

# A comparative cross-sectional study for understanding the difference in prevalence of skin changes in patients with primary and secondary Sjögren's syndrome

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**UNIVERSITY OF SPLIT  
SCHOOL OF MEDICINE**

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**A COMPARATIVE CROSS-SECTIONAL STUDY FOR UNDERSTANDING THE  
DIFFERENCE IN PREVALENCE OF SKIN CHANGES IN PATIENTS WITH  
PRIMARY AND SECONDARY SJÖGREN'S SYNDROME**

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## **1. INTRODUCTION**

## 1.1 Sjögren's syndrome

### 1.1.1 Terminology

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease characterized primarily by sicca symptoms owing to immune-mediated destruction of lacrimal and salivary glands. Sicca symptoms are mainly xerophthalmia and xerostomia (1). It is important to note that 20% of patients with SS do not present with sicca symptoms, and other criteria are needed to be fulfilled to diagnose the disease (2).

Not every person with sicca symptoms fulfills the criteria for Sjögren's syndrome, and not every patient with SS present with sicca symptoms. The use of the term SS will exclusively be used to describe cases that fulfill the diagnostic criteria.

### 1.1.2 History

The syndrome was named after a Swedish ophthalmologist Henrik Sjögren. Sjögren investigated a group of women in the early 1900s with symptoms of dry eyes and mouth, occurring in the presence of chronic arthritis. Through these investigations he connected the triad of typical symptoms (3).

However, even if Sjögren gave name to the syndrome, and was the first person to correlate the classical triad of symptoms, he was not the first physician to describe the syndrome. In 1871 Walter B. Hadden and John W. Hutchinson reported the first case of dry eyes and mouth (4).

Sjögren's syndrome was also described under the name of Mikulicz's disease when Johann von Mikulicz-Radecki in 1888 used this term to describe other syndromes with enlargement of parotid, submandibular and lacrimal glands. This term however became obsolete in 1953 when the English physician Morgan made the connection between SS and lymphoproliferative diseases, proving that SS and Mikulicz's disease are histologically equivalent (4).

### *1.1.3 Epidemiology*

The syndrome most commonly affects women with the highest incidence being in the age group between 34-57 years and of 40-67 years (5). There is a predominance of women being affected over men with an incidence described in some studies as high as 16:1 in women compared to men (6).

SS is one of the commonest rheumatic diseases, second in prevalence only to rheumatoid arthritis (RA) (7). The disease prevalence varies significantly according to different demographics, and also depend on the classification criteria used. Among ethnic groups the syndrome is reported with the highest prevalence recorded in Asian women, followed by Caucasian women (8).

With limited data available, accurately determining the true incidence of SS poses a challenge. Three prospective studies from Minnesota, USA, Slovenia and Greece have estimated the incidence of primary Sjögren's syndrome to be 3.9 per 100,000, 3.9 per 100,000 and 5.3 per 100,000, respectively (9).

There are likely many undiagnosed cases of SS owing to the unspecific nature and wide range of symptoms. The sicca symptoms might be mistaken for another disease with similar symptoms, common medication side effects or even as natural part of aging (10).

### *1.1.4 Female predominance in Sjögren's syndrome*

Autoimmune diseases commonly affect women much more frequently than men, with about 80% of those affected being women. SS is the autoimmune disease with the highest women to men predominance (6).

The higher prevalence of autoimmune diseases among women remains a question we do not yet have a complete understanding of. We already know that women respond to trauma, infection and vaccination with higher antibody production in comparison to men. It is suggested that the same tendency for higher antibody production contributes to an increased risk of developing autoimmune diseases (9).



Estrogen stimulates B cell activity, whereas androgen suppresses B cell maturation and antibody production. Consequently, women tend to produce more antibodies and harbor a greater reservoir of autoantibodies. This imbalance in sex hormones likely contributes significantly to the gender discrepancy in the prevalence of SS, where B cell hyperactivity plays a significant role in disease development. Given estrogen's positive influence on B cell production and maturation, it is reasonable to speculate that variations in sex hormone levels play a crucial role in female predominance of the disease (9).

Suggestions have also been made that there is rather the change in the androgen-estrogen ratio which causes the increased risk in women, rather than the estrogen levels by themselves. To add to this theory, we know that ovaries produce low levels of testosterone that decline at time of menopause, as well as the dehydroepiandrosterone (DHEA) produced by the adrenal cortex also declining with age (11).

Knowing that the disease prevalence increases with age, this could further support the indication of androgen-estrogen ratio in the pathogenesis. The decline in production of testosterone and DHEA both correspond well to the peak age of onset of SS. The possible role of low androgen levels is also supported by findings of decreased DHEA levels in the saliva of SS patients (11).

#### *1.1.5 Primary and secondary SS*

SS is classified as primary and secondary. The syndrome is defined as primary SS (pSS) when the hallmark sicca symptoms occur in the absence of other autoimmune disorders. It is diagnosed according to the 2016 ACR-EULAR classification criteria (12).

The diagnosis of secondary SS (sSS) is usually established when the typical sicca symptoms occur in conjunction with another coexisting autoimmune disease, e.g. RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc) (13).

Whilst pSS is clearly defined by classification criteria after excluding other possible disorders with similar symptoms, there is no established classification criteria, nor any universally accepted standards for diagnosing sSS. This makes sSS a rather subjective diagnosis compared to primary disease (13).

Overlap syndrome is a medical condition that describes the coexistence of three connective tissue diseases. For example, the combination of polymyositis, SLE and SSc is described as an overlap syndrome. When SS occurs in the setting of overlap syndrome, it is classified according to whether SS was diagnosed prior to or after the development of the other connective tissue diseases, where it will be classified as primary or secondary, respectively (14).

#### *1.1.6 Etiology and pathogenesis*

SS is an autoimmune disorder of idiopathic etiology. While multiple studies have been conducted to identify specific factors involved in establishing the condition, we still have not established a certain trigger nor cause in pSS. The disease is considered to have a multifactorial pathogenesis, and it is believed that an interplay between genetical, environmental, immunological and hormonal factors is responsible for the development of the disease (15).

In the pathogenesis of SS, chronic immune system stimulation with an exaggerated activation of innate immunity is suggested to play an integral role. Epithelial cells in salivary and lacrimal glands, dendritic cells and interferon alpha, CD4 T lymphocytes, cytokines and B-cell activating factor (BAFF) have all been reported in literature to contribute to the development of Sjögren's syndrome. Histopathological findings of focal lymphocytes around glandular ducts in affected glands further support their involvement in disease pathogenesis (15).

B-cell hyperactivity is another hallmark characteristic of the syndrome. The activation of B cells leads to production of immunoglobulins, causing hypergammaglobulinemia. Production of autoantibodies against Ro/SS-A and La/SS-B, as well as activation of Toll-like receptors and B cell activating factor (BAFF), in turn increases production of interferons. BAFF and interferons interact with each other in a positive feedback loop. Elevated BAFF levels have been found to correlate with the levels of autoantibodies in patients with established SS (6).

B cells involved in the pathogenesis produce specific autoantibodies that are both organ-specific and non-organ-specific. These autoantibodies contribute to organ and tissue dysfunction. It appears that the T cells in SS are autoreactive, allowing the production of these autoantibodies (16). About 60% of SS patients have positive non-organ-specific autoantibodies, including rheumatoid factor (RF), antinuclear antibodies (ANA) and Ro/SS-A and La/SS-B, which are antibodies to small RNA protein complexes (10). In addition to the non-organ specific autoantibodies, organ-specific autoantibodies towards thyroid gland, stomach, smooth muscles, DNA and salivary glands have been identified (17).

In the early stages of disease, T cells form a large part of the pool of lymphocyte infiltration. The infiltration of T cells participates in the loss of tolerance to self-antigens as well as secretion of pro-inflammatory cytokines. The migration of T cells into salivary glands is followed by decreased levels in the periphery, a finding commonly associated with higher disease activity in patients. Among the subsets of T cells, Th1 and Th17 specifically have been suggested as important mediators in inflammatory response in early disease, through cytokine secretion and triggering T cell migration. Th2 cells have been implicated in early B cell response (18).

Genetics are suggested to play an essential role in the pathogenesis of SS, and the HLA genes most likely are responsible for the strongest genetic predisposition. HLA class II is associated with autoantibody production and confers a possible genetic susceptibility to production of Anti-SSA (Ro) and Anti-SSB (La) specifically. HLA allele variants vary among ethnical groups, and among the more frequent haplotypes associated with SS are HLA-B8, HLA-DR15, HLADRw52 and HLA-DR3. HLA-DR15 is associated with Anti-SSA synthesis, while HLA-DR3 is associated with production of both Anti-SSA and Anti-SSB (19, 20).

It is evident that genetics alone do not account for the development of SS, and there is a common presumption that exogenous environmental factors have a critical role in the disease activation in an already genetically and immunologically predisposed individual (21).

Various viruses have been considered potential triggering factors, and antigens associated with Epstein-Barr virus (EBV) have been identified in lacrimal gland biopsies of SS patients; yet, no clear association has been reported. The lack of finding of these EBV-associated antigens in other unaffected tissues in SS patients, as well as not being detectable in healthy individuals, further supports a potential role of EBV in the pathogenesis. Additionally, the amount of EBV DNA in saliva of SS patients has been proven to be significantly higher in comparison to persons with other autoimmune diseases, suggesting that EBV may be implicated as a triggering factor in SS specifically, and not solely as a trigger of autoimmune disease in general (22).

There are multiple theories suggesting different mechanisms of EBV involvement in SS pathogenesis. One theory suggests that EBV exists in normal salivary gland epithelial cells, and that the destruction of salivary glands is caused by an exaggerated immune response to the EBV DNA. Another suggested mechanism involves the concept of molecular mimicry, as there is a significant similarity between the viral EBNA-2 protein and the Ro-antigen, as well as between the viral EBNA-1 and EBNA-2 proteins and the La-antigen (23).

#### *1.1.7 Clinical features*

Patients with SS typically have sicca symptoms with mouth and eye dryness and parotid gland enlargement, related to the decreased functioning of lacrimation and salivary glands. The reduced salivary production not only interferes with daily activities such as eating and speaking but may also make individuals susceptible to various infections, as well as accelerate the process of tooth decay and periodontal disease due to loss of antibacterial properties of saliva. Mucous gland secretion of upper and lower respiratory tract may also be diminished, which could result in dry nose, throat and trachea and consequently development of chronic dry cough. Exocrine glands may also be affected, leading to skin and vaginal dryness (10).

SS additionally includes a wide variety of systemic manifestations, including the presence of fatigue in as many as half of the patients. The cause of fatigue is mostly idiopathic but is often related to hypothyroidism when associated with the syndrome, or fibromyalgia which has been reported in up to 22% of patients with pSS (10, 24).

Joint affection is common with arthralgias and myalgias. The syndrome usually affects small joints, often with asymmetrical involvement. The typically targeted joints have a similar distribution to patients with rheumatoid arthritis. A possible relationship to osteoporosis and osteomalacia has also been established (25).

Clinical pulmonary involvement may occur, usually in the form of chronic cough or subclinical pulmonary involvement. Findings on chest computed tomography imply that as many as 30% of patients with SS might have subclinical pulmonary disease. Other patients may have gastroenterological affection with lymphocytic infiltration of the intestines causing malabsorption. Patients also may have lymphocytic tubulointerstitial involvement of the kidneys (10).

Neurologic involvement is one of the most common systemic manifestations of the syndrome, which may involve cranial and peripheral nerves, and more rarely the central nervous system. Peripheral neuropathy has an incidence of up to 22% in patients with SS and it even has been reported as the first disease presentation in some patients. Its manifestation is mainly sensory (10).

Patients may present with hematologic manifestations including anemia, cytopenia and monoclonal gammopathies (26). Owing to the nature of strong B-cell polyclonal proliferation infiltrating the tissues, there also exists an increased risk of development of lymphoid malignancies (27). SS has the strongest association with B-cell lymphoma compared to other rheumatic autoimmune diseases, and the risk of developing lymphomas is approximately 16-fold increased. Up to 10% of patients with SS are at risk of developing malignant lymphoma (28).

Nearly half of patients with SS develop skin manifestations including but not limited to xeroderma, dermatitis, purpura and urticaria-like lesions, and vasculitis (29). The detailed variation of dermatologic manifestations will be emphasized in a later section for a thorough understanding.

### *1.1.8 Quality of life and psychosocial impact*

Health is defined by WHO as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (30). Health-related quality of life (HRQoL) is an indicator of the individual's subjective perception of overall health, and the impact of the health status on physical and mental health (31). A disease-specific HRQoL have been defined for patients with pSS, the Primary Sjögren's Syndrome Quality of Life Questionnaire (PSS-QoL) (32).

HRQoL have been reported in multiple studies to be significantly decreased in patients with SS. The reduction in life quality is comparable to other chronic illnesses. Reduced HRQoL in patients with SS is associated with the presence of fatigue, pain, arthralgias and musculoskeletal involvement, reduced sleep quality, sicca symptoms, sexual dysfunction, pruritus, pulmonary disease, psychological dysfunction and impaired physical functioning (33).

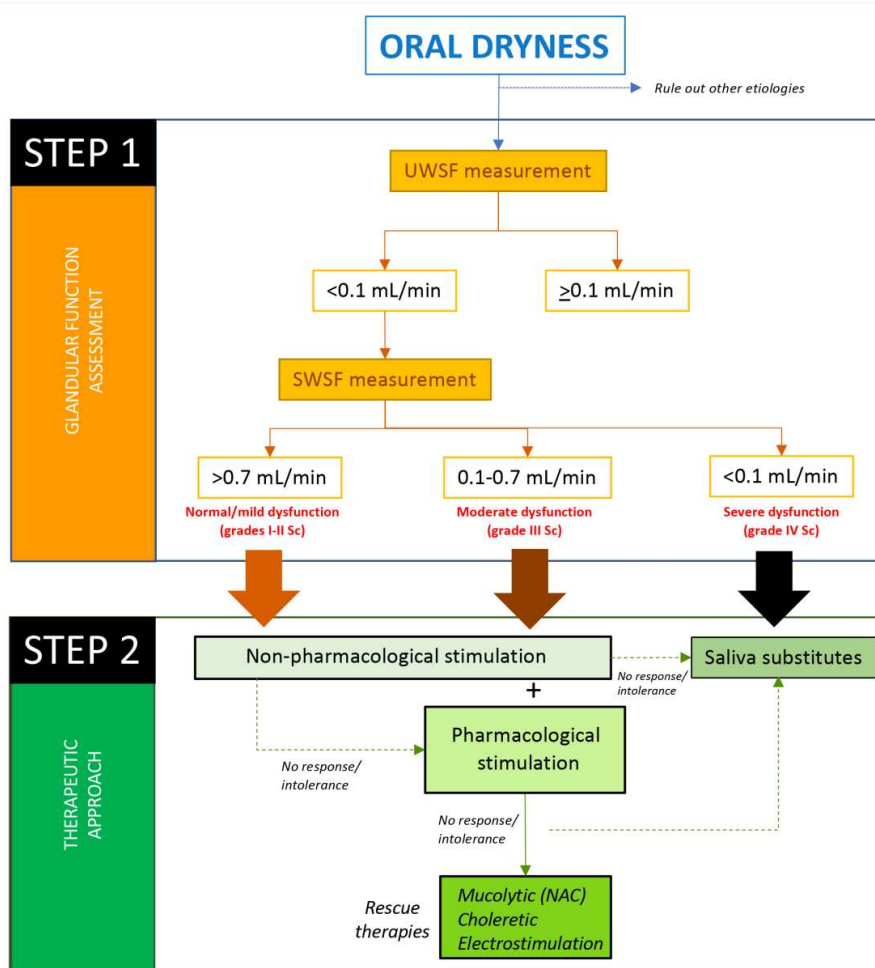
Mental health issues like depression and anxiety have a higher prevalence in patients with SS. A study from 2018 conducted in China compared the prevalence of anxiety and depression in pSS and healthy controls. Both the prevalence of anxiety and depression were significantly higher in SSs compared to healthy controls, with 33.8% of the patients reporting to experience anxiety and 36.9% reporting dealing with depression. Oral health and swallowing difficulties were reported to be associated with anxiety, and the reporting of fatigue had a significant association with depression (34).

### *1.1.9 Treatment modalities*

More than 95% of patients with SS have sicca symptoms, which have a significant impact on HRQoL. Seeking to alleviate these symptoms is naturally of great importance. No study has been able to identify any treatment modality that is able to reverse glandular dysfunction and cure sicca symptoms. The mainstay of treatment is therefore seeking to alleviate the sicca symptoms, together with other systemic symptoms, as well as prevention of possible disease complications. A daily, long-term application of topical therapies is recommended, and has been proven to have a significant impact on life quality. Evaluation of baseline salivary gland function is recommended before treatment start (35).

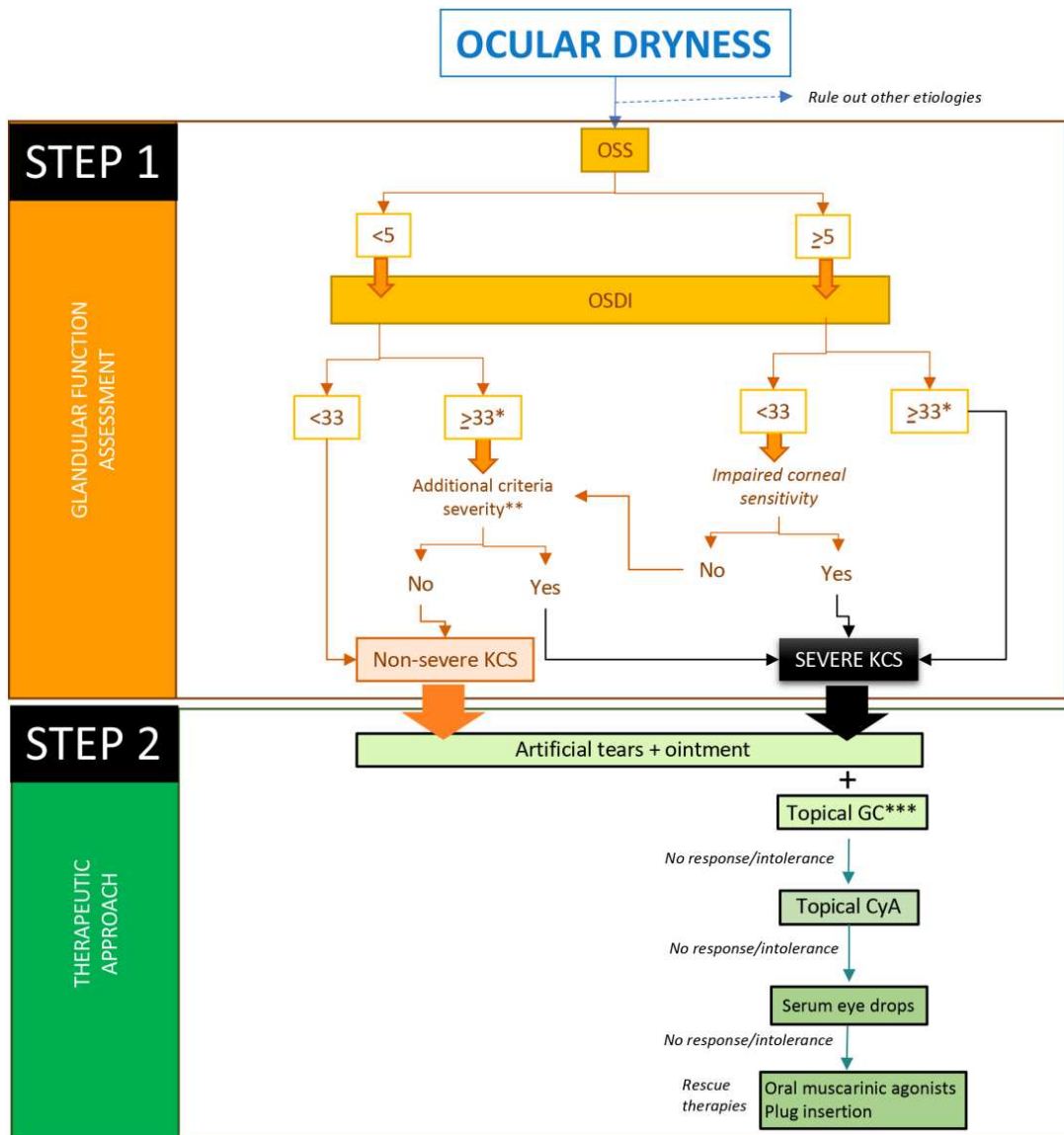
In 2019 the European League Against Rheumatism (EULAR) promoted an international study for development of a consensus on recommendations regarding management of SS with topical and systemic therapy. The recommendation included algorithms for treatment of oral and ocular dryness, glandular, articular, cutaneous, pulmonary, renal, neurological and hematological involvement (35).

Treatment of xerostomia is managed according to level of gland dysfunction with non-pharmacological approach like sugar-free chewing gum as preferred mode of treatment for mild dysfunction, while moderate dysfunction requires pharmacological treatment such as pilocarpine or bromhexine. Saliva substitution is reserved for severe gland dysfunction (36).



**Figure 1:** Algorithm of therapeutic approach in patients with xerostomia. UWSF: Unstimulated whole salivary flows, SWSF: Stimulated whole salivary flows, NAC: N-acetylcysteine. Source: Algorithm of therapeutic approach in patients with xerophthalmia. Source: Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T, et al. EULAR recommendations for the management of Sjögren’s syndrome with topical and systemic therapies. Ann Rheum Dis.

First-line therapy for dry eyes include use of ocular gel, ointment or artificial tears, while refractory cases are managed stepwise using either topical NSAIDs or glucocorticoids, topical cyclosporine or serum eye drops. If patients do not respond to any of the aforementioned modalities, rescue therapy with oral muscarinic agonist might be the therapeutic approach (36).



**Figure 2.** Algorithm of therapeutic approach in patients with xerophthalmia. OSS: Ocular Staining Score, OSDI: Ocular Surface Disease Index, KCS: Keratoconjunctivitis Sicca, GC: Glucocorticoids, CyA: Cyclosporin A. Source: Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T, et al. EULAR recommendations for the management of Sjögren’s syndrome with topical and systemic therapies. Ann Rheum Dis.



Treatment of systemic disease involvement should be tailored according to EULAR SS disease activity index (ESSDAI). Glucocorticoids, immunosuppressive agents like methotrexate and cyclophosphamide, and monoclonal antibodies like rituximab may be included in the therapy. The implementation of these medications should however be restricted to patients with active systemic disease and can only be implemented after careful review of severity and organ damage (36).

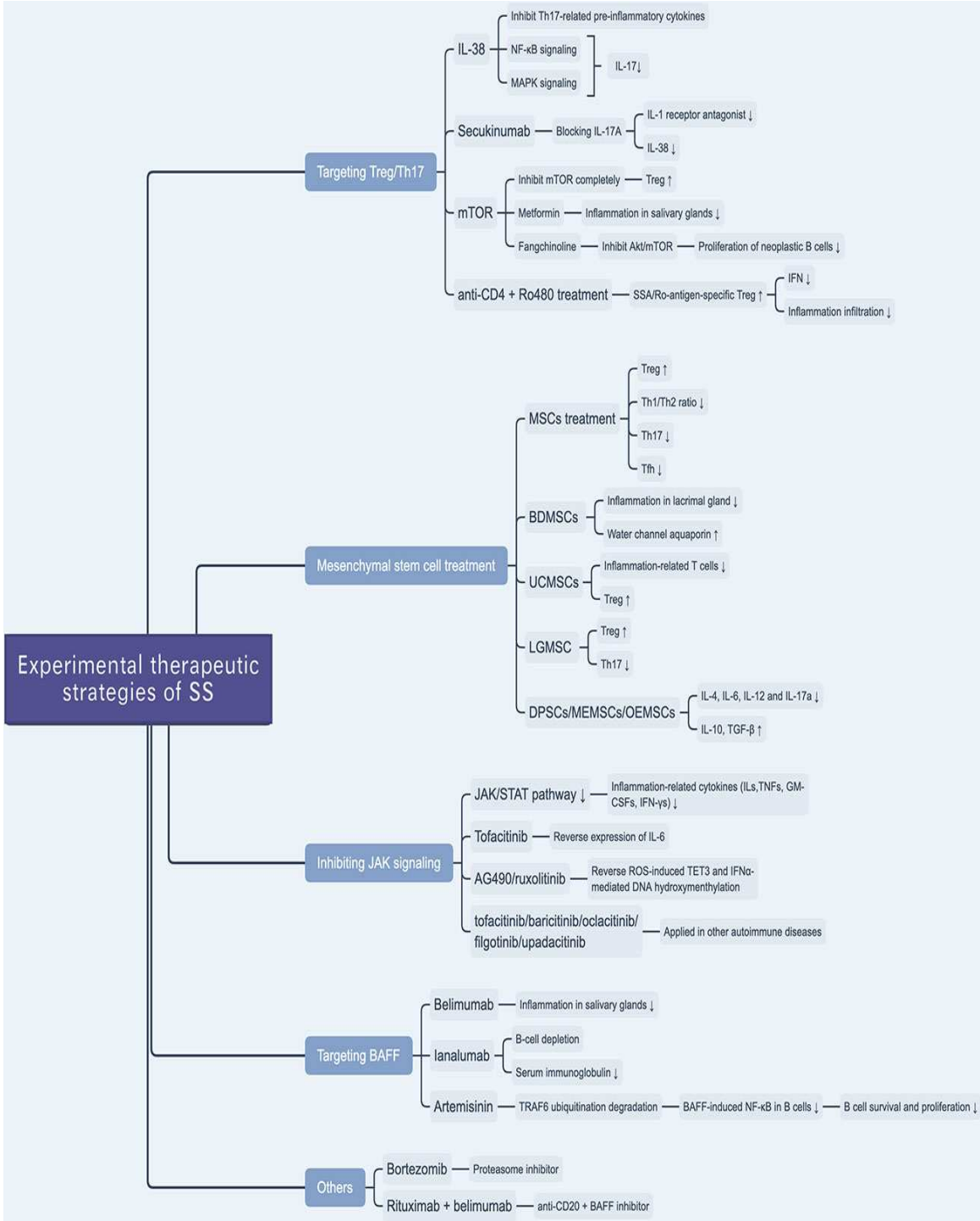
#### *1.1.10 Emerging treatment strategies*

Treg and Th17 subsets of T cells are implicated in the disease pathogenesis, and consequently one of the novel treatment strategies aims to target molecular mechanisms involved in activation of these. A selective anti-IL-17A monoclonal antibody, secukinumab, is currently being used in psoriasis treatment, and has a potential role in future treatment of SS patients (37).

Immunomodulatory functions of mesenchymal stem cells have been shown to be impaired in mesenchymal stem cell Sjögren-like animal models. In a study from 2012, 24 patients with SS were treated with mesenchymal stem cells from umbilical cord, and all the patients showed a relief of symptoms, pointing us to an exciting future role of mesenchymal stem cell treatment (38).

The JAK/STAT pathway regulates interleukins involved in inflammation and autoimmunity. Multiple JAK inhibitors are already being used in the treatment of autoimmune diseases, and the potential role of JAK inhibitor tofacitinib have been suggested in treatment of SS patients (39).

BAFF is a central cytokine in the pathogenesis of the disease, and consequently several anti-BAFF monoclonal antibodies have been studied as potential treatment options. An example is the monoclonal antibody Ianalumab, which causes B-cell depletion, and was found to reduce the systemic disease activity index, patient-reported severity of symptoms and serum immunoglobulin levels in patients with SS (40).



**Figure 3:** Experimental therapeutic strategies of Sjögren’s syndrome. MSC: Mesenchymal Stem Cell, BDMSC: Bone-derived Mesenchymal Stem Cell, UCMSC: Umbilical Cord-derived Mesenchymal Stem Cell, LGMSC: Labial gland-derived Mesenchymal Stem Cell, DPSC: Dental Pulp Stem Cells, MEMSC: Murine Embryonic Mesenchymal Stem cell, OEMSC: Olfactory-ecto Mesenchymal Stem Cell. Source: Zhan Q, Zhang J, Lin Y, Chen W, Fan X, Zhang D. Pathogenesis and treatment of Sjogren’s syndrome: Review and update.

## 1.2 Diagnostic criteria

### 1.2.1 Diagnostic criteria

12 different diagnostic criteria have been published in the period between 1965 and 2012, however none of them were consistently and universally used. In 2016, an expert panel developed an international set of diagnostic criteria, the 2016 ACR-EULAR classification, using guidelines from American College of Rheumatology and European League against Rheumatism (41).

### 1.2.2 2016 ACR-EULAR classification

The diagnosis of SS according to the 2016 ACR-EULAR classification applies to any individual with a score  $\geq 4$  when summing the points from the domains included. Additionally, for the diagnosis to be made an individual cannot have any condition listed in the exclusion criteria: history of head and neck radiation treatment, active hepatitis C infection with positive PCR, acquired immunodeficiency syndromes, sarcoidosis, amyloidosis, graft-versus-host disease or IgG4-related disease (42).

**Table 1.** 2016 ACR-EULAR diagnostic criteria (42)

<b>Item</b>	<b>Score</b>
Focal lymphocytic sialadenitis in minor salivary gland with $\geq 1$ lymphocytic focus/4 mm <sup>2</sup> of glandular tissue	<b>3</b>
Anti-SSA/Ro positive	<b>3</b>
Ocular staining score $\geq 5$ (or $\leq 4$ according to the Bijsterveld scale) in at least one eye	<b>1</b>
Schirmer test $\leq 5$ mm/5 min, in at least one eye	<b>1</b>
Unstimulated salivary flow $\leq 0.1$ mL/minute	<b>1</b>

Source: Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol.* 2017;69(1):35–45.

### *1.2.3 Disease activity indexes*

Multiple disease activity indexes are utilized for the purpose of understanding disease severity and symptom severity in patients. These indexes include but are not limited to EULAR Sjogren Syndrome Patient Reported Index (ESSPRI), Visual Analog Scale (VAS) and EULAR Sjogren Syndrome Disease Activity Index (ESSDAI). The indexes give a comprehensive picture of the experienced severity of symptoms, pain and the severity of disease activity in different organ systems respectively (43).

ESSPRI was developed to measure severity of patient symptoms based on their subjective experience. The index identifies dryness, pain, and fatigue as the main symptoms, and the patient rates experienced severity of pain, fatigue and dryness on a scale from 0-10 in the previous two weeks (44).

VAS is a subjective measure of acute and chronic pain and is the most frequent method for evaluating pain. Scores are recorded by the patient making a mark on a 10-cm line ranging from no pain to worst pain (45).

ESSDAI is a systemic activity index developed to assess disease activity in pSS and is often used as the gold standard to assess outcomes in clinical studies. The index is scored according to 12 different domains and the presence or lack of symptoms in these domains: constitutional, lymphadenopathy and lymphoma, glandular, articular, cutaneous, pulmonary, renal, muscular, PNS, CNS, hematological and biological. Each domain is divided into three to four levels of disease activity ranking from no disease activity to high level of disease activity. ESSDAI is an important tool in guiding treatment of systemic disease manifestation (46).

**Table 2.** EULAR Sjogren Syndrome Disease Activity Index (ESSDAI) (46)

<b>Domain</b>	<b>Activity level</b>	<b>Description</b>
<b>Constitutional</b> (Exclude infection/ involuntary weight loss)	No=0	No symptoms
	Low=3	Fever 37.5–38.5°C/night sweats/involuntary weight loss of 5–10%
	Moderate =6	Fever >38.5°C/night sweats and/or involuntary weight loss of >10%
<b>Lymphadenopathy and lymphoma</b> (Exclude infection)	No=0	None of the following
	Low=4	Enlarged lymph node ≥1 cm in any region or ≥2 cm in inguinal
	Moderate =8	Enlarged ≥2 cm any region or ≥3 cm inguinal
	High=12	Active B cell lymphoma
<b>Glandular</b> (Exclude lithiasis or infection)	No=0	None of the following
	Low=2	Small enlargement - parotid (≤3 cm), submandibular (≤2 cm) or lachrymal (≤1 cm)
	Moderate =4	Big enlargement - parotid (>3 cm), submandibular (>2 cm) or lachrymal (>1 cm)
<b>Articular</b> (Exclude osteoarthritis)	No=0	No articular involvement
	Low=2	Joint pai, morning stiffness >30 min
	Moderate =4	1–5 (out of 28) synovitis
	High=6	≥6 (out of 28) synovitis
<b>Cutaneous</b>	No=0	No cutaneous involvement
	Low=3	Erythema multiforme
	Moderate =6	Limited cutaneous vasculitis
	High=9	Diffuse cutaneous vasculitis

<b>Pulmonary</b>	No=0	No pulmonary involvement
	Low=5	Persistent cough with no imaging showing interstitial lung disease and normal lung function test
	Moderate =10	
	High=15	Lung changes on imaging /dyspnea (NYHA II) or abnormal lung function test: 70% >DLCO $\geq$ 40% or 80% >FVC $\geq$ 60%  Severe lung involvement (NYHA III/IV) or abnormal lung function test DLCO <40% or FVC <60%
<b>Renal</b>	No=0	No renal involvement
	Low=5	Limited to tubular acidosis
	Moderate =10	Tubular acidosis with renal failure or glomerular affection with proteinuria 1-1.5 g/day
	High=15	Glomerular affection with proteinuria >1.5 g/day, hematuria, renal failure or proliferative glomerulonephritis
<b>Muscular</b> (Exclude myopathy)	No=0	No muscular involvement
	Low=6	Abnormal EMG, biopsy or MRI. No weakness or elevated creatinine kinase (CK)
	Moderate =12	
	High=18	Abnormal EMG/biopsy/MRI plus weakness or elevated CK  Very active myositis with abnormal EMG/biopsy/MRI and weakness or elevated creatinine kinase

<b>PNS</b>	No=0	No involvement
	Low=5	Mildly involved, e.g. sensory polyneuropathy
	Moderate =10	Moderately involved e.g. axonal sensory-motor neuropathy
	High=15	Highly active peripheral nervous system involvement
<b>CNS</b>	No=0	No involvement
	Moderate =10	Moderately involved, e.g. optic neuritis
	High=15	Very active, e.g. cerebral vasculitis
<b>Hematological</b>	No=0	No autoimmune cytopenia
	Low=2	Mild neutropenia and/or anemia, and/or thrombocytopenia due to autoimmunity
	Moderate =4	Moderate neutropenia and/or anemia, and/or thrombocytopenia due to autoimmunity
	High=6	Severe neutropenia and/or anemia, and/or thrombocytopenia due to autoimmunity
<b>Biological</b>	No=0	No biological involvement
	Low =1	Clonal component and/or low complement, and/or elevated IgG
	Moderate=2	Cryoglobulinemia and/or elevated IgG

Source: Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. RMD Open. 2015;1(1):e000022.

## **1.3 Dermatologic manifestations**

### *1.3.1 Dermatologic manifestations*

Cutaneous manifestations are among the most common extra glandular features of SS. Nearly half of the patients develop skin manifestations. Similarly to the prevalence of SS, the prevalence of dermatologic manifestations also has a female predominance. There is a wide distribution of skin changes, and the severity may range from dry skin to severe vasculitis (47).

While the hallmark symptoms of the disease, the sicca symptoms, have been extensively researched, a gap remains in the understanding and reporting of dermatological changes in literature.

### *1.3.2 Clinical importance*

Skin changes may be the first or only manifestation of SS and can be of great aid in the diagnosing of the syndrome. The presence of skin manifestations can also be an indicator of disease severity, as seen in the ESSDAI tool where level of skin involvement is one of the main domains (46).

Skin involvement additionally has a significant impact on patient's quality of life, owing to distressing symptoms such as itchiness, dry skin and skin lesions that are not only responsible for discomfort and pain, but may also cause cosmetic concerns. Patients with SS report lower HRQoL compared to the general population, and skin changes may be a significant contributor (48).

### *1.3.3 Non-vascular lesions*

The most common skin manifestation is xeroderma or dry skin, which has a prevalence of up to 72 percent (49). Other common manifestations include angular cheilitis, eyelid dermatitis presenting as lichenification, angular erythema, photosensitive dermatitis, pigmentation and papules. Less common non-vascular lesions include but are not limited to alopecia, vitiligo, pruritus and lichen planus (50). Raynaud phenomenon has been reported with a prevalence of 16-35%. Importantly, this may be the first disease manifestation in some patients (51).



#### *1.3.4 Vascular lesions*

About 10% of SS patients develop cutaneous vasculitis, and in many patients it is even observed before the onset of sicca symptoms. Vasculitis may present as both small-vessel and medium-vessel vasculitis, but the most common finding is small-vessel leukocytoclastic vasculitis. Clinically, it typically presents as purpuric lesions. In urticaria vasculitis the clinical finding will be urticarial lesions (51). Cases of necrotizing vasculitis of medium-sized vessels resembling polyarteritis nodosa and ANCA-associated granulomatous vasculitis have also been reported (52).

#### *1.3.5 Pathogenesis in skin manifestations*

In xeroderma, infiltration of the epithelium with autoreactive T and B lymphocytes causes decreased sebaceous and sweat gland secretion, and consequently a decreased protective in function of the outer skin barrier. Additionally, circulating immune complexes, cytokines and activation of complement also contribute to the alteration in the skin barrier. Eyelid dermatitis is explained by chronic mechanical trauma through itching and rubbing the periorbital area. It is characterized by interface dermatitis on histopathology (47,53).

In vasculitis the most common histopathologic finding is leukocytoclastic vasculitis, which is characterized by leukocytosis and fibrinoid necrosis. Urticarial vasculitis is the consequence of mast cell activation causing histamine release with increased vessel permeability and vasodilation (47).

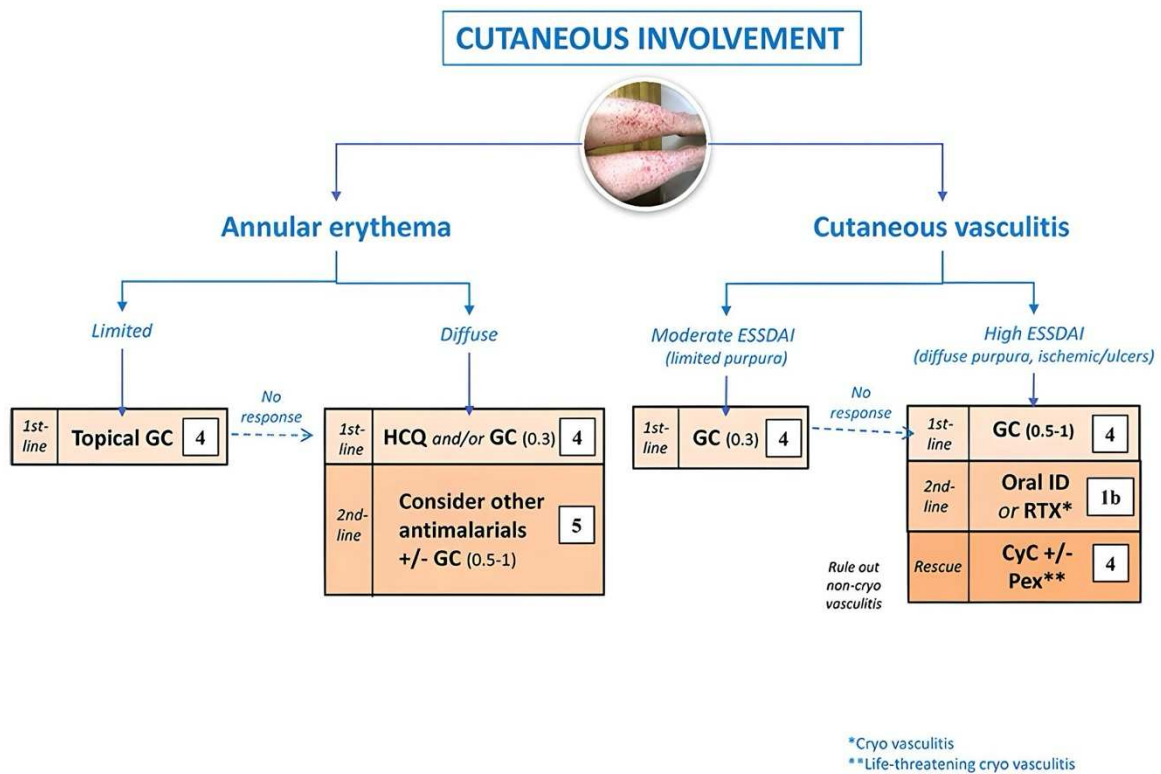
#### *1.3.6 Diagnostic approach of skin manifestations*

While diagnosis of skin changes is mainly clinical, skin biopsy may be necessary in unclear, complicated cases. Recently, biological elements have been identified that may be used as a predictive parameter for cutaneous manifestations in SS patients. A study from 2022 established an association between Neutrophil-to-Lymphocyte ratio (NLR), Platelet-to-Lymphocyte ratio (PLR), Monocytes-to-Lymphocyte ratio (MLR) and the development of cutaneous vasculitis. Increased levels of NLR, PLR and MLR had a positive predictive correlation with cutaneous vasculitis (54).

### 1.3.7 Treatment of skin manifestations

Xeroderma as a manifestation is usually treated with different topical moisturizers. Other more complex manifestations may require local or systemic immunosuppression. Using gentle soaps with a natural pH and limiting skin washing is also helpful in protecting the skin's lipid barrier (47).

Cutaneous vasculitis requires treatment with glucocorticoids, either alone or together with systemic immunosuppression. Annular erythema responds poorly to topical therapy and is better treated by glucocorticoids, calcineurin inhibitors or hydroxychloroquine. Similar to other disease manifestations, treatment of skin manifestations should be guided by the ESSDAI (47).



**Figure 4.** Algorithm for therapeutic approach in cutaneous involvement in SS patients. ESSDAI = Eular Sjögren's Syndrome Disease Index, GC = Glucocorticoids, HCQ = Hydroxychloroquine, ID = Immunosuppressive agents, RTX = Rituximab, CyC = Cyclophosphamide, Pex = Plasma exchange. Source: Ramos-Casals M, Brito-Zerón P, Bombardieri S, Bootsma H, De Vita S, Dörner T, et al. EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. Ann Rheum Dis.

## **2. OBJECTIVES**

The aim of this study was to:

- Seek to address an existing gap in research and existing literature regarding the nature of symptoms in SS, as dermatologic manifestations, although being reported, are often overshadowed in the literature by the sicca symptoms.
- Investigate the prevalence and characteristics of skin changes in patients with SS, more specifically differentiating between those with primary and secondary SS.
- Identify different dermatological manifestations in each patient, with assessment of severity and distribution, and potential correlation between skin changes and disease duration.

The hypothesis guiding this study:

- Skin changes occur more frequently in patients with sSS compared to patients with pSS.

### **3. SUBJECTS AND METHODS**

### **3.1 Study design and participants**

This is an observational cross-sectional study conducted in the Internal Clinic, Department of Rheumatology and Clinical Immunology, University Hospital of Split and University of Split, School of Medicine, Split, Croatia. The study involves an analysis of data collected from a cohort of 317 patients (55).

The population of interest are patients with confirmed diagnosis of SS, whom are being followed up at the Department of Rheumatology and Clinical Immunology in the last 10 years. The sample was collected by convenient sampling, and with the following inclusion criteria: confirmed diagnosis of SS by experienced rheumatologist or clinical immunologist, age above 18 years old, and relevant clinical data being available, with emphasis on categorization of primary (pSS) or secondary (sSS) disease and the presence of skin changes. Patients with incomplete medical records and lacking documentation of primary or secondary disease subtype were excluded from this study.

Patients with sSS are included in the experimental group, while patients with pSS are included in the control group. Patients with overlapping syndrome have been included in the experimental group when their SS was diagnosed after the development of other connective tissue diseases, while they have been included in the control group when their SS was diagnosed prior to the development of other connective tissue diseases. Accordingly, the experimental group includes a total of 117 patients, while there are 200 patients included in the control group.

The participants in the study are from Split-Dalmatia County and include 300 women and 17 men, with a 17:1 ratio of women and men. The participants range from the age of 19 to 87. Because disease onset most commonly is in the age of 40 to 60 years old, the participants were divided into three age groups of <40, 40-60 and >60 years. 22 patients were younger than 40 years old, 104 patients were between 40-60 years old, and 191 patients were older than 60 years old.

Ethical approval was obtained from the Ethics Committee of University Hospital of Split on 4<sup>th</sup> May 2021 (No: 2181-147/01/06/M.S.-21-02).

### **3.2 Data extraction**

Data for the study was obtained from patient papers and digital medical records of the 317 participants, collected from the department, daily hospital and outpatient clinic of Rheumatology and Clinical Immunology. The patients of whom the medical records have been collected are followed in ten-years intervals.

From the study sample we included age groups, sex, organ involvement, and skin changes as categorical variables.

### **3.3 Measures of outcome**

The main outcome measures of this study aim to quantify the proportion of patients with pSS and sSS who exhibit skin changes, as well as to investigate the association between disease duration and presence of skin changes and organ involvement. The aim is to explore whether the prevalence of skin changes increase with disease duration and organ involvement, and whether any of the two patient groups exhibit skin changes more frequently.

Secondary outcome measures focus on determining the distribution of specific types of skin changes in both pSS and sSS patients, while also differing between localized and general dermatological manifestations to investigate whether certain skin changes are more prevalent in either primary or secondary syndrome.

### **3.4 Statistical analysis**

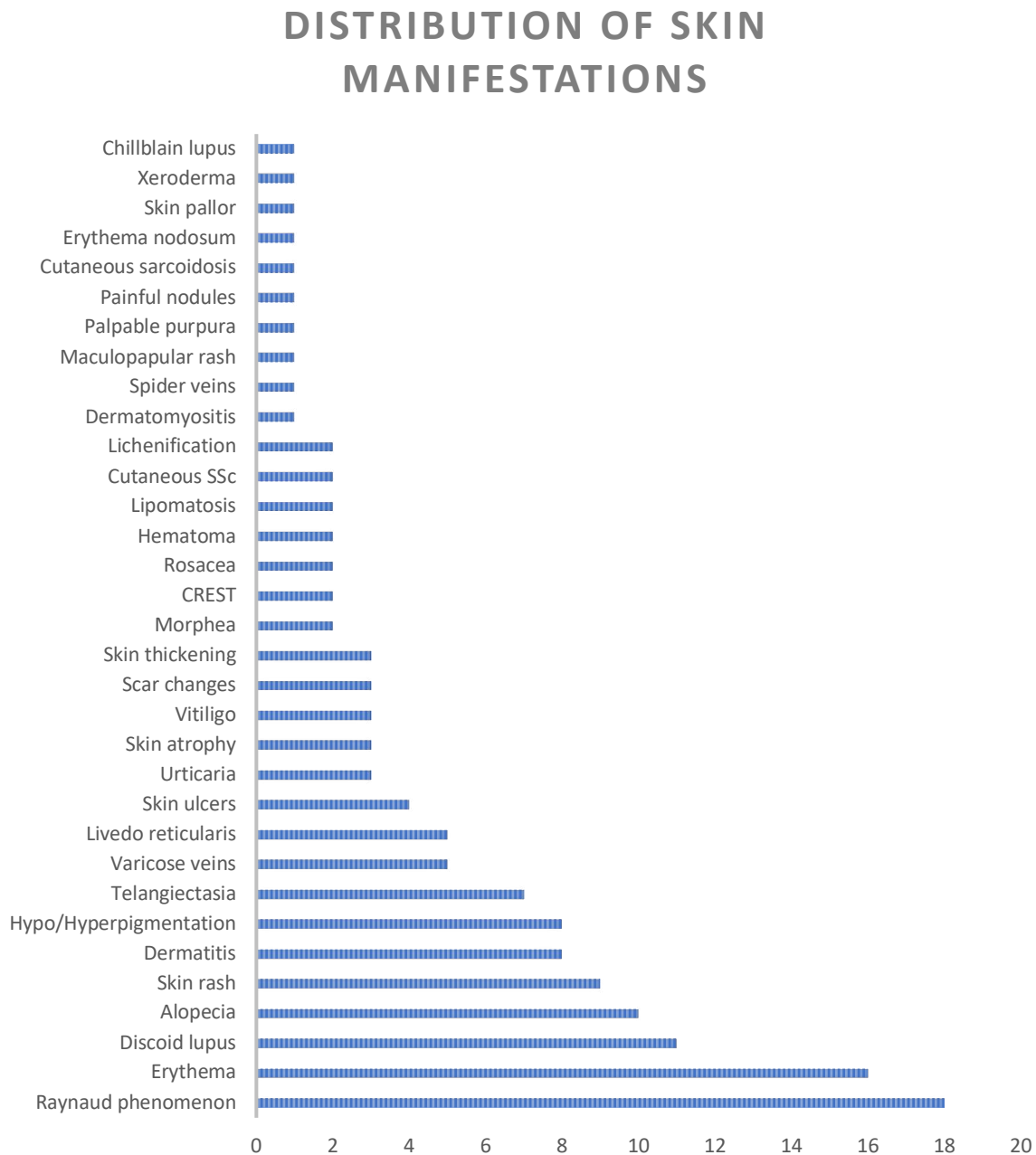
To ensure validity of the study in terms of proper sample size, the proper size of minimal sample size was calculated, and we found an appropriate minimal sample size of 90 patients. To test the hypothesis that skin changes occur more frequently in patients with sSS compared to patients with pSS, the Chi-Square Test of Independence was used. This test was also used to assess the association between skin changes and disease duration, and between skin changes and organ involvement. Prevalence ratio was used to compare the prevalence in experimental and control group. Statistical significance was set at  $p < 0.05$ . IBM SPSS for Mac OS version 29 was used.

## **4. RESULTS**



#### 4.1 Distribution of dermatologic manifestations and baseline demographics

Among the 317 study participants there was reported a total of 113 patients that exhibited skin changes. Most of the patients had a single type of skin manifestations, while 31 patients had two or more different skin changes. The most frequent skin manifestations of the participants were Raynaud phenomenon, erythema, discoid lupus, alopecia, telangiectasia and hyperpigmentation.



**Figure 4** Distribution of skin manifestations in study participants. The X axis represents the absolute number of patients exhibiting the skin manifestation.

Baseline demographic characteristics of the studied population are presented in Table 3. sSS group had significantly greater percentage of female participants when compared to pSS group ( $p < 0.001$ ). On the other hand, no differences in age distribution were established between the groups ( $p = 0.113$ ).

**Table 3.** Baseline demographics of age groups in pSS and sSS.

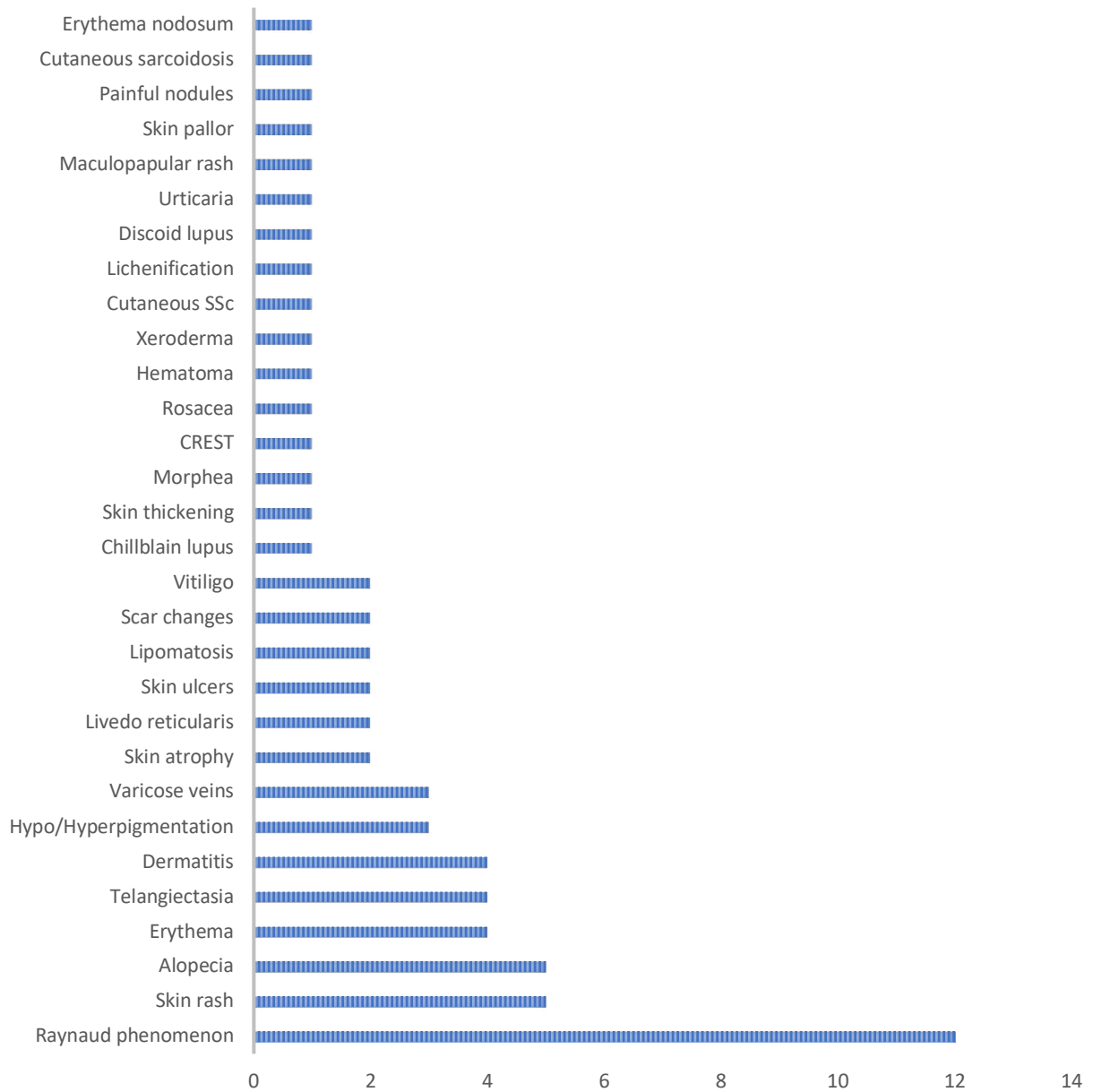
Characteristic	pSS (N = 200)	sSS (N = 117)	p*
Sex, N (%)			
Female	184 (92.0)	116 (99.1)	<0.001
Male	16 (8.0)	1 (0.9)	
Age group, N (%)			
<40 yrs.	18	4	0.113
40-60 yrs.	74	31	
>60 yrs.	108	82	

pSS: primary Sjögren's syndrome, sSS: secondary Sjögren's syndrome, \*Chi squared test.

#### 4.2 Difference in manifestations in pSS vs sSS

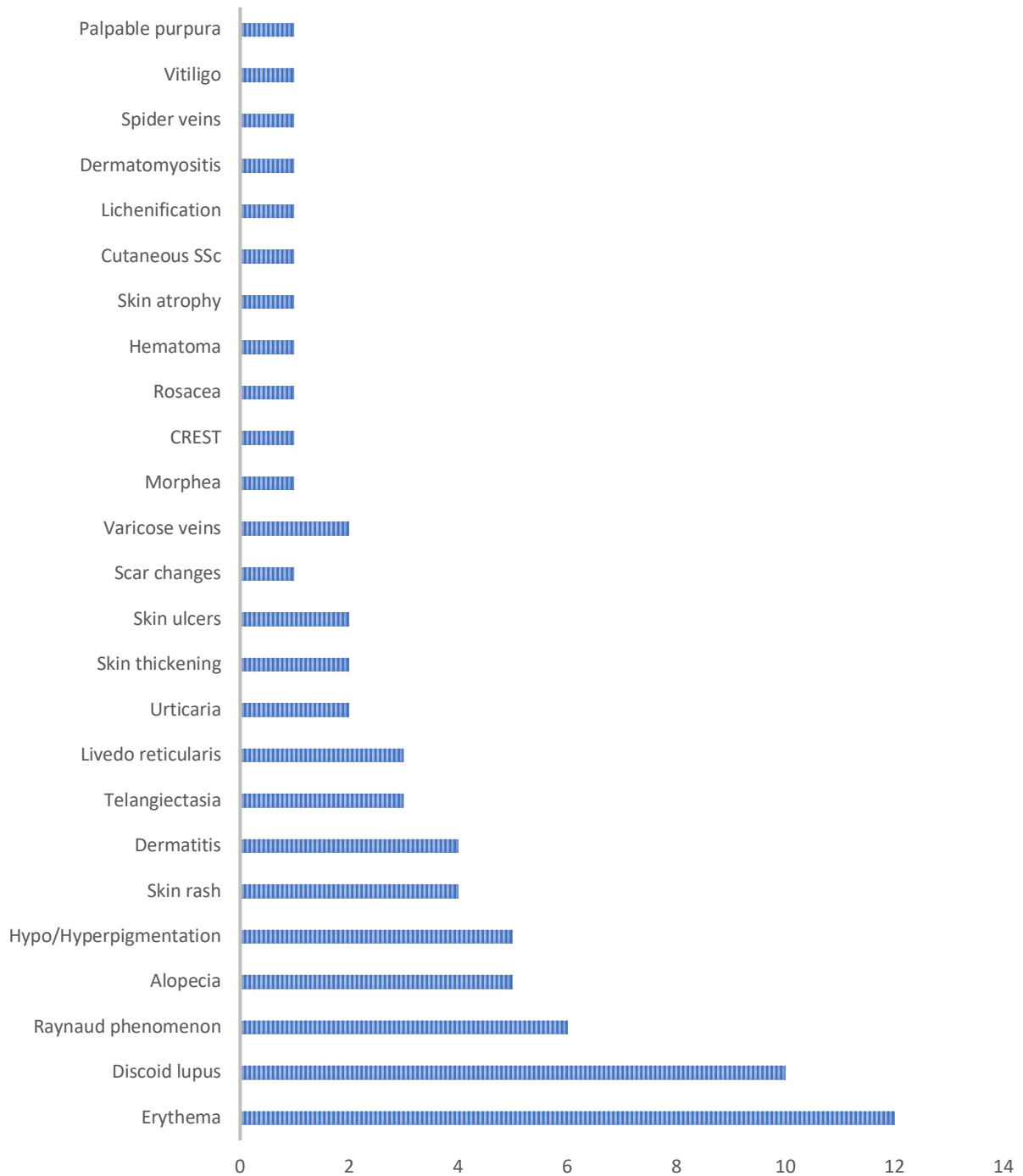
The hypothesis guiding this study was whether patients with sSS exhibit skin changes more frequently compared to patients with pSS. Patients included in the study with sSS were more likely to exhibit skin changes compared to patients with pSS (53 (45.3) vs. 60 (30.0),  $p = 0.006$ ).

## pSS DISTRIBUTION OF SKIN MANIFESTATIONS



**Figure 5** Distribution of skin manifestations in pSS patients. The X axis represents the absolute number of patients exhibiting the skin manifestation.

## sSS DISTRIBUTION OF SKIN MANIFESTATIONS



**Figure 6.** Distribution of skin manifestations in sSS patients. The X axis represents the absolute number of patients exhibiting the skin manifestation.

### **4.3 Association between skin changes and disease duration**

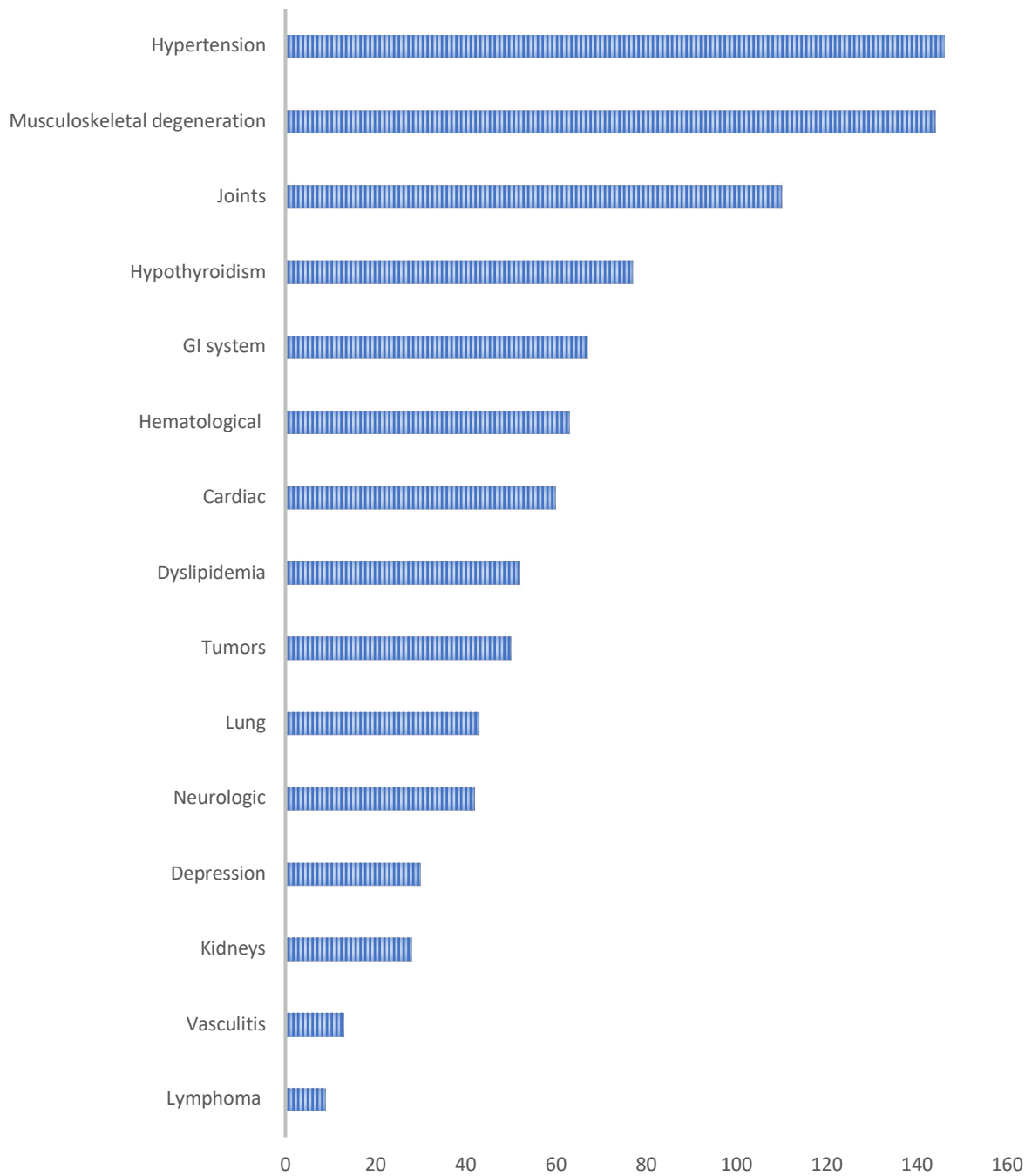
There was no statistical significance for the relation between skin changes and the different age groups (7 (31.8) vs 35 (33.6) vs 71 (37.2),  $p = 0.773$ ). Older patients presumed to have a longer disease duration did not have a significantly higher likelihood of exhibiting skin changes compared to patients with shorter disease duration.

### **4.4 Association between skin changes and organ involvement**

For all the study participants the presence or absence of organ involvement was recorded, including the presence of any heart involvement, hypertension, kidney involvement, lung involvement, gastrointestinal involvement, neurologic involvement, depression, musculoskeletal degenerative disease, joint involvement and diabetes mellitus. The most frequent systemic involvements were hypertension, musculoskeletal degeneration, joint affection, and hypothyroidism.

There was no statistically significant difference in the presence of skin change in patients with organ involvement compared to patients without organ involvement (105 (35.8) vs 7 (29.2),  $p = 0.511$ ).

## SYSTEMIC INVOLVEMENT



**Figure 7.** Distribution of organ involvement. The X axis represents the absolute number of people with a specific organ involvement.

## **5. DISCUSSION**

We observed in this study that patients with sSS had a higher frequency of skin manifestations in comparison to pSS patients. We detected a wide spectrum of skin changes and majority of them are expected in clinical picture of SS. Although a greater spectrum of skin changes was observed in patients with pSS, overall, patients with sSS had more skin changes, as well as the coexistence of multiple skin changes in the same patient.

Skin involvement in pSS is very well established (29). Argyropoulou et al. reported a study on 1083 patients with pSS, where 10.6% of patients had cryoglobulinemia and 6.5% had cryoglobulinaemic vasculitis (56). We noticed the majority of expected dermatological disorders in our population of patients, although less cases of cryoglobulinaemic vasculitis were detected. In our study only four (1.26%) had the presence of cryoglobulinemia, while only two patients (0.63%) exhibited cryoglobulinaemic vasculitis. Some of the skin disorders were neglected by the patients or physicians and were recorded in late stages or even after resolution of symptoms.

sSS has been recognized as an entity that generally follows the diagnosis of another connective tissue disease, ten years on average (10). Some investigators describe it as “secondary,” others as “associated”, implying that clinical presentation is part of the spectrum of the underlying connective tissue disease (57). In case of underlying SLE, dermatomyositis or SSc in sSS, disorders with predominant skin involvement, it is expected that sSS in that case will have higher prevalence of skin changes reflecting typical skin pattern of the underlying disease. This is a probable explanation for higher prevalence of skin changes in our study group. We found particularly higher prevalence of face erythema and discoid lupus lesions in sSS patients, while discoid lesions among pSS patients were observed in one case only.

In the literature there is only one study that assessed cutaneous manifestation of patients with pSS. An Argentinean group of authors reported on 335 pSS patients of whom 67 with cutaneous manifestations. Among them, 60% had purpura, 19% urticaria, 19% petechiae, 16% ulcers, 7% erythema multiforme, 4% erythema nodosum and 9% subcutaneous nodules. No statistically significant differences in age, sex and time of evolution of the disease between the patients with or without skin changes were found (58).



In our control group, we detected skin rashes/purpura (5 patients), erythema (4 patients), ulcers (2 patients), dermatitis (4 patients), hyperpigmentation (3 patients), maculopapular rash (1 patient) haemorrhages (1 patient) and erythema nodosum (1 patient). All those findings were considered as features of leukocytoclastic vasculitis in different phases of development that was overrepresented in pSS in respect to sSS. Thus, generally we could say that various forms of vasculitis are more present in pSS, while other dermatological conditions predominantly affect patients with sSS.

By far the most severe cutaneous complications of SS are generated by vasculitis. The histopathological hallmark of vasculitis consists of perivascular cellular infiltrates of small vessels, and its clinical presentation fluctuates from the most benign manifestations, such as petechiae, to the most serious complications, such as palpable purpura or widespread ecchymoses (59). The morphology of these inflammatory lesions is dependent on the level of blood vessel involvement in the skin and the magnitude of the inflammatory response. Purpura is a common vasculitis-related feature. This appears as recurrent crops of round, pink, separated or confluent lesions. After a few days, the lesions turn dull purple then brown, finally leaving a pale brown stain (60). Sometimes vasculitis lesions can progress to deep ulcers and even to areas of skin necrosis. The most of vasculitis lesions in our cohort were mild to moderate and all responded well to immunosuppressive treatment.

Lin et al. reported manifestation of Raynaud phenomenon in 11.41% in a retrospective cohort study with 333 pSS patients. Patients with this manifestation had an earlier disease onset and tendencies to manifest with higher disease activity compared to patients without Raynaud phenomenon (61). We observed that Raynaud phenomenon was the most common skin manifestation in pSS and the third most common in sSS in our cohort, with 6% and 5.13% exhibiting the manifestation, respectively.

While there are very few studies on erythematous lesions in SS patients, Brito-Zerón et al. reported manifestations of annular erythema in 9% in a retrospective cohort study with 377 Spanish patients with pSS. Interestingly, the presence of annular erythema preceded the diagnosis of SS in 77% of patients. The lesions mainly involved face and upper extremities, and all patients reported photosensitivity (62). Erythematous lesions were the most frequent skin manifestations in sSS and the fourth most frequent in pSS in our cohort, with 10.26% and 2% presenting with erythematous lesions, respectively. Among our patients, erythema was most commonly presented on face, chest and hands.

In our study several potential biases and confounding factors, which could influence the interpretation of the results, have been identified. Regarding biases, selection biases might be a concern due to unbalanced ratio of 17:1 between women and men in our sample. However, it is important to note that such inequities are common in autoimmune diseases. Additionally, an unbalanced ratio between women and men should not significantly affect the primary and secondary outcomes that we have explored in this study.

As a way of reducing recall bias, this study uses patient medical records to collect data rather than relying solely on patient recall. There is however a potential for misclassification bias in this study, in the case that patients have been wrongly classified in the primary or secondary group, which might have a significant impact on the research results. As there are specific criteria set for the diagnosis of pSS, while no specific criteria exist to this date for the diagnosis of sSS, diagnosing and classifying the disease correctly can be challenging. This is further challenged by the third group of patients with overlap syndrome, which should be correctly placed into either pSS or sSS based on whether SS was diagnosed prior to or after the other connective tissue diseases. Incorrect placement of these patients may directly affect the results we achieved.

There is a possibility of lead-time bias due to the relationship between disease duration and skin changes influencing the observed prevalence in skin changes in pSS and sSS. The relationship between skin changes and disease duration was thus investigated as an outcome measure to reduce this bias.

The study did not show any significant association between disease duration and frequency of skin manifestation. What could potentially be a confounding factor in this outcome measure is the fact that we did not have available data on the disease duration in every specific patient and had to rely on indirectly measuring the disease duration by sorting the patients into specific age groups, with the assumption that older age groups had a longer disease duration. Thus, as we did not directly measure the association between disease duration and skin changes, it is possible that this could affect the statistical calculations.

Demographical differences for sex and age groups between the two groups was compared. No major differences in the ages between the two groups were found, and if age distribution would have been different, we might have seen different results. On the other hand, female sex was more prevalent in the sSS than in the pSS, making the groups unbalanced in this regard.

Moreover, there are some possible confounding variables worth mentioning. The presence of cryoglobulinemia in a patient may have a possible influence on development of skin rash, and we have therefore sought for the presence of cryoglobulins in the serum of all the subjects. Cryoglobulinemia was however only identified in a total of four patients, and two of these patients had skin changes. We can therefore not conclude whether the presence of cryoglobulinemia has an impact on the development of skin changes, but it is worth mentioning that only one of these patients exhibited a rash. Regardless, number of patients with proven cryoglobulinemia should not have a significant impact on the results.

Additionally, every medication that possibly can result in skin changes was considered and all patients taking any of these medications were excluded from the study. Another possible confounding factor is the reporting of skin changes in the patients.

We noticed that xeroderma was only noted in one of the participants of this study. Knowing from data of other studies that xeroderma is the most common skin manifestation, present in up to 72 percent, it is very likely that more patients than reported manifested xeroderma (49). A retrospective analysis performed from 1990 to 1996 following 102 patients at an outpatient clinic in Tokyo reported a total of 13 cases (12.7%) of xeroderma (63). Although this study still had higher numbers than our study low as our numbers, it also showed a significantly lower number than one would expect. A possible reason for underreporting this specific skin manifestation could be the unspecific nature of xeroderma, making it less obvious and harder to recognize in comparison to more obvious skin changes. Underreporting of this manifestation could lead to patients not being correctly classified as having skin changes, which could affect the association between skin changes and one of the types of SS.

## **6. CONCLUSION**

Our study revealed that skin changes are more frequent in patients with sSS compared to pSS. A wide spectrum of skin changes was observed. The most frequent cutaneous disorder in pSS was Raynaud phenomenon, while in sSS the most frequent was erythema.

Regarding the association between skin changes and disease duration or organ involvement, we were not able to find an association that was statistically significant for either of the factors.

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## **8. SUMMARY**

**Background:** Skin changes are among the most common manifestations of Sjögren's syndrome (SS). While being reported in literature, there is a substantial gap in existing literature regarding skin manifestations, as they are often overshadowed by sicca symptoms.

**Objectives:** Explore the difference in skin changes between primary SS (pSS) and secondary SS (sSS), as well as the association between skin changes and organ involvement and disease duration. Additionally, an assessment of distribution and severity of skin manifestations.

**Materials and methods:** Observational cross-sectional study included patients aged 18 years or older with diagnosis of pSS or sSS. Clinical data was collected from patient papers and digital medical records from clinical department, daily hospital and outpatient clinic of Department of Rheumatology and Clinical Immunology, Internal Clinic, University Hospital of Split, Croatia. Experimental group and control included 117 and 200 patients, respectively. For the analysis of difference in skin changes between pSS and sSS group, and association between skin changes and organ involvement and disease duration, Chi-square test of Independence was used.

**Results:** Among the 317 study participants there was reported a total of 113 patients that exhibited skin changes. Most of the patients had a single type of skin manifestations, while 31 patients had two or more different skin changes. The most frequent skin changes in pSS patients were Raynaud phenomenon, rash and alopecia, while the most frequent manifestations in sSS were erythema, discoid lupus and Raynaud phenomenon. We noted a statistically significant difference in skin changes in pSS and sSS (30% vs 45%,  $p = 0.006$ ). The relationship between the existence of organ involvement and skin changes was not statistically significant ( $p = 0.511$ ). Similarly, we were not able to prove a statistically significant association between disease duration and manifestation of skin changes in patients with SS ( $p = 0.773$ ).

**Conclusion:** Our study revealed that skin changes are more frequent in patients with sSS compared to pSS. A wide spectrum of skin changes was observed. The most frequent cutaneous disorder in pSS was Raynaud phenomenon, while in sSS the most frequent was erythema. Regarding the association between skin changes and disease duration or organ involvement, we were not able to find an association that was statistically significant for either of the factors.

## **9. CROATIAN SUMMARY**

**Naslov:** Usporedna presječna studija za razumijevanje razlike u prevalenciji promjena na koži kod pacijenata s primarnim i sekundarnim sjögrenovim sindromom

**Pozadina:** Kožne manifestacije su među najčešćim manifestacijama Sjögrenova sindroma (SS). Iako se o njima izvještava u literaturi, postoji značajan nedostatak u istraživanju i postojećoj literaturi u vezi s dermatološkim manifestacijama, budući da su one često zasjenjene *sicca* simptomima.

**Ciljevi:** Istražiti razliku u pojavnosti kožnih promjena između primarnog SS (pSS) i sekundarnog SS (sSS), kao i povezanost između kožnih promjena i zahvaćenosti organa i trajanja bolesti. Dodatni cilj bio je procijeniti distribuciju i ozbiljnost kožnih manifestacija.

**Materijali i metode:** Opservacijska presječna studija. Uključeni su bolesnici stariji od 18 godina s dijagnosticiranim pSS-om ili sSS-om. Klinički podaci prikupljeni su iz povijesti bolesti i digitalnih medicinskih zapisa iz odjela, dnevne bolnice i poliklinike Zavoda za reumatologiju i kliničku imunologiju, Klinike za unutarnje bolesti, KBC Split, Hrvatska. Pokusnu skupinu činilo je 117, a kontrolnu 200 bolesnika. Za analizu razlika u kožnim promjenama između pSS i sSS skupine te povezanosti kožnih promjena i zahvaćenosti organa i trajanja bolesti, korišten je Chi-kvadrat test neovisnosti.

**Rezultati:** Među 317 sudionika istraživanja utvrđeno je ukupno 113 pacijenata koji su imali kožne promjene. Većina bolesnika imala je jednu vrstu kožnih manifestacija, dok je 31 bolesnik imao dvije ili više različitih kožnih promjena. Najčešće kožne promjene u bolesnika s pSS-om bile su Raynaudov fenomen, osip i alopecija, dok su najčešće manifestacije sSS-a bile eritem, diskoidni lupus i Raynaudov fenomen. Primijetili smo statistički značajnu razliku u pojavnosti kožnih promjenama između pSS i sSS (30 % vs. 45 %,  $p=0,006$ ). Nije utvrđena povezanost između zahvaćenosti unutarnjih organa i promjena na koži ( $p = 0,511$ ). Slično tome, nismo uspjeli utvrditi povezanost između trajanja SS bolesti i pojave kožnih promjena ( $p = 0,773$ ).

**Zaključci:** Naše je istraživanje pokazalo da su kožne promjene češće kod pacijenata sa sSS-om u odnosu na pSS. Uočen je širok spektar kožnih promjena. Najčešći kožni poremećaj u pSS-u bio je Raynaudov fenomen, dok je u sSS-u najčešći eritem. Što se tiče povezanosti između promjena na koži i trajanja bolesti ili zahvaćenosti organa, nismo uspjeli pronaći povezanost koja je statistički značajna ni za jedan od čimbenika.