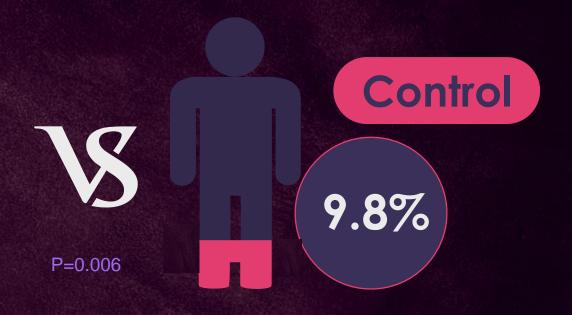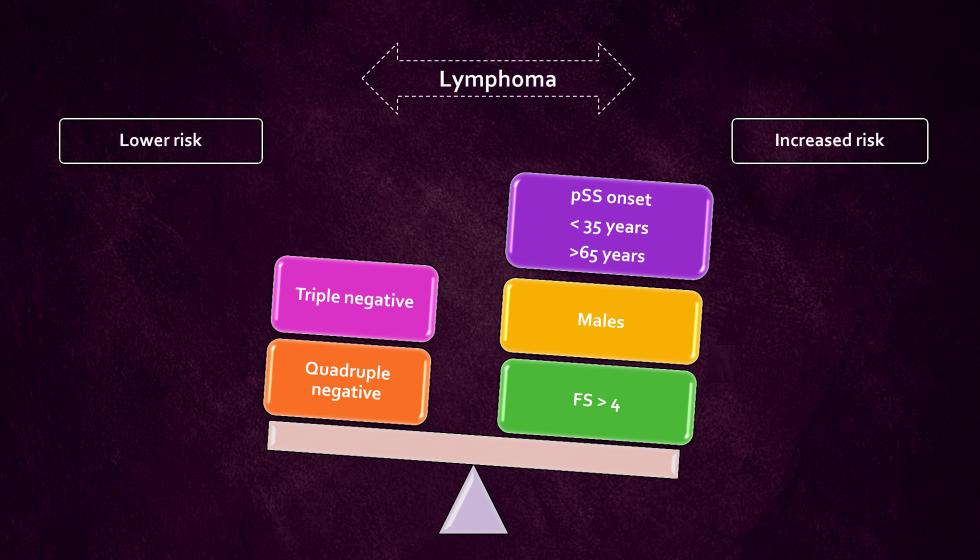
Chatzis LG et Combined seronegativity in Sjögren's Syndrome Under review

Lymphoma

0%

4pl(-)

VS

Control

9.8%

P=0.006

Ro(-), La(-), Rf(-), **Ana(-)**

Sjögren's Syndrome: different pSS groups prompting evaluation for lymphoma development

✓ Thank you