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Severe organ involvement related to Sjogren's Disease

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IIBEAA
ΙΔΡΥΜΑ ΙΑΤΡΟΒΙΟΛΟΓΙΚΩΝ ΕΡΕΥΝΩΝ ΑΚΑΔΗΜΙΑΣ ΑΘΗΝΩΝ

Rethymnon October 2025

Disclosures

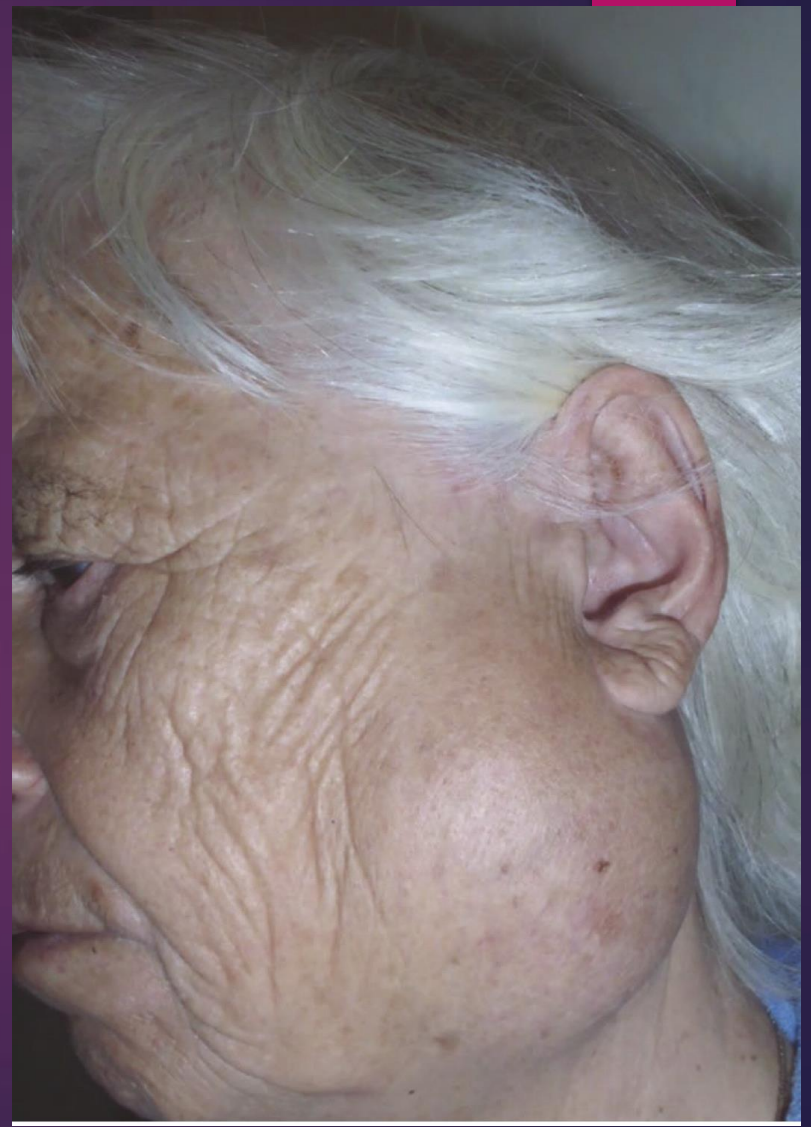
- Received Research Grants from Novartis, Pfizer, ABBVIE, Genesis, Eli-Lilly. NONE related to the current presentation
- Coordinator of HarmonicSS, an EU sponsored Research Grant
- Chairman of eSSential, the Study Group of EULAR, devoted to Sjögren's Disease

SJÖGREN DISEASE

- Female disease
  ♀/♂ :20:1
- Common disease
  0,1-0,5 % prevalence
- 4th -5th decade of life
- Affects in all the exocrine glands
- Slowly progressive and difficult to treat
- Primary or associated with:
  - ❑ RA
  - ❑ SLE
  - ❑ Dermatopolymyositis
  - ❑ Scleroderma

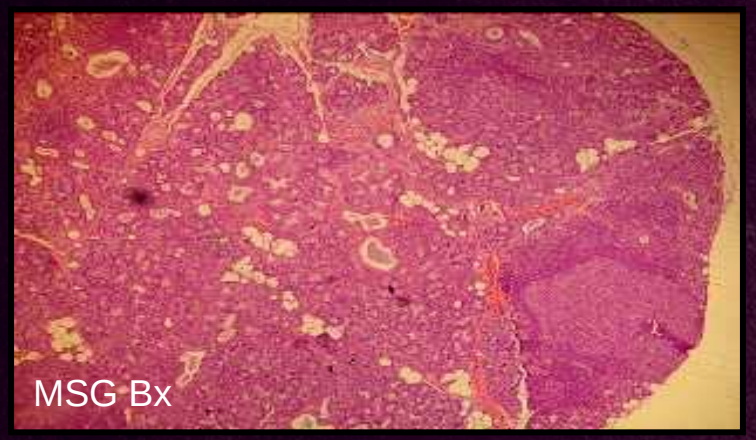
2nd most common rheumatic disease

2nd most common autoimmune disease affecting women

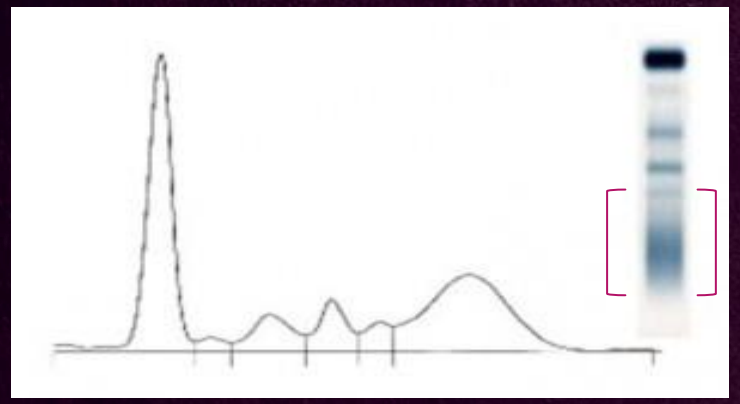


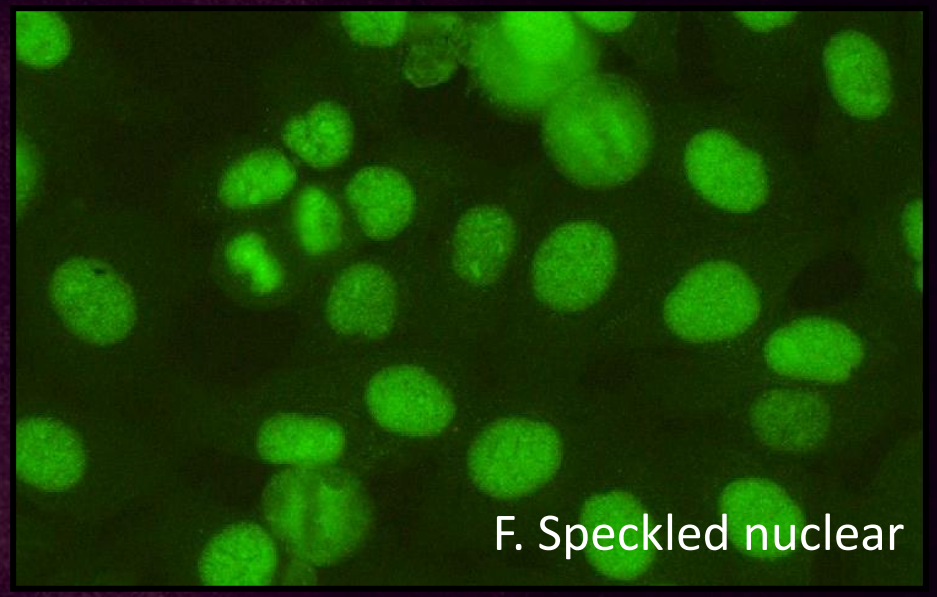
E. Pelechas et al., Illustrated Handbook of Rheumatic and Musculo-Skeletal Diseases

✓ Sjögren's Syndrome: Immunopathology



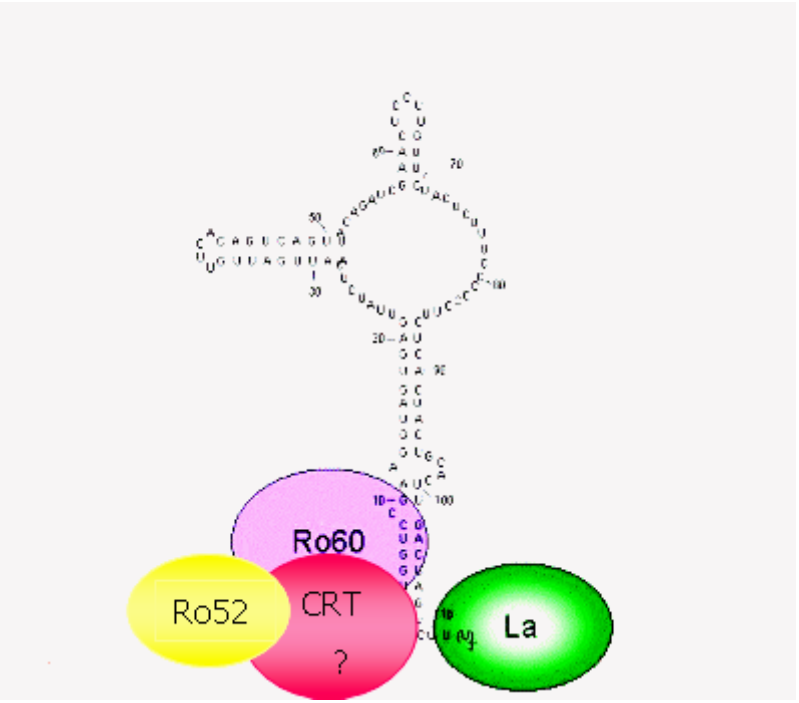
Infiltration by activated T- & B- cells





Autoantibodies to cellular autoantigens in pSS by IVTT and RIA

Autoantibody to:	Percent
Ro 60	66
Ro 52	49
La	57
Calreticulin	20
Carbonic anhydrase II	11
M3R	11
VAMP-2	4
a-fodrin	4
U1RNP	2
Nucleolin	0
Calpastatin	0
NPY	0

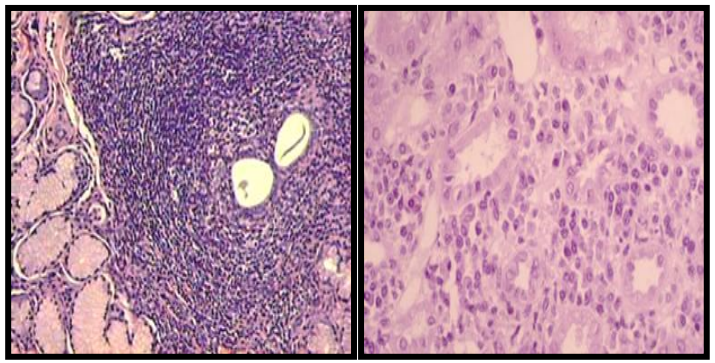


Tzioufas et al Arthritis Rheum 58 :S791, 2008

Sjögren's Disease: *Clinical Manifestations*

Peri-epithelial

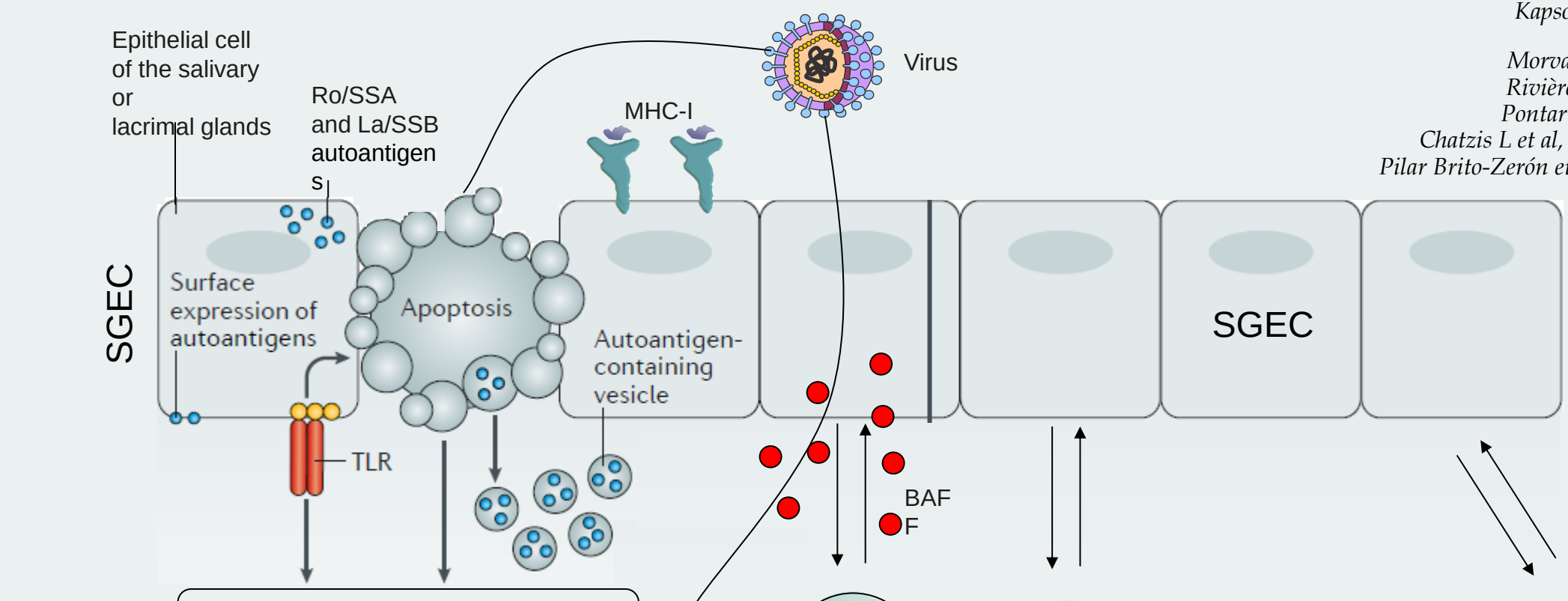
- Appear early in the course of the disease
- Remain stable for many years
- Low frequency of terminal organ damage

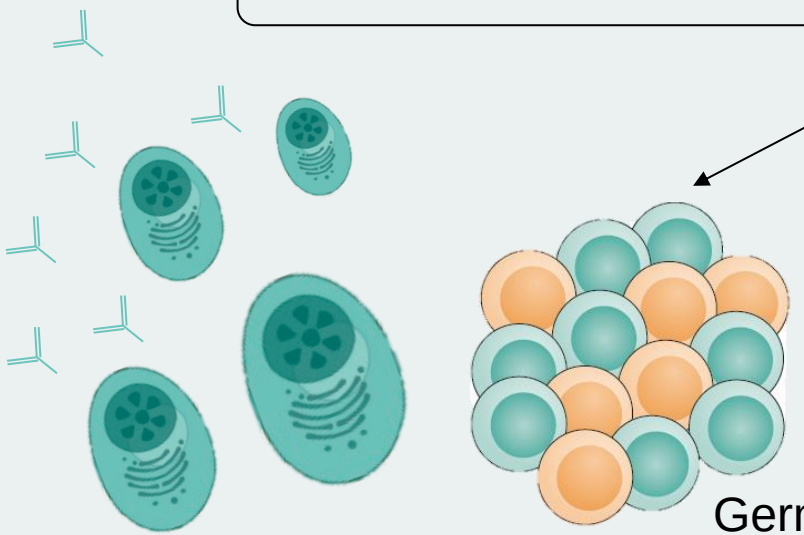


Extra-epithelial

- Late clinical sequel
- Severe organ damage if untreated
- Predictive factors for non-Hodgkin lymphoma development

Kapsogeorgou et al, J. Immunol., 2001
Gong et al, J. Autoim, 2014
Morva A et al.,. Ann Rheum Dis, 2013
Rivière E et al.,. Ann Rheum Dis, 2020
Pontarini et al, Ann. Rheum. Dis, 2020
Chatzis L et al, Expert Rev Clin Immunol. 2021
Pilar Brito-Zerón et al, Dis Primers, 2016 (modified)





Germinal center

B cell

When co-cultured:
- ↑ Gene expression
- ↑ B cell survival
- ↑ CD40 & CD268 (BAFF-R) expression
- ↑ Marginal zone B cells

T cell

- ❖ Mediate IL-2 driven T cell proliferation
- ❖ Drive CD4+ T differentiation into Tfh cells

T_{FH} cell

- ↑ SS peripheral blood and SG with GC
- ❖ Main source of IL-21
- ❖ Express ICOS and its blockage in ex vivo SG-organ cultures significantly reduced the production of IL-21 and inflammatory cytokines

A variety of Systemic Clinical Manifestations beyond exocrine gland involvement

- 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

H M Moutsopoulos

FEATURE	%, (1/n)
GLANDULAR MANIFESTATIONS	
Dry mouth	89,7 (6101/6800)
Dry eyes	89,0 (6046/6794)
Salivary gland enlargement	37,4 (1897/5083)
Parotid gland swelling	42,0 (2227/3843)
Submandibular swelling	5,0 (139/2787)
NON-SPECIFIC MANIFESTATIONS	
Raynauds phenomenon	26,5 (1577/5942)
Fatigue	54,0 (2840/5256)
Arthritis	16,6 (993/5999)
EXTRAGLANDULAR MANIFESTATIONS	
Renal disease	2,6 (162/6183)
Tubulointerstitial nephritis	1,4 (66/4729)
Glomerulopathy	0,9 (37/4330)
Pulmonary disease	7,1 (415/5466)
Small airway disease	3,0 (157/5169)
Interstitial lung disease	2,5 (112/4414)
Liver disease	2,4 (131/5431)
Autoimmune hepatitis	0,85 (40/4722)
Primary biliary cirrhosis	1,4 (81/5616)
Nervous System Disease	9,1 (560/6137)
Peripheral nervous disease	5,4 (267/4979)
Central nervous disease	2,7 (125/4612)
Palpable purpura	7,0 (396/5653)
Muscular System Disease	7,2 (357/4990)
Inflammatory myopathies	0,3 (10/3852)
Inclusion body myositis	3,3 (150/4579)

SEROLOGY	
Anti Ro/SSA	72,8 (4564/6268)
Anti La/SSB	43,2 (2670//6169)
Rheumatoid Factor	49,1 (2282/4644)
Antinuclear Antibodies	79,9 (4354/5450)
Low C_4 levels	59,0 (2485/4210)
Cryoglobulinemia	5,7 (266/4675)
LYMPHOMA	
Any type of Lymphoma	5,7 (354/6007)
MALT lymphoma	4,4 (245/5569)
DLBCL lymphoma	0,8 (45/ 5371)

HarmonicSS

A Goules et al in preparation

Extraglandular manifestations

Related to disease

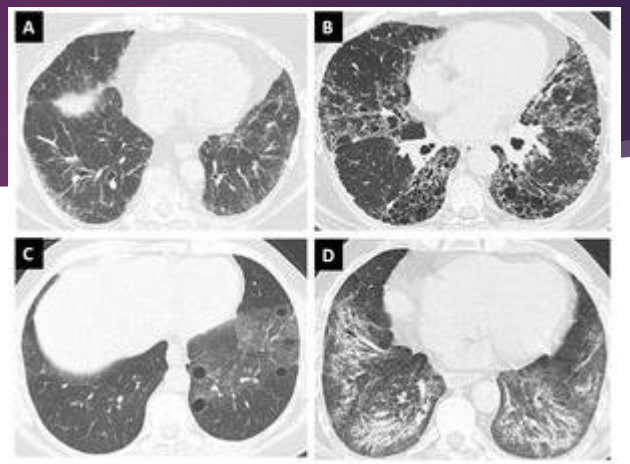
- **Autoimmune epithelitis**
  - PBC
  - Lung
  - Tubulointerstitial nephritis (TIN)
- **Immune complex mediated disease**
  - Cryoglobulinemic vasculitis (purpura)
  - Glomerulonephritis
  - Peripheral neuropathy
  - Lymphoma

Associated to disease

- Not a clear pathogenetic link in common
- Unknown association
  - CNS manifestations
  - Muscular involvement

Lung disease in SjD

- Prevalence in SjD: 9-20%
- Age: 55-61 years
- A late complication of SjD
- **Imaging/Histopathologic types of ILD in SjD:**
  - Non-Specific Interstitial Pneumonia (NSIP)
  - Usual Interstitial Pneumonia (UIP)
  - Organizing Pneumonia (OP)
  - Lymphocitic Interstitial Pneumonia (LIP)
- **Pathogenesis:**
  a) Epithelial injury of the exocrine glands of the large airways -> xerotrachea, xerobronchitis
  b) Lymphocytic infiltrates around exocrine submucosal glands
  c) Follicular bronchiolitis or hyperplasia of bronchus associated lymphoid tissue in the peripheral airways



A. **NSIP**. Ground glass opacities
B. **UIP**. basal-predominant fibrosis, honeycombing
C. **LIP**. cysts, nodules
D. **NSIP+ OP**. patchy alveolar involvement, consolidations

La Rocca et al J Clin Med. 2023

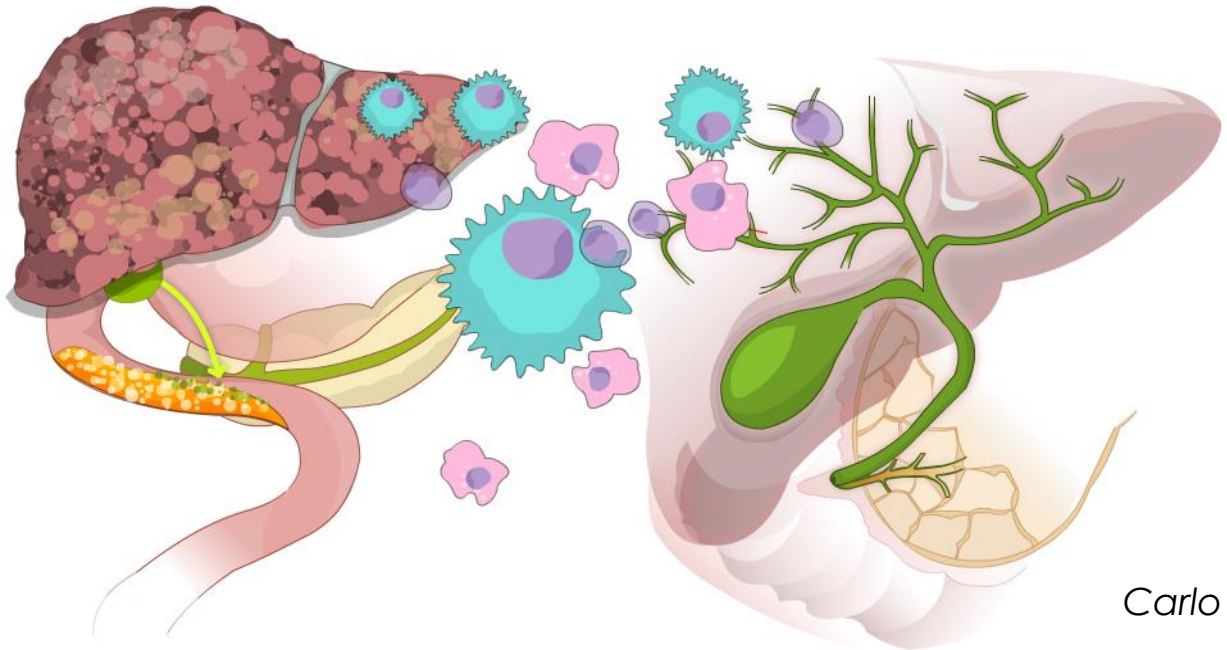
PBC

Clinical manifestations

- 50-60% of patients are asymptomatic
- Fatigue
- Pruritus
- Portal hypertension
- Fat soluble vitamin malabsorption
- Xanthomas

Complications

- Malabsorption →steatorrhea
- Metabolic bone disease
- Cirrhosis
- Hepatocellular carcinoma



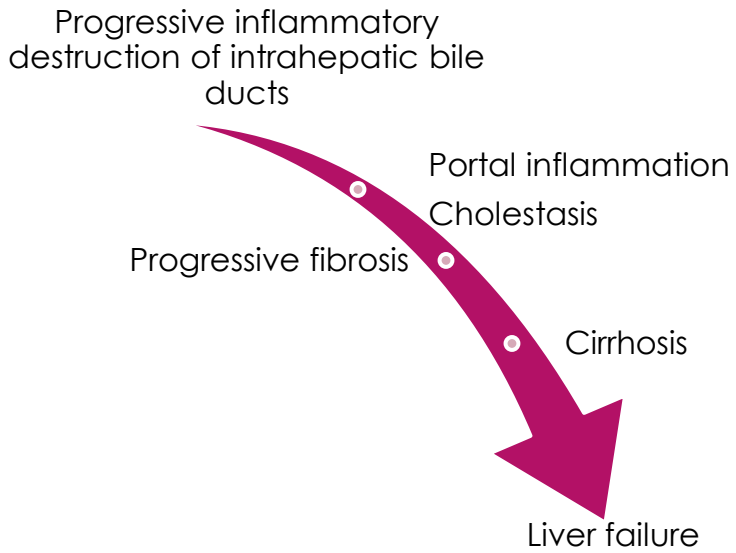
Carlo Selmi et al J Autoimmun. 2011

Primary Biliary Cholangiitis (PBC) and SjD

- SjD and PBC represent two major models of autoimmunity that share common pathogenetic mechanisms: Both characterized by chronic immune-mediated epithelitis

- They often coexist:
  - ~20% of patients with SjD have liver abnormalities
  - ~40% occurrence of SjD in patients with PBC

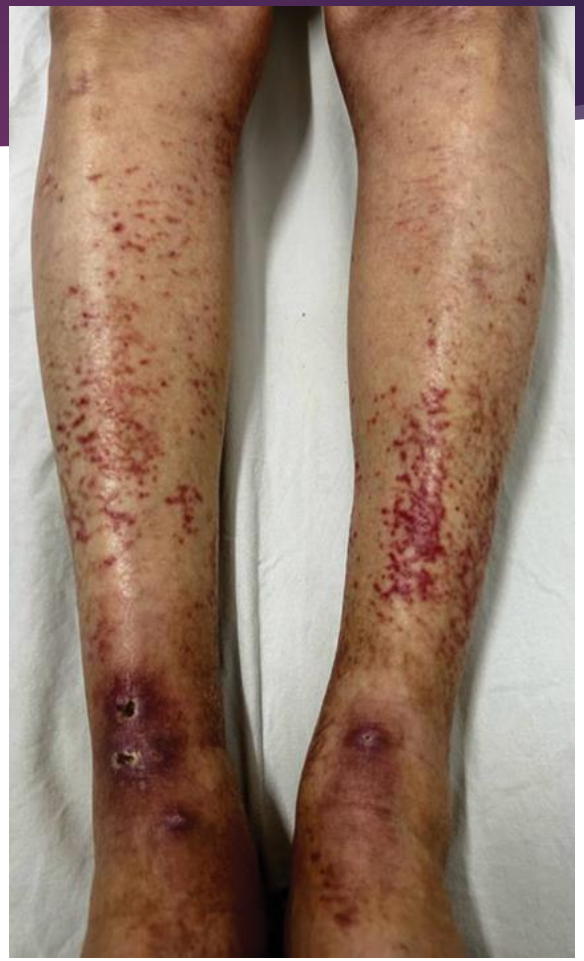
- Female to male ratio: 9-10:1



- Highly specific circulating autoantibodies: Antimitochondrial Abs (AMA) in 90-95% of patients

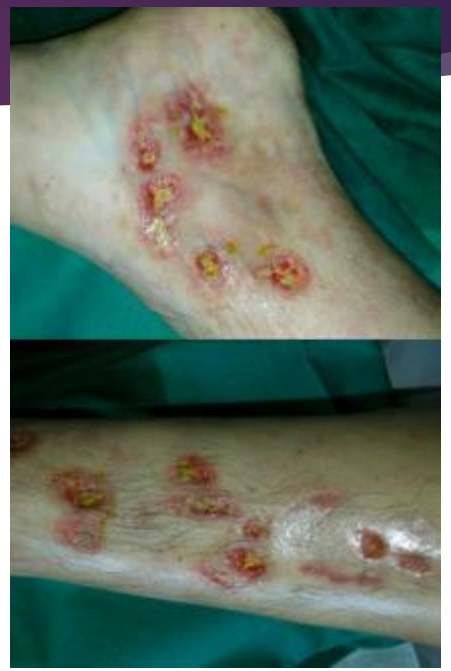
Extraepithelial manifestations in SjD

- Almost 15% of SS patients manifest extraepithelial features that constitute the systemic form of the disease
- **Immune complex mediated** due to deposition of immune complexes (i.e. type-II cryoglobulins), as a result of an ongoing B cell oligoclonal/monoclonal expansion
- Examples:
  1. Vasculitis (purpura)
  2. Peripheral neuropathy
  3. Glomerulonephritis



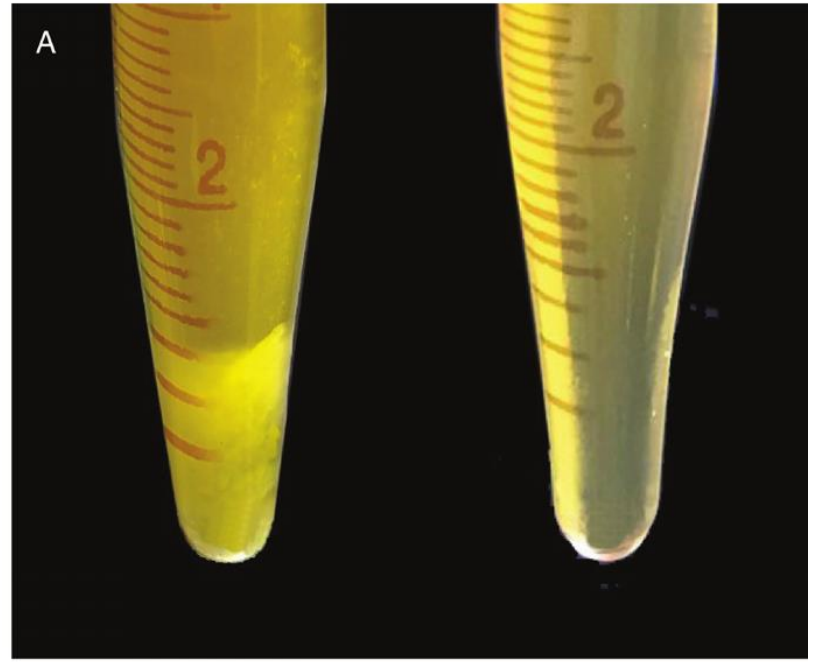
Cryoglobulinemic vasculitis

- Immune complex mediated small vessel vasculitis
- Involves: skin, kidneys, peripheral nerves
- Presence of cryoglobulins: predominantly Type II (IgMκ monoclonal rheumatoid factor(RF))
- Higher risk for future lymphoma development



Clinical	Serological	Pathological
• Purpura • Weakness • Arthralgias • Liver involvement • Skin ulcers • Peripheral neuropathy	• Mixed cryoglobulins • RF+ • Low C4	• Leukocytoclastic vasculitis • B cell expansion

Tzioufas et al A&R 1986, Tzioufas et al A&R 1996
Roccatello, D. et al. Cryoglobulinaemia. Nat Rev Dis Primers , 2018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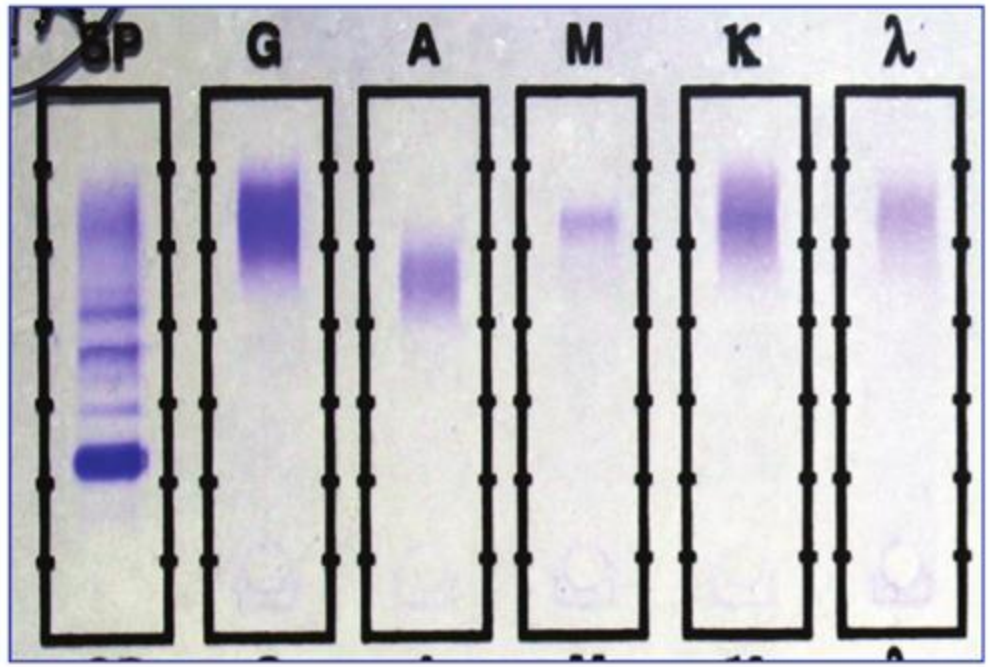
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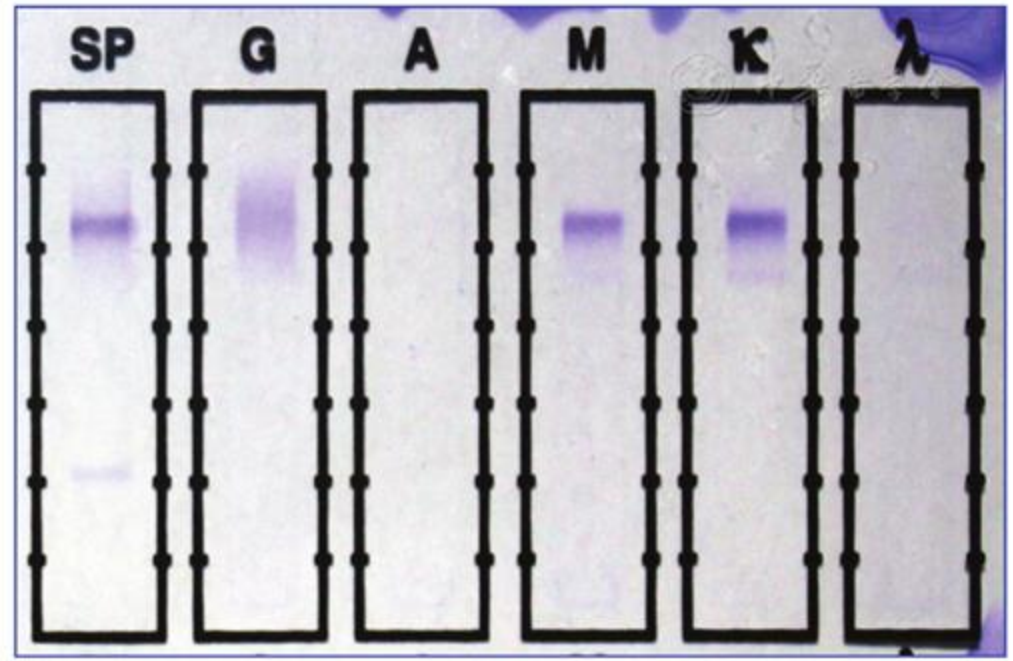
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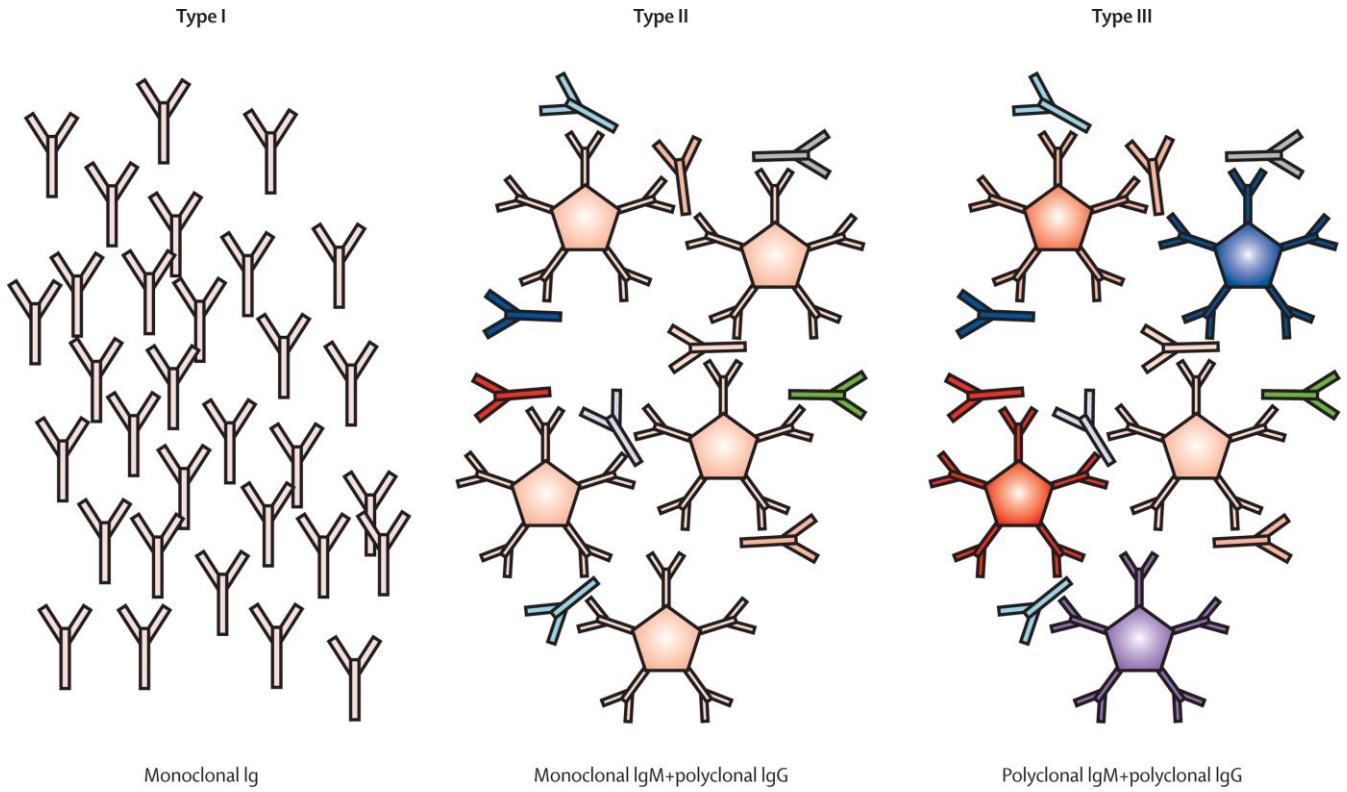
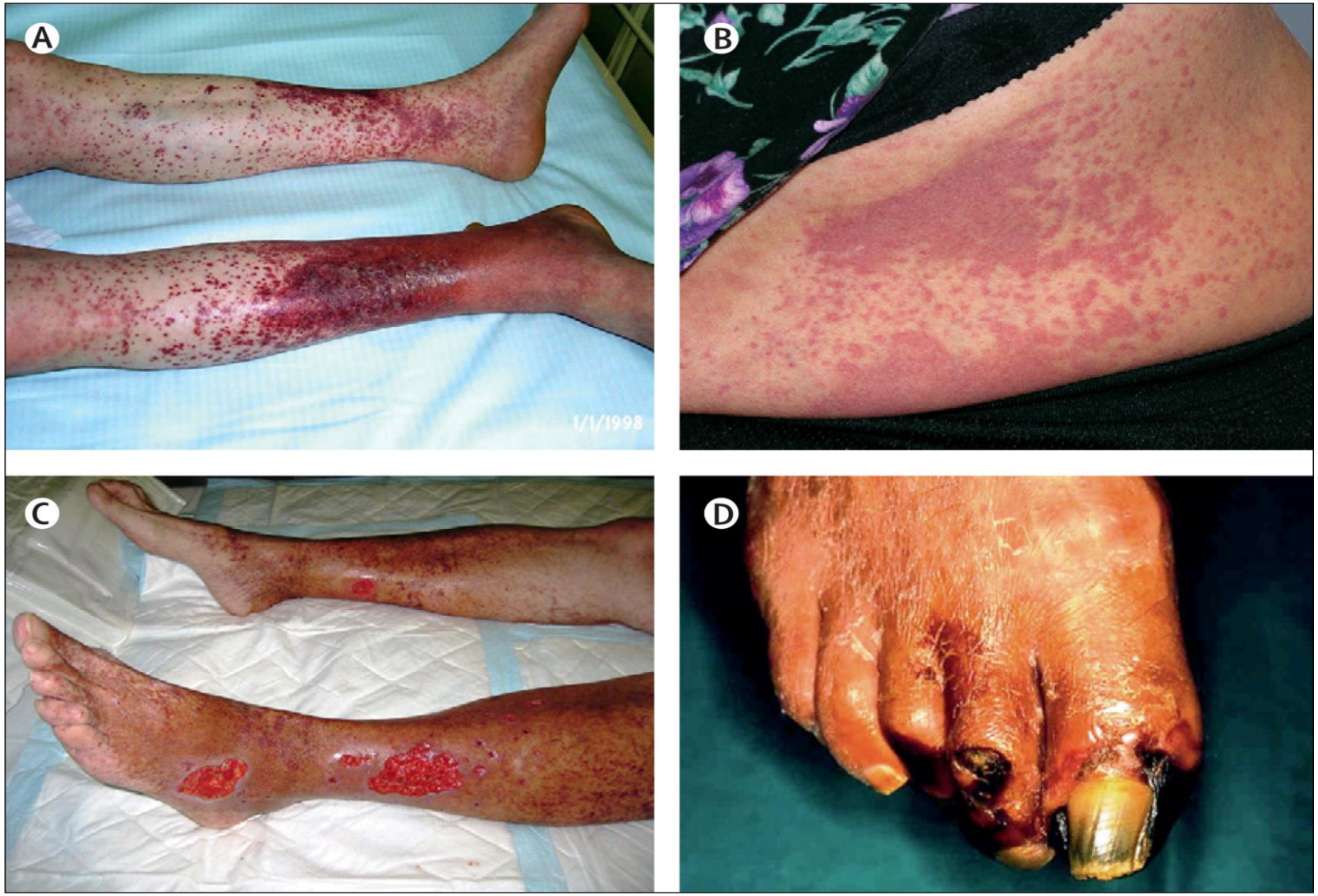
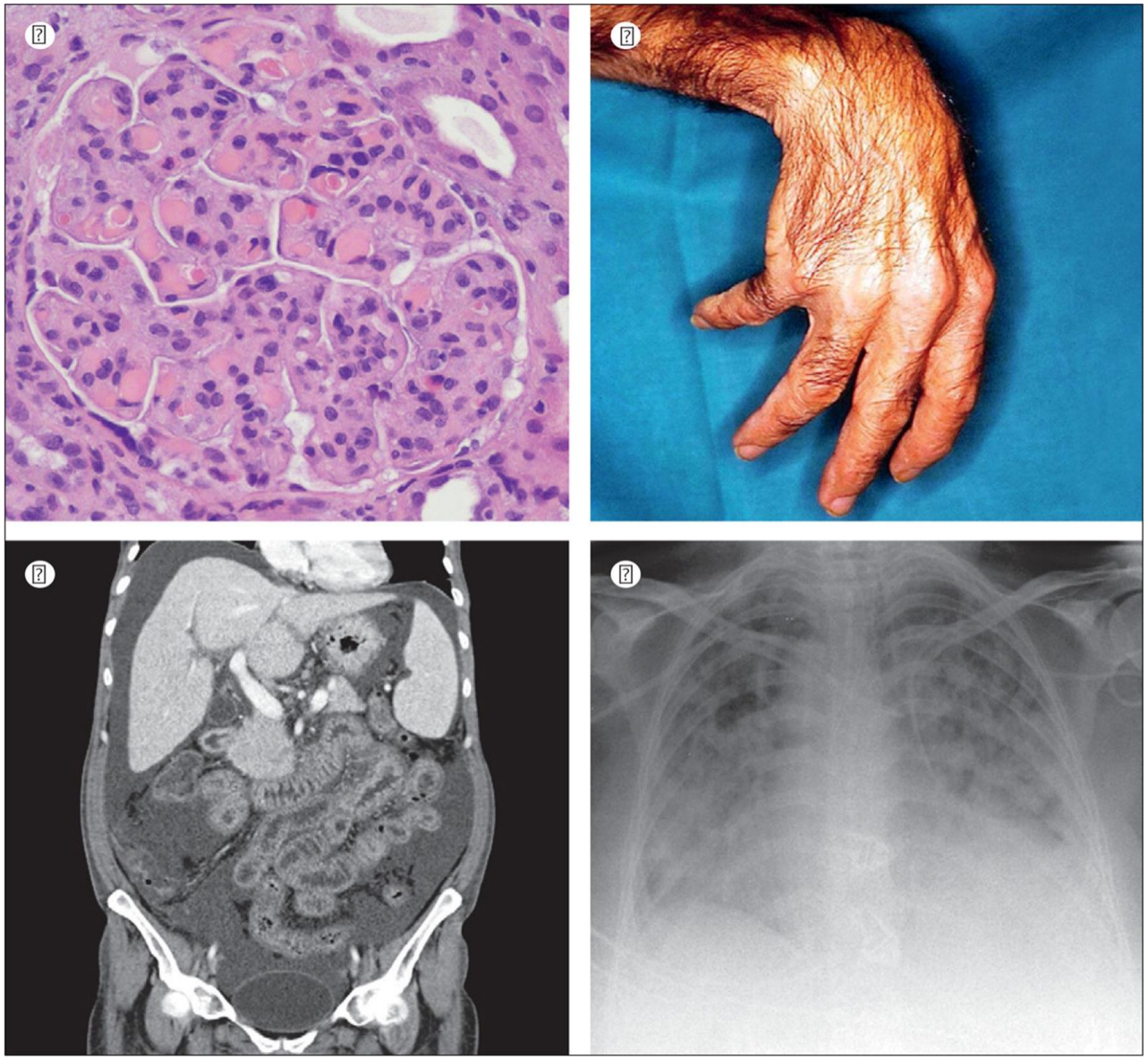


Ramos Casals et al Lancet 2012



Ramos Casals et al Lancet 2012



Ramos Casals et al Lancet 2012

Peripheral nervous system (PNS) involvement in SjD

PNS is more commonly affected than CNS

May precede typical glandular manifestations

- Small-fiber Sensory Neuropathy
- Sensory Ataxic Neuronopathy (Also Known As Sensory Ganglionopathy)
- Axonal Sensory And Sensorimotor Polyneuropathies
- Cranial Neuropathy (Including Trigeminal Neuropathy)
- Radiculoneuropathy
- Autonomic Neuropathy

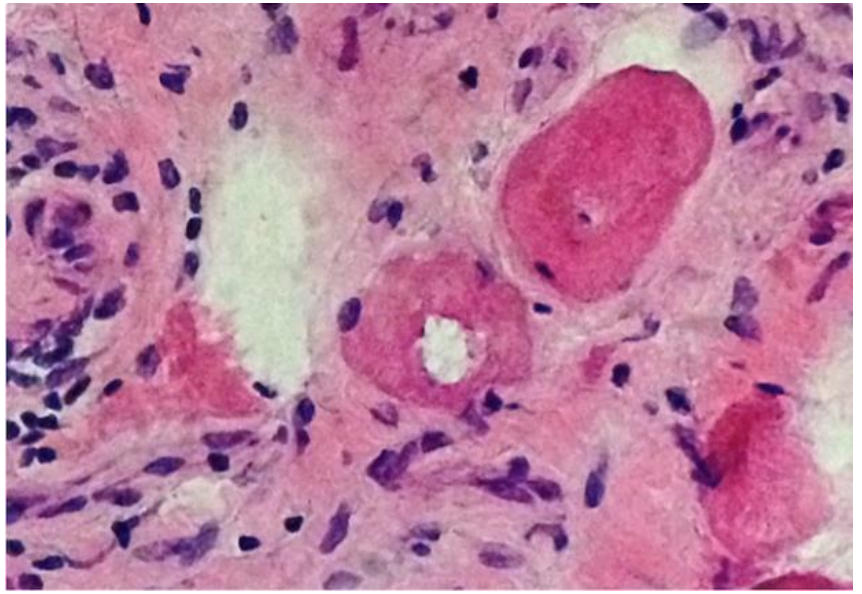
Pavlakis P et al J Autoimmunity 2012

Pathogenesis:

- Lymphocytic infiltration of dorsal root ganglia → sensory neuropathy.
- Small fiber neuropathy: immune damage to nociceptive C and Aδ fibers
- Vasculitis of vasa nervorum → ischemic nerve injury (mononeuritis multiplex)
- Autoantibodies and immune complexes contribute to chronic neuropathic damage

Inclusion Body Myositis (IBM)

- Classified among idiopathic IM
- Slow-progressing muscle weakness
- Frequently asymmetrical and predominantly distal (affects the quadriceps and finger flexors)
- Histolopathology: lymphocytic infiltration (primarily CD8 T cells) and protein inclusions, rimmed vacuoles and mitochondrial changes within muscle fibers
- Resistant to conventional anti-inflammatory and immunosuppressive drugs



Kanellopoulos P, et al Rheumatology 2002
Astouati Q et al, Rheumatology (Oxford). 2025
Zeng L, et al , Front Immunol. 2023

CNS involvement in SjD

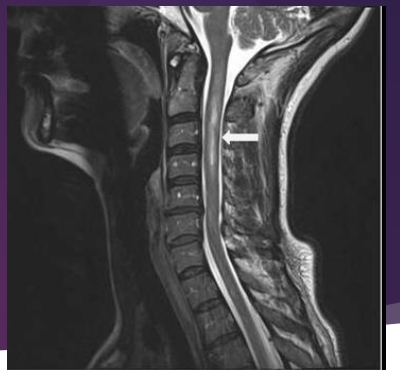
Much less common than peripheral neuropathy (1-5% of patients)

Insidious progressive neurologic deficit

Wide spectrum of disorders

Cognitive disorders	Aseptic meningitis	Epileptic seizures
Headache	Transverse myelitis	Optic neuritis
Disseminated encephalopathy	Lesions resembling MS	

CNS involvement in SjD



MS-like presentations

- Demyelinating disorder
- Patients with primary MS: higher prevalence of SjD
- Brain and/or spinal cord MRI abnormalities
- Homozygous MTHFR mutations frequently encountered

Mavragani CP et al. J Rheumatol. 2007

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- Inflammatory demyelinating disorder
- Clinically: optic neuritis, transverse myelitis
- Presence of AQP4 antibody
- Not a direct manifestation of SjD, but rather an overlap of two distinct autoimmune diseases

Kampylafka et al J Autoimmmunity 2011

✓ 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

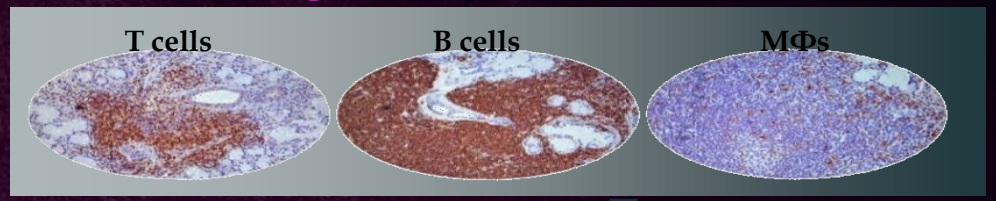
Sjögren's Disease-Biomarkers

A conceptual step-wise categorization

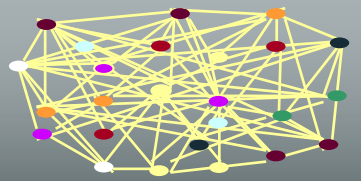
Clinical stratification

CLINICAL PHENOTYPING

Histologic stratification



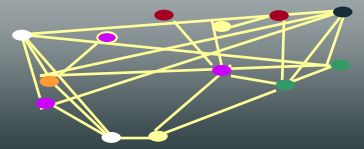
System biology approach



Candidate Biomarkers

- Preliminary
- Clinical utility
- Sensitivity

Molecular stratification



Homogenous patient groups for targeted therapy

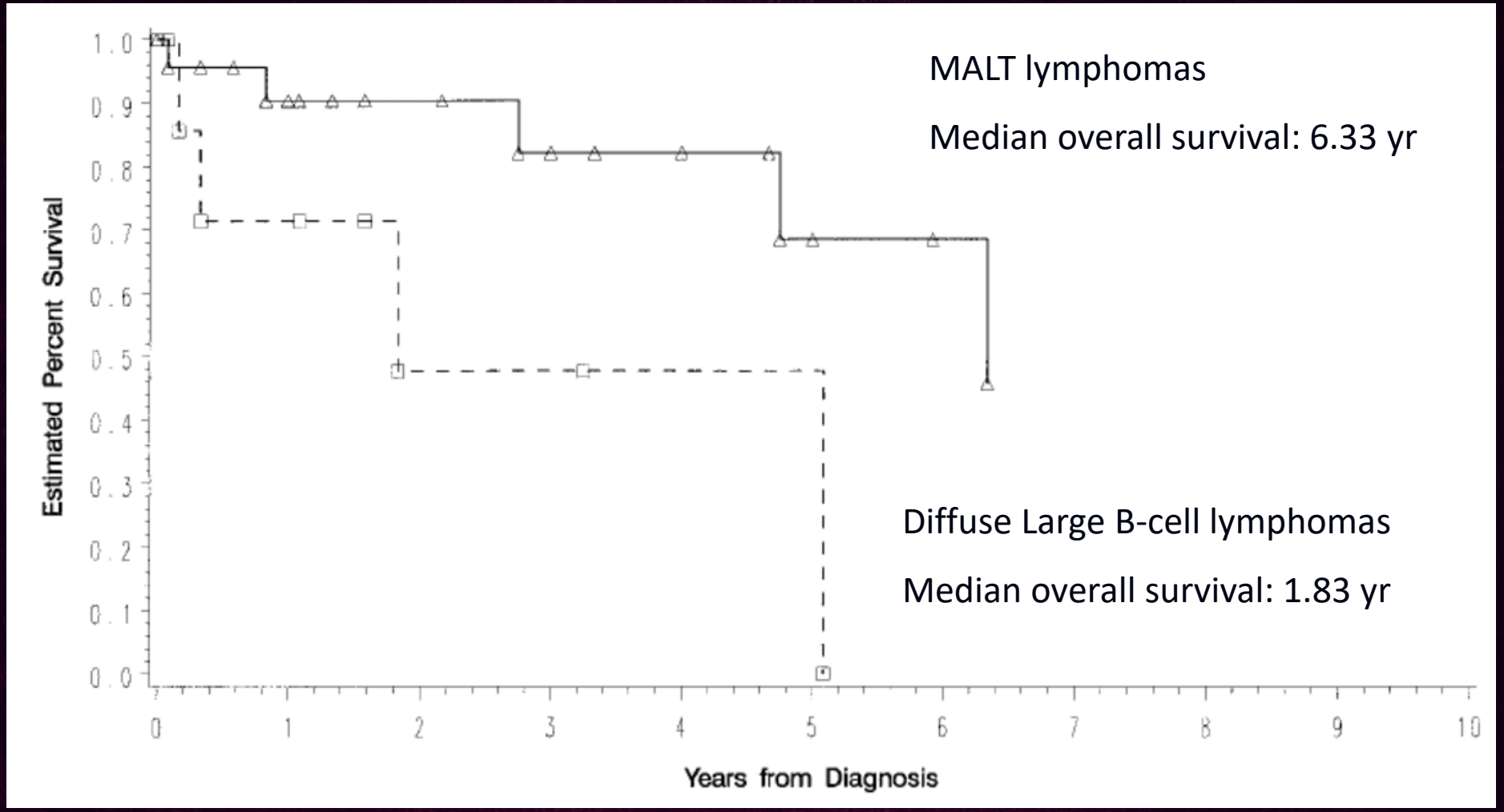
Mortality in SS with or without lymphoma

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	

Theander Ann Rheum Dis. 2006

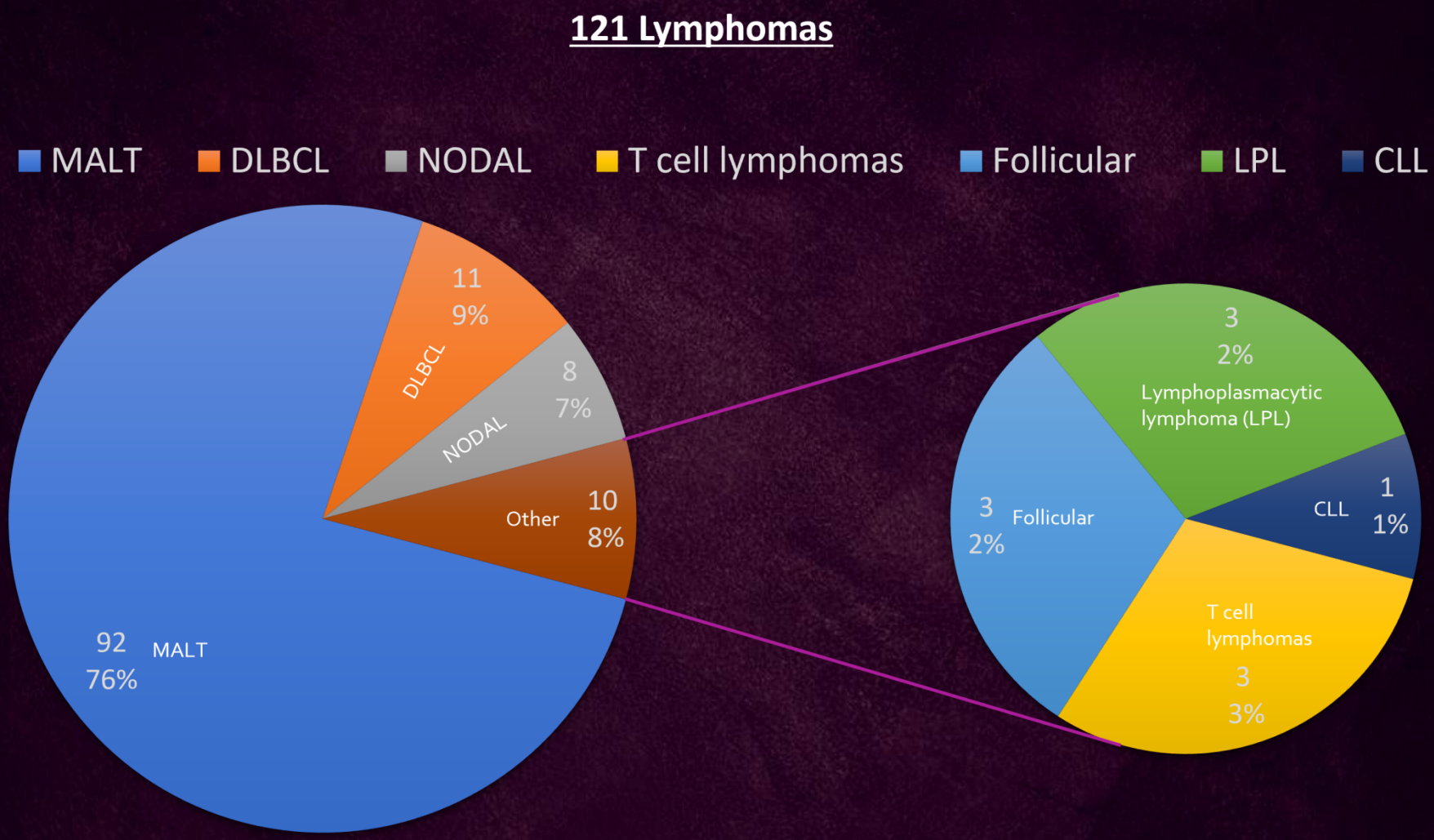
Sjögren's Syndrome/Lymphoma

Survival curves 22 years ago (Pre- Rituximab era)



Voulgarelis M, et al. Arthritis Rheum 1999

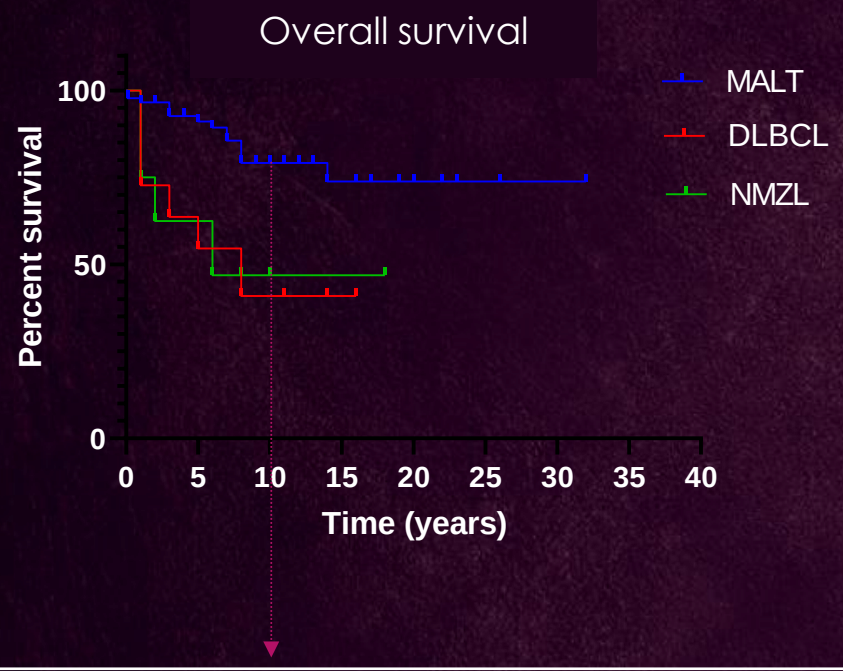
Sjögren's Syndrome Associated Lymphomas (UOA)



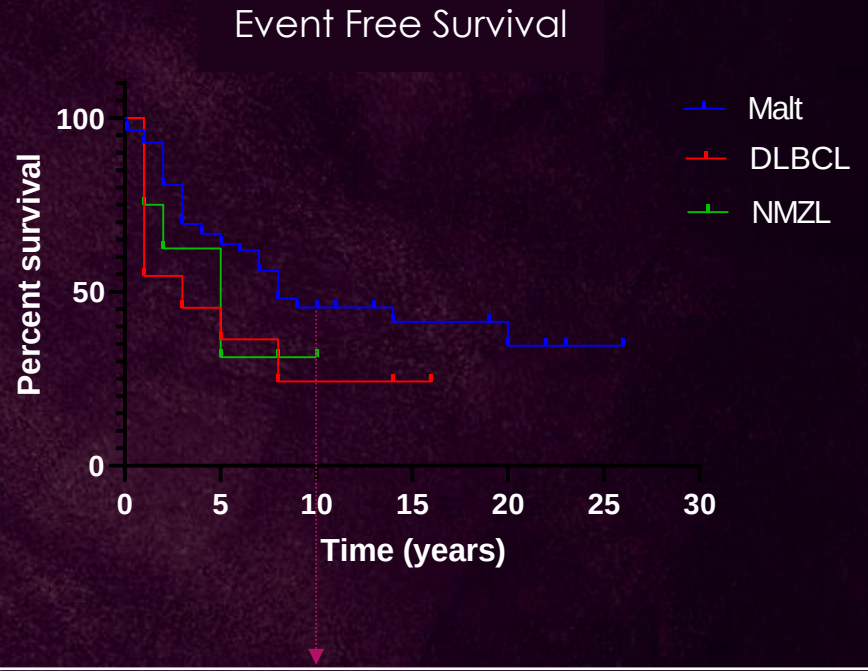
Chatzis et al. Rheumatology 2022

OR and EFR Survival curves

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



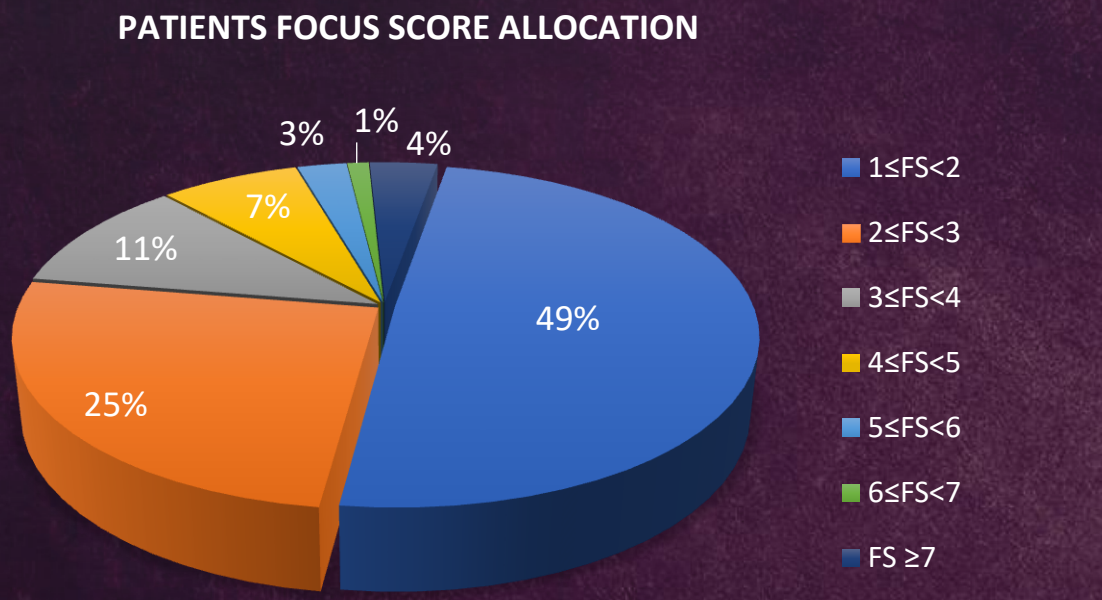
10-year OS	Malt	DLBCL	NMZL
	79.140	40.909	46.875

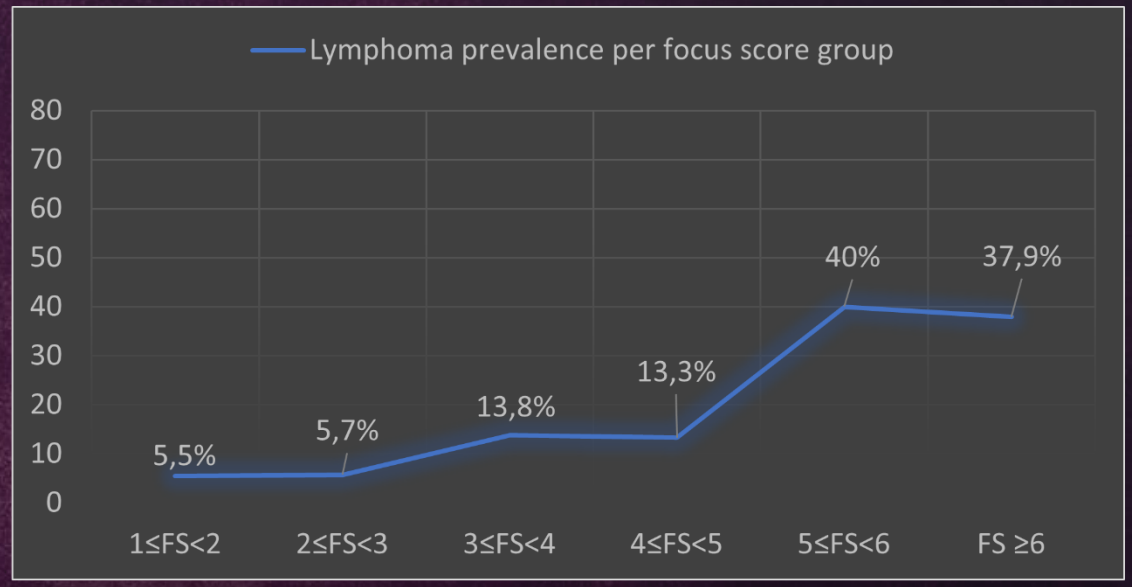


10-year EFS	Malt	DLBCL	NMZL
	45.552	24.242	31.250

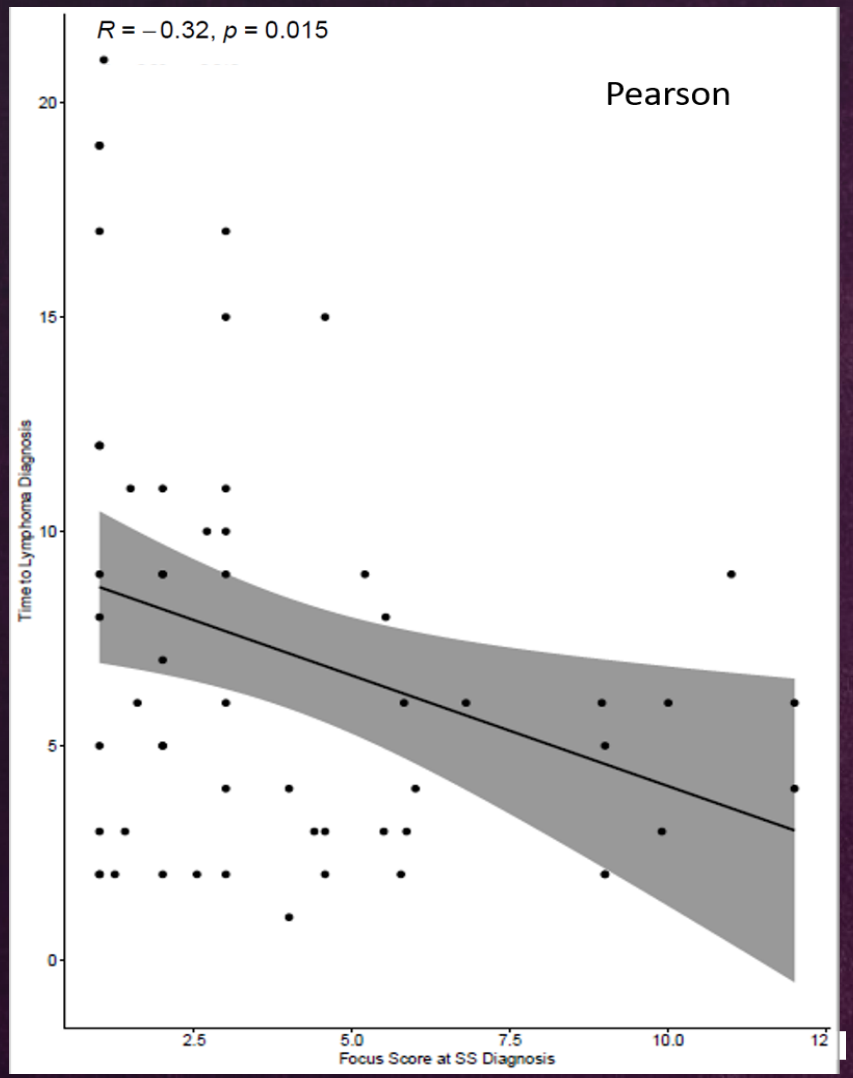
Chatzis et al. Rheumatology 2022

Focus score





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



Sequential algorithm for time interval from SjD 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

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

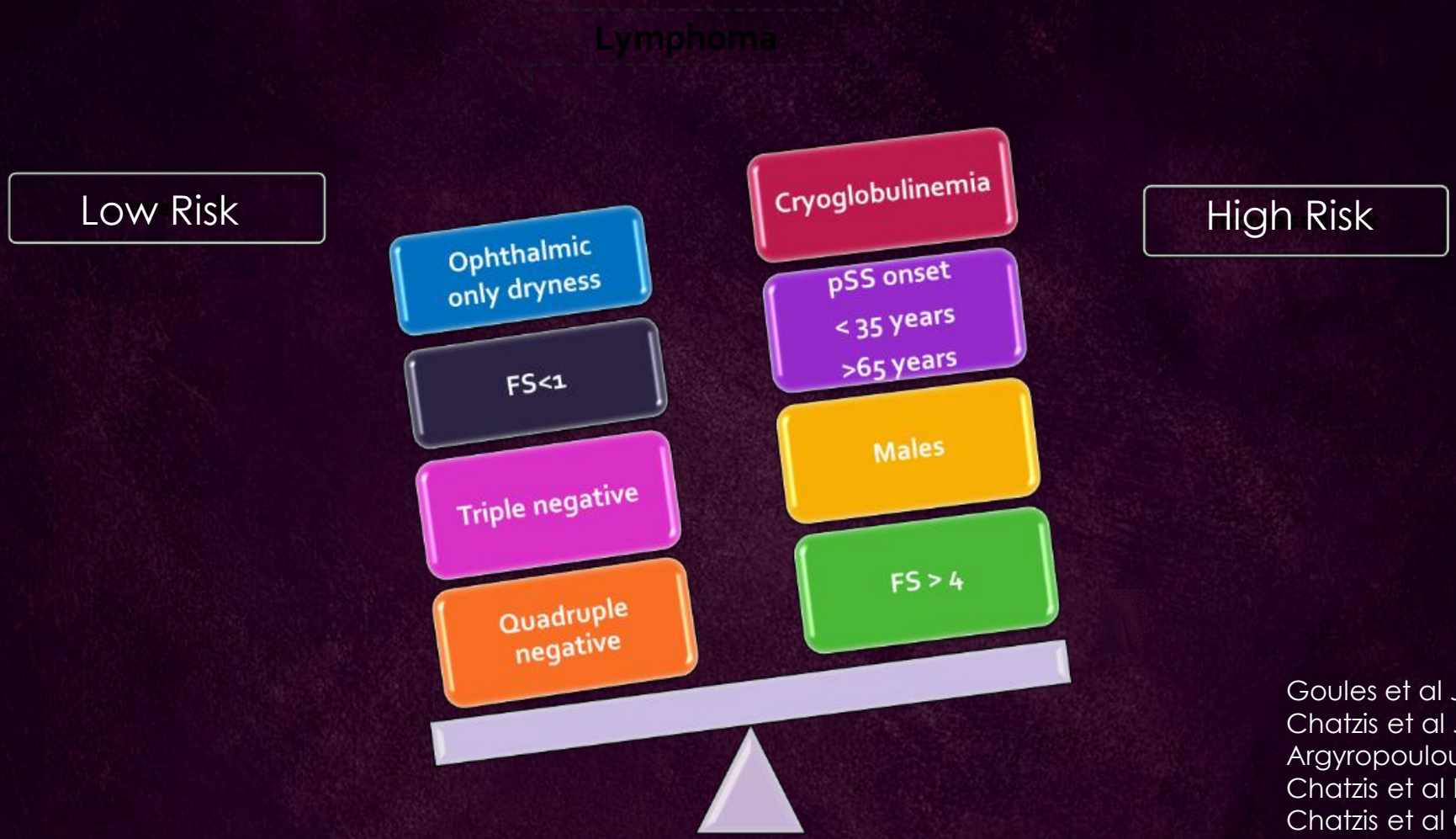
Prominent feature*	Regression coefficient	Odds ratio	p-value	CI low	CI upper
Cryoglobulinemia	0.917	2.571	0.421	0.288	24.681
Low serum C4	1.306	3.836	0.147	0.701	21.575
Rheumatoid Factor	1.027	2.877	0.282	0.484	17.654
Salivary gland enlargement	0.815	2.34	0.345	0.47	11.777
Focus score	0.333	1.409	0.035**	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

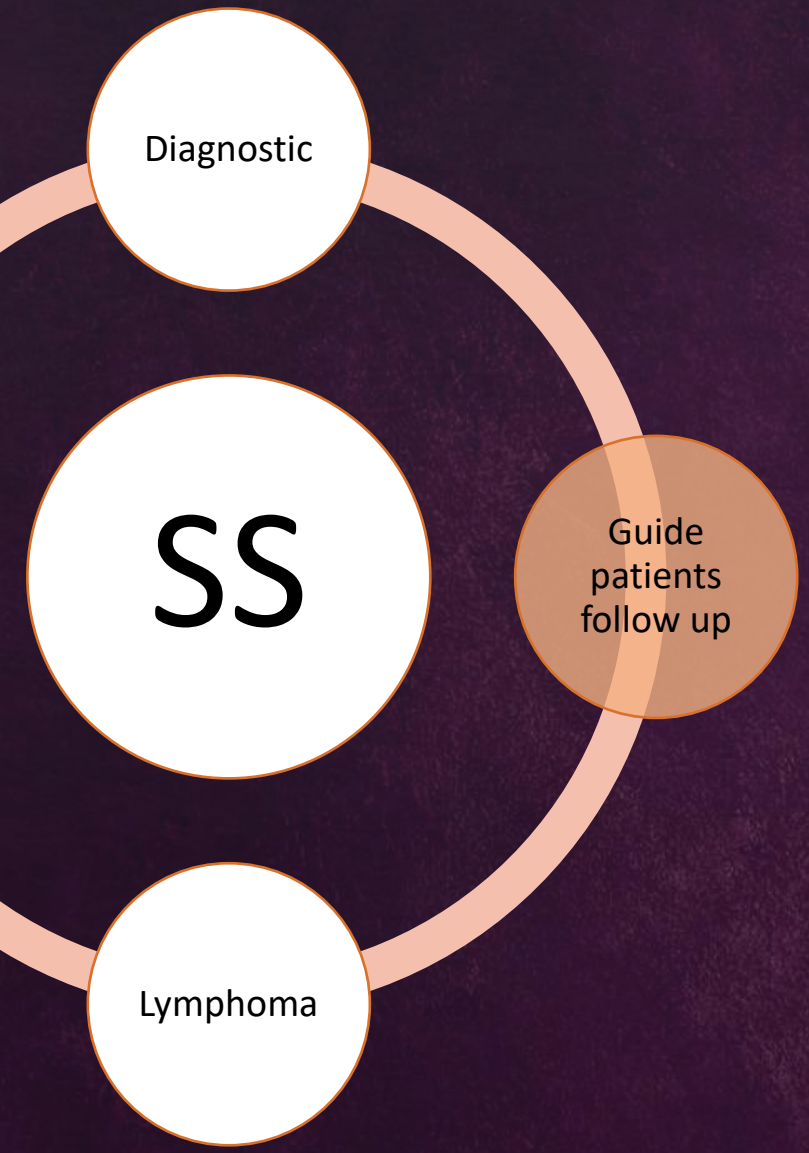
Focus score

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

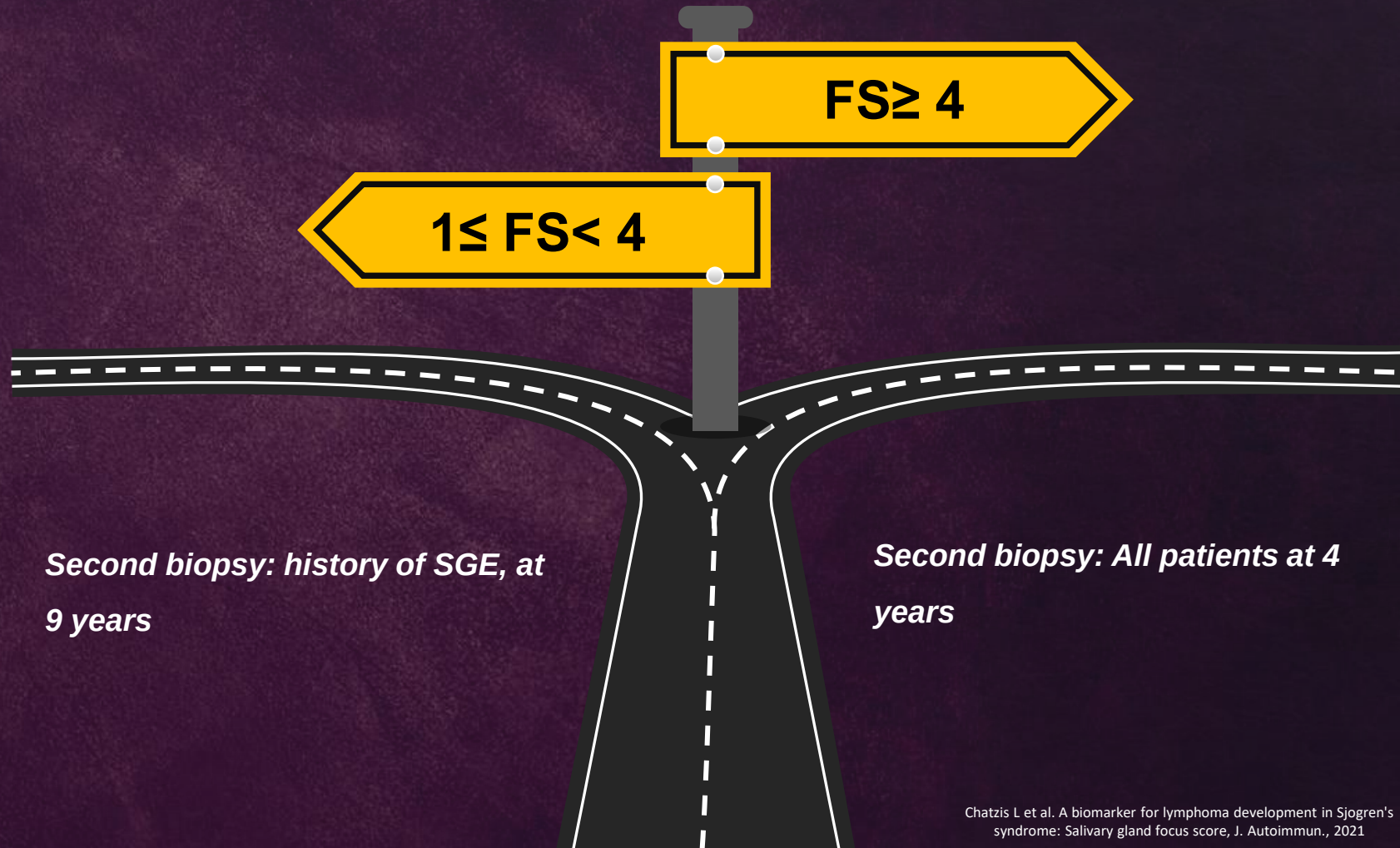
✓ *Sjögren's Disease: different SjD groups display different risk for lymphoma development*



Goules et al J Autoimmunity 2020
Chatzis et al J Clin med 2019
Argyropoulou et al Semin A&R 2019
Chatzis et al Rheumatology 2021
Chatzis et al Clin Exp Rheum 2020
Chatzis et al Clin Exp Rheumatol 2021
Stergiou et al Clin Exp Rheumatol 2021



- Offers guidance for the performance of a second biopsy



Second biopsy: history of SGE, at 9 years

Second biopsy: All patients at 4 years

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

Take home messages

- Clinical phenotyping is necessary during the examination of the patient
- B-cell lymphomas are the major extraraglandular manifestations related to disease process
- Associated features are severe, pointing the need of detailed physical examination of the patient

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