

Parotid gland ultrasonographic findings are milder in patients with primary Sjögren's disease-related interstitial lung disease

Primer Sjögren hastalığına bağlı interstisyel akciğer hastalığı olan hastalarda parotis bezi ultrasonografik bulguları daha hafiftir

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Abstract

Objective: To evaluate parotid gland ultrasonography findings in patients with Sjögren's disease (SjD) with interstitial lung disease (ILD) and to compare them with those of SjD patients without ILD.

Methods: This single-center, cross-sectional study included 20 patients with SjD-related ILD and 110 SjD patients without ILD. Parotid gland ultrasonography was graded according to the Outcome Measures in Rheumatology (OMERACT) semiquantitative scoring system (grades 0-3). Parotid gland ultrasonography findings, along with clinical and laboratory characteristics, were compared between the two groups.

Results: Demographic characteristics were largely comparable between groups, with no significant differences in mean age or age at diagnosis ($p>0.05$). However, the proportion of male patients was significantly higher in the ILD group than in the non-ILD group (20.0% vs. 1.9%, $p=0.005$). Regarding the primary outcomes, parotid gland ultrasonography scores indicated milder involvement in patients with SjD-related ILD. The proportion of patients with a total OMERACT score ≥ 2 in both parotid glands was significantly lower in the ILD group than in the non-ILD group (65.0% vs. 84.5%, $p=0.03$). As a secondary finding, at diagnosis, 70% of patients with ILD ($n=14$) presented predominantly with pulmonary symptoms, whereas only 30% had sicca manifestations.

Conclusion: This study demonstrates that patients with SjD-related ILD more frequently present with pulmonary symptoms rather than sicca symptoms and exhibit milder parotid-gland involvement on ultrasonography. These findings suggest that SjD-related ILD may represent a distinct clinical subgroup characterized by relatively low-grade parotid gland ultrasonographic changes.

Keywords: Interstitial lung disease, ultrasonography, Sjögren's disease, parotid gland

Özet

Amaç: Bu çalışmanın amacı, interstisyel akciğer hastalığı (İAH) olan Sjögren hastalığı (SH) hastalarda parotis bezi ultrasonografisi bulgularını değerlendirmek ve bu bulguları İAH olmayan SH hastaları ile karşılaştırmaktır.

Yöntem: Bu tek merkezli, kesitsel çalışmaya SH'ye bağlı İAH tanısı olan 20 hasta ve İAH olmayan 110 SH hastası dahil edildi. Parotis bezi ultrasonografisi bulguları, Romatolojide Sonuç Ölçümleri (OMERACT) yarı-kantitatif skorlama sistemine (derece 0-3) göre değerlendirildi. Parotis bezi ultrasonografisi bulguları ile birlikte grupların klinik ve laboratuvar özellikleri karşılaştırıldı.

Bulgular: Gruplar arasında ortalama yaş ve tanı yaşı açısından istatistiksel olarak anlamlı fark saptanmadı ($p>0.05$). Ancak erkek hasta oranı, İAH grubunda İAH olmayan gruba kıyasla anlamlı derecede daha yüksekti (%20,0 vs. %1,9; $p=0,005$). Birincil sonuçlar açısından, SH'ye bağlı İAH olan hastalarda parotis bezi ultrasonografisi skorlarının daha hafif olduğu görüldü. Her iki parotis bezinde toplam OMERACT skoru ≥ 2 olan hasta oranı, İAH grubunda İAH olmayan gruba göre anlamlı olarak daha düşüktü (%65,0 vs. %84,5; $p=0,03$). İkincil bir bulgu olarak, tanı anında İAH grubundaki hastaların %70'inde ($n=14$) baskın semptomların pulmoner tutulum ile ilişkili olduğu, yalnızca %30'unda ise kuruluk (sikka) semptomlarının ön planda olduğu saptandı.

Sonuç: Bu çalışma, SH'ye bağlı İAH'si olan hastaların sikka semptomlarından ziyade pulmoner semptomlarla daha sık başvurduğunu ve parotis bezi ultrasonografik tutulumunun daha hafif olduğunu göstermektedir. Bu bulgular, SH'ye bağlı İAH'nin nispeten düşük dereceli parotis bezi ultrasonografik değişiklikleri ile karakterize ayrı bir klinik alt grup olabileceğini düşündürmektedir.

Anahtar Kelimeler: İnterstisyel akciğer hastalığı, ultrasonografi, Sjögren hastalığı, parotis bezi

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Introduction

Sjögren's disease (SjD) represents a chronic immune-mediated disorder in which persistent lymphocytic activity predominantly targets exocrine tissues, leading to progressive glandular dysfunction. The incidence of SjD is estimated to be approximately 4-7 per 100,000 individuals, while its prevalence is estimated at around 2-3%.^[1] In 30-40% of patients with SjD, extraglandular manifestations may also occur, including arthritis, nephritis, neuropathy, and pulmonary involvement.^[2]

Pulmonary involvement is one of the most common extraglandular manifestations of SjD, with a reported prevalence ranging from 9% to 75%.^[3] This wide variability in prevalence is mainly attributable to differences in the definitions used to classify pulmonary involvement. Interstitial lung disease (ILD) is, generally, a late complication of SjD, and is associated with significantly increased morbidity and mortality.^[3,4]

In a study by Gao et al.^[5], 49% of patients with SjD-ILD initially presented with non-sicca symptoms. Another study reported that only 49.4% of SjD-ILD patients had sicca symptoms as their initial complaint.^[6] These findings suggest that patients with SjD who present with sicca or non-sicca symptoms may have different initial targets of immune dysregulation and potentially distinct pathogenic mechanisms.^[3]

There is growing evidence supporting the use of major salivary gland ultrasonography (SGUS), a non-invasive method, in the diagnosis of SjD.^[7] Whether it can replace invasive methods, such as minor salivary gland biopsy, is debated. Furthermore, SGUS could facilitate stratification of heterogeneous SjD phenotypes and provide deeper insights into their distinct pathophysiological pathways. This study was conducted to assess parotid gland ultrasonographic changes in SjD and to examine their relationship with the presence of ILD.

Materials and Methods

Ethical Approval

This study was initially approved by the Akdeniz University Clinical Research Ethics Committee (approval number: KAEK-242, date: 22.03.2023). An additional approval regarding the extension of the data collection period to cover June 2023-May 2024 was subsequently granted by the Akdeniz University Medical Scientific Research Ethics Committee (approval number: TBAEK-623, date: 03.07.2025). Following the ethical guidelines of the Declaration of Helsinki, we secured written informed consent from every participant before enrollment.

Study Population

A total of 130 primary SjD patients (20 with ILD and 110 without ILD) aged over 18 and fulfilling the 2016 American

College of Rheumatology and the European League Against Rheumatism (EULAR) SjD classification criteria^[8] were enrolled in the study. We excluded individuals with a history of head and neck radiotherapy, sarcoidosis, or viral infections (human immunodeficiency virus and hepatitis C). Furthermore, those with other systemic autoimmune diseases, a history of parotid gland procedures, or technical limitations affecting SGUS assessment were not enrolled.

Descriptive Data and Clinical Assessments

A comprehensive medical history was obtained from all patients, and physical examinations were performed. Clinical and laboratory data were collected from the hospital data system: demographic characteristics (age, sex, and smoking status), disease duration, comorbidities, former and ongoing treatments, complete blood count, inflammatory markers [C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)], antinuclear antibody (ANA) patterns and titers, extractable nuclear antigen profiles, minor salivary gland biopsy results, Schirmer test findings, pulmonary function test (PFT) results, and thoracic computed tomography (CT) results. The presence of ILD in patients with SjD was determined based on a combination of clinical features, imaging studies, and PFTs.

Imaging Protocols

Parotid gland imaging was performed with a high-frequency linear transducer (12 MHz) on a LOGIQ S7 EXPERT platform to ensure standardized grayscale image acquisition. Long-axis US images of two parotid glands were obtained while patients were in the supine position. An experienced rheumatologist evaluated all ultrasound images. Significantly, the operator was blinded to the ILD status of the patients at the time of SGUS assessment. The grading was performed according to the 2019 Outcome Measures in Rheumatology (OMERACT) Greyscale Ultrasound Scoring System,^[9] which defines the following categories: Grade 0: Normal glandular appearance with homogeneous echotexture and no abnormalities; Grade 1: Mild changes with preserved echogenicity, without anechoic or hypoechoic areas; Grade 2: Moderate alterations, including focal anechoic or hypoechoic lesions; Grade 3: Severe glandular inhomogeneity or signs of fibrosis throughout the glandular tissue. Representative SGUS images corresponding to each grade from our cohort are shown in Figure 1. In this study, only two parotid glands were assessed by ultrasound. The submandibular glands were not included. Therefore, unlike the original OMERACT semi-quantitative score (minimum-maximum: 0-12), the OMERACT score ranged from a minimum of 0 to a maximum of 6 (grades 0-3 for both parotids).

PFT results, including spirometry and diffusing capacity of the lung for carbon monoxide, were retrieved from the institutional electronic medical record system. Thoracic CT images were re-

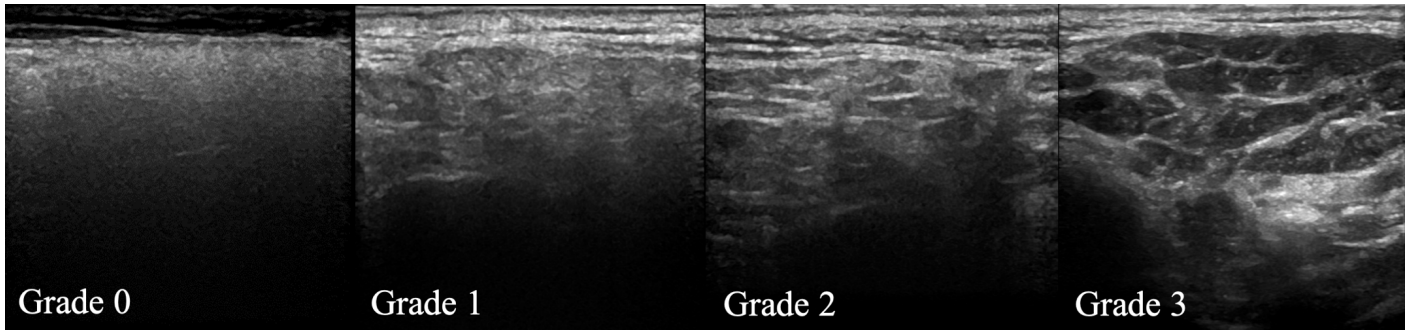


Figure 1. Representative parotid gland greyscale ultrasound images demonstrating Grades 0 to 3 according to the 2019 OMERACT scoring system^[9]
OMERACT: Outcome Measures in Rheumatology

evaluated and classified according to American Thoracic Society guidelines^[10,11] as follows: definite, probable, and indeterminate usual interstitial pneumonia (UIP); non-specific interstitial pneumonia (NSIP); organizing pneumonia; hypersensitivity pneumonitis (HP); and lymphocytic interstitial pneumonia (LIP).^[12,13] The ILD diagnosis was conducted based on clinical features, PFT, and high-resolution CT imaging patterns.

Statistical Analysis

SPSS for Windows version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Patient characteristics and laboratory results were analyzed using descriptive statistics. Categorical data were expressed as frequency (n) and percentage (%). The chi-square test or Fisher's exact test (whichever was appropriate) was used to compare categorical data; the Student's t-test was used for normally distributed numeric data; and the Mann-Whitney U test was used for non-normally distributed numeric data. A p-value <0.05 was considered statistically significant.

Results

The baseline characteristics of patients with SjD-related ILD and non-ILD are presented in Table 1. Patients with an SGUS total OMERACT score for parotid glands ≥ 2 were less frequent in the ILD group compared to the non-ILD group (65.0% vs. 84.5%, $p=0.03$). The proportion of patients with a total SGUS score ≥ 3 was also lower in the ILD group, but the difference was not statistically significant ($p=0.09$). SGUS scores for the right and left parotid glands were consistent in both groups (Kappa=0.604 and 0.665, respectively; $p<0.001$) (Table 2). No significant difference was found in biopsy focus scores between SjD-ILD and non-ILD patients (66.7% vs. 77.4%, $p=0.37$). Medication use data are summarized in Table 1. In the study population, the use of immunosuppressive and immunomodulatory agents differed significantly between patients with SjD and those without ILD. Azathioprine, methotrexate, rituximab, or mycophenolate mofetil were used by 95.0% of patients in the ILD group, compared to 16.2% of patients in the group without ILD ($p<0.001$). Hydroxychloroquine use was significantly less

frequent in the ILD group (40.0% vs. 72.4%, $p=0.005$). Pilocarpine use was reported only in the non-ILD group (10.6%), whereas none of the ILD patients received this medication. Glucocorticoid use was markedly higher in the ILD group (47.4% vs. 6.7%, $p<0.001$).

The clinical and functional characteristics of patients with SjD-related ILD are presented in Table 3. At the last clinical visit, respiratory symptoms were not observed in 35.0% of ILD patients; among these, cough ($n=7$) and dyspnea ($n=10$) occurred in 50.0% of cases. Based on thoracic CT findings, the most common radiological pattern was UIP, observed in 14 patients (70%); 8 patients (40%) were classified as having definite UIP. An NSIP pattern was observed in 5 patients (25%). One patient had HP, and another showed features of both NSIP and LIP.

There were no significant differences between the ILD and non-ILD groups in mean age or age at SjD diagnosis. Sicca symptoms as the initial manifestation were less common in the ILD group (30.0%), whereas pulmonary symptoms predominated (70.0%). ILD was significantly more prevalent in males than in females (20.0% vs. 1.9%, $p=0.005$). A higher proportion of patients in the ILD group had a history of smoking (45.0% vs. 22.7%, $p=0.008$). No significant differences were observed between the groups in terms of age, age at SjD diagnosis, autoantibody positivity (ANA, anti-Ro/SS-A, anti-La/SS-B), hemoglobin or platelet count.

However, leukocyte (8.62 ± 1.76 vs. $6.05 \pm 1.79 \times 10^3/\text{mm}^3$) and neutrophil (5.64 ± 1.37 vs. $3.43 \pm 1.32 \times 10^3/\text{mm}^3$) counts were significantly higher in the ILD group (both $p<0.001$). CRP levels were also significantly elevated in ILD patients (7.9 ± 11.6 vs. 3.2 ± 3.7 mg/L, $p=0.01$). No significant differences were found in ESR or in serum complement levels 3 and 4 (C3, C4).

Discussion

In this study, patients with SjD-related ILD demonstrated milder ultrasonographic involvement of the parotid glands compared with patients without ILD. High-grade parotid SGUS abnormalities were less frequent in the ILD group, suggesting that glandular structural changes may be less pronounced despite the presence of significant extraglandular disease.

Table 1. Baseline characteristics of SjD patients with and without interstitial lung disease			
	SjD-ILD (n=20)	SjD without ILD (n=110)	p
Age, years (mean ± SD)	59.9±11.2	56.3±12.3	0.10
Age at SjD diagnosis, years (mean ± SD)	54.1±13.0	49.4±11.4	0.23
Sex (male), n (%)	4 (20.0)	2 (1.9)	0.005
Smoking (ever), n (%)	9/20 (45.0)	17/75 (22.7)	0.008
ANA positivity, n (%)	12/20 (60.0)	75/110 (68.2)	0.474
Anti-Ro52 positivity, n (%)	8 (40.0)	55 (50.0)	0.43
Anti-Ro/SS-A positivity, n (%)	6 (30.0)	54 (49.1)	0.10
Anti-La/SS-B positivity, n (%)	5 (25.0)	23 (20.1)	0.71
Hemoglobin, gr/dL (mean ± SD)	12.7±1.24	12.7±1.15	0.96
Leucocytes, thousand/mm ³ (mean ± SD)	8.62±1.76	6.05±1.79	<0.001
Neutrophils, thousand/mm ³ (mean ± SD)	5.64±1.37	3.43±1.32	<0.001
Trombocytes, thousand/mm ³ (mean ± SD)	288.5±62.4	246.4±63.9	0.08
Complement C3 level, g/L (mean ± SD)	1.24±0.2	1.21±0.2	0.52
Complement C4 level, g/L (mean ± SD)	0.24±0.06	0.23±0.09	0.48
CRP, mg/L (mean ± SD)	7.9±11.6	3.2±3.7	0.01
ESR, mm/hour (mean ± SD)	17.2±8.9	18.3±9.4	0.63
Medications used, n (%)			
Azathioprine, methotrexate, mycophenolate mofetil, rituximab	19 (95.0)	17/105 (16.2)	<0.001
Hydroxychloroquine sulfate	8 (40.0)	76/105 (72.4)	0.005
Pilocarpine	0	11/104 (10.6%)	0.21
Glucocorticoid	9 (47.4)	7/104 (6.7)	<0.001
Schirmer test <5 mm, n (%)	8 (40.0)	26 (23.6)	0.12
MSGB Focus score ≥1, n (%)	10/15 (66.7)	65/84 (77.4)	0.37
SGUS OMERACT for parotid glands			
≥2 points, n (%)	13 (65.0)	93 (84.5)	0.03
≥3 points, n (%)	2 (10.0)	32 (29.1)	0.09
ANA: Antinuclear antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ILD: Interstitial lung disease, MSGB: Minor salivary gland biopsy, OMERACT: Outcome Measures in Rheumatology, SD: Standard deviation, SGUS: Salivary gland ultrasonography, SjD: Sjögren's disease			

Table 2. Comparison of right and left parotid gland ultrasonographic OMERACT grades between SjD patients with and without interstitial lung disease														
SjD-ILD							SjD without ILD							
		Right parotid gland (n)						Right parotid gland (n)						
		Grade 0	Grade 1	Grade 2	Grade 3	Total			Grade 0	Grade 1	Grade 2	Grade 3	Total	
Left parotid gland (n)	Grade 0	4	0	0	0	4	Left parotid gland (n)	Grade 0	5	6	0	0	11	
	Grade 1	3	11	0	0	14		Grade 1	6	61	1	0	68	
	Grade 2	0	1	1	0	2		Grade 2	0	5	16	1	22	
	Grade 3	0	0	0	0	0		Grade 3	0	1	0	8	9	
	Total	7	12	1	0	20		Total	11	73	17	9	110	
Kappa value: 0.604, p<0.001							Kappa value: 0.665, p<0.001							
ILD: Interstitial lung disease, OMERACT: Outcome Measures in Rheumatology, SjD: Sjögren's disease														

These findings point to a dissociation between salivary gland involvement and pulmonary manifestations in SjD.

SjD-related ILD is associated with increased morbidity and mortality. Numerous observational studies have investigated demographic, clinical, and serological features in patients with SjD-related ILD; however, the results have been inconsistent.^[14]

Studies specifically examining the relationship between SGUS findings and organ involvement in SjD remain limited. In this context, our study compared SGUS grades, clinical features, and radiological features between SjD patients with and without ILD, and demonstrated that the ILD group had lower parotid OMERACT scores.

	Age	Gender	Age at ILD/type of ILD		Age at pSS	Smoking (ever)	Respiratory symptoms	FVC (%)	FEV ₁ (%)	FEV ₁ /FVC	DLCO (%)	Focus score ≥1	Treatment
Patient 1	80	M	76	Definite UIP	76	(+)	--	85	95	82	49	+	AZA, GC
Patient 2*	55	F	47	Ind. UIP	35	(-)	D	81	84	87	95	--	MMF, GC
Patient 3	61	F	59	NSIP	59	(-)	--	66	73	92	53	-	MMF, GC
Patient 4*	61	F	57	Possible UIP	47	(+)	D	66	70	89	53	+	MTX, GC
Patient 5	56	F	54	NSIP	54	(-)	--	85	97	96	58	+	HCQ, GC
Patient 6	62	F	53	Definite UIP	53	(+)	C, D	74	69	78	36	-	MMF
Patient 7	30	F	29	NSIP	29	(+)	C, D	75	78	87	57	+	MMF, GC
Patient 8	65	F	57	Possible UIP	61	(-)	C	63	69	91	39	-	MMF, RTX, GC
Patient 9	72	M	70	Definite UIP	70	(+)	D	53	64	91	39	-	MMF
Patient 10	77	F	64	Possible UIP	65	(-)	--	100	109	84	66	+	MTX, HCQ, GC,
Patient 11	62	M	60	Definite UIP	60	(+)	--	71	80	88	74	-	MMF, GC
Patient 12*	61	F	57	Definite UIP	51	(-)	D	46	55	100	24	+	MMF, HCQ, GC
Patient 13*	44	F	44	Ind. UIP	30	(-)	--	101	107	90	84	-	MMF
Patient 14	62	M	57	NSIP	57	(-)	C	76	90	92	45	+	MMF, HCQ, GC
Patient 15	61	F	56	Definite UIP	56	(-)	D	61	63	86	69	-	MMF, HCQ, GC
Patient 16	50	F	48	HS	48	(-)	C	74	79	89	50	+	MMF, HCQ, GC
Patient 17	69	F	66	Definite UIP	66	(+)	C, D, OC	42	50	76	38	--	MMF, HCQ
Patient 18	59	F	49	Definite UIP	49	(+)	C, D	48	42	71	48	+	RTX
Patient 19*	71	F	62	Ind. UIP	57	(+)	--	142	158	87	75	--	MMF, HCQ
Patient 20*	49	F	42	NSIP, LIP	38	(-)	D	60	65	89	49	--	AZA, GC

Cases marked with * had sicca onset, whereas the others presented with ILD as the initial manifestation

AZA: Azathioprine, C: Cough, D: Dyspnea, DLCO: Diffusing capacity of the lung for carbon monoxide, F: Female, FEV₁: Forced expiratory volume in 1 second, FEV₁/FVC, Ratio of forced expiratory volume in 1 second to forced vital capacity, FVC: Forced vital capacity, GC: Glucocorticoid, HCQ: Hydroxychloroquine, HS: Hypersensitivity pneumonitis, ILD: Interstitial lung disease, Ind: Indeterminate, LIP: Lymphoid interstitial pneumonia, M: Male, MMF: Mycophenolate mofetil, MSGBFS: Minor Salivary Gland Biopsy Focus Score, MTX: Methotrexate, NSIP: Non-specific interstitial pneumonia, OC: Oxygen concentrator, RTX: Rituximab, SjD: Sjögren's disease, UIP: Usual interstitial pneumonia

The reported prevalence of SjD-related ILD varies widely, ranging from 10% to 20%, depending on ethnicity and diagnostic criteria.^[15,16] Consistent with the literature, our cohort had a prevalence of 15.4%. In a meta-analysis by He et al.^[15], older age, male sex, and elevated CRP levels were identified as risk factors for SjD-related ILD. Although SjD is more common in females, male patients tend to present with more severe disease and worse outcomes.^[17] In our cohort, CRP, leukocyte, and neutrophil levels were significantly higher in the ILD group. These elevated inflammatory markers, which reflect immune activation, may play a critical role in systemic damage, including pulmonary and pleural complications.^[5] However, these findings should be interpreted with caution because glucocorticoid use was more frequent in the ILD group; steroid therapy is known to increase circulating leukocyte and neutrophil counts and thus may represent a potential confounding factor.

The proportion of patients with OMERACT scores ≥ 2 and ≥ 3 on SGUS was lower in the ILD group compared to the non-ILD group (65.0% vs. 84.5% and 10.0% vs. 29.1%, respectively). La Rocca et al.^[3] proposed that in newly diagnosed SjD patients, the presence of pulmonary symptoms may mask classical sicca symptoms. Similarly, in our cohort, patients with SjD-ILD exhibited significantly lower SGUS scores, suggesting that SGUS

alone may be insufficient for the diagnosis of SjD in patients being evaluated for ILD.

Immunological differences in organ involvement may explain the variations observed in clinical, histopathological, and radiological findings in SjD. Epithelial cells in salivary glands may, in response to unknown triggers, initiate innate immune responses that lead to acquired immunity against self-antigens. These epithelial cells act as both targets and mediators of the immune response.^[18] Ductal epithelial cells produce pro-inflammatory cytokines, including B-cell-activating factor, interleukin-1 (IL-1), IL-6, IL-21, and tumor necrosis factor- α , and express major histocompatibility complex class II, thereby activating both innate and adaptive immune responses. These mechanisms stimulate B-cells within follicular-like structures, promoting the production of autoantibodies and local inflammation.^[18] In murine models of SjD, pulmonary lesions were characterized by a predominance of B-cells, distinguishing them from salivary gland lesions.^[19] Lung inflammatory infiltrates resembling bronchus-associated lymphoid tissue have been observed, where CD23⁺ follicular B-cells, under a T helper type 2-polarized immune environment, contribute to pulmonary autoimmune lesions in a CD4⁺ T-cell-dependent manner.^[19]

The presence of anti-Ro antibodies has been associated with more active disease in SjD, including ILD,^[20] and higher SGUS scores are more frequently observed in anti-Ro/SSA- and anti-La/SSB-positive patients.^[7,21] Dong et al.^[22] reported a correlation between anti-Ro52 antibodies and ILD in a SjD cohort. Anti-Ro52 (TRIM21) antibodies have also been detected in a significant proportion of patients with idiopathic interstitial pneumonia.^[23] Despite the lower SGUS scores observed in our ILD group, there were no significant differences in autoantibody positivity between groups. This suggests that the difference in SGUS findings in SjD-ILD may be independent of serological autoantibody status.

Consistent with clinical expectations, immunosuppressive therapy was more frequently administered to the SjD-related ILD group than to the non-ILD group. The TEARS^[24] and TRACTISS^[25] trials evaluated SGUS as an outcome parameter in SjD. In the TEARS trial, 50% of patients treated with rituximab showed improvement in SGUS scores compared to only 7% in the placebo group.^[24] Similarly, in the TRACTISS trial, patients treated with rituximab demonstrated significantly lower SGUS scores at weeks 16 and 48 compared to those receiving placebo.^[25] In the present study, patients with SjD-related ILD received immunosuppressive agents more frequently, and the observed differences in SGUS findings may reflect treatment-related responses to immunosuppression.

Study Limitations

Our study has several limitations. First, parotid gland US, minor salivary gland biopsy, CT scans, and Schirmer testing were not performed simultaneously. Secondly, there were no SGUS scores available at the time of diagnosis or prior to immunosuppressive therapy; therefore, the effects of such therapy on SGUS findings could not be entirely eliminated. In addition, the ultrasonographic assessment was limited to the parotid glands; the submandibular glands—which may demonstrate earlier or more pronounced involvement in SjD—were not evaluated, representing an important methodological limitation. Additionally, salivary flow rates and overall disease activity (EULAR Sjögren's Syndrome Disease Activity Index and EULAR Sjögren's Syndrome Patient-Reported Index) were not assessed. Moreover, the single-center study design limits the generalizability of the results, and multicenter studies are essential to validate these results.

Conclusion

Parotid gland ultrasonographic changes were milder in SjD patients with ILD compared with patients without ILD. These findings suggest that SjD may comprise distinct clinical subgroups, including predominantly glandular and predominantly non-glandular phenotypes, with differing parotid ultrasonographic characteristics when systemic organ involvement is present. Diagnostic approaches relying

solely on parotid gland imaging via SGUS may underdiagnose SjD, particularly in patients with significant extraglandular manifestations but limited involvement of the major salivary gland. Further studies employing comprehensive salivary gland assessments are essential to elucidate the diagnostic utility of SGUS across the diverse clinical phenotypes of SjD, characterized by varying degrees of glandular and systemic involvement.

Ethics

Ethics Committee Approval: This study was initially approved by the Akdeniz University Clinical Research Ethics Committee (approval number: KAEK-242, date: 22.03.2023). An additional approval regarding the extension of the data collection period to cover June 2023-May 2024 was subsequently granted by the Akdeniz University Medical Scientific Research Ethics Committee (approval number: TBAEK-623, date: 03.07.2025).

Inform Consent: We secured written informed consent from every participant before enrollment.

Footnotes

A preliminary version of this work was presented at the XXIV National Rheumatology Congress (26-30 October 2024) and published in the supplementary issue of Journal of Turkish Society for Rheumatology (2025).

Authorship Contributions

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