The association between autoantibody types and salivary gland hypofunction in patients with primary Sjögren's syndrome

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The association between autoantibody types and salivary gland hypofunction in patients with primary Sjögren's syndrome

Directed by Professor Hyung-Joon Ahn, D.D.S., Ph.D.

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Bok Eum Kim

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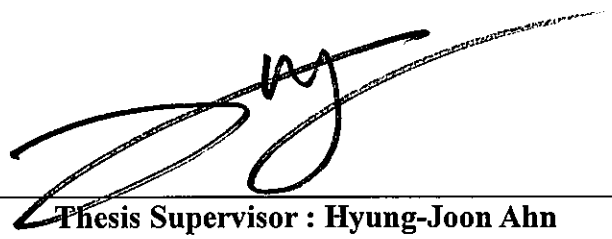
This certifies that the doctoral dissertation

of Bok Eum Kim is approved.



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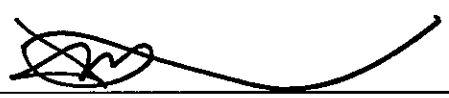

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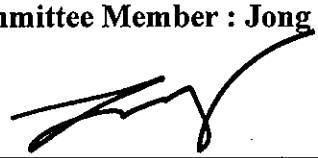

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힘든 여정이지만 제가 하는 모든 일에 대하여 항상 응원해주시고 격려해주신 저희 부모님과 하나뿐인 소중한 동생 믿음이에게도 감사 인사를 전합니다. 소중한 가족이라는 버팀목이 있었기에 오늘의 제가 있을 수 있었습니다. 마지막으로 항상 부족하고 연약한 저를 채워 주시고, 붙들어 주신 사랑하는 하나님 아버지께 이 모든 영광을 돌립니다. 연구하는 치과의사로서 많은 이들에게 선한 영향력을 끼치는 사람이 되도록 하겠습니다. 감사합니다.

2021년 12월

저자 김복음 드림

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The association between autoantibody types and salivary gland hypofunction in patients with primary Sjögren's syndrome

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This study analyzed the association between autoantibody types and salivary gland hypofunction in patients with primary Sjögren's syndrome (pSS). A retrospective analysis was performed on patients who visited the Department of Orofacial Pain and Oral Medicine at Yonsei University Dental Hospital from January 1, 2010 to May 31, 2021, and who were diagnosed with pSS. Out of 191 patients who fulfilled the 2002 American European Consensus Group classification criteria, 50 were positive for both anti-Ro/SSA and anti-La/SSB, whereas 97 had anti-Ro/SSA but not anti-La/SSB antibodies. Forty-four patients

for whom neither anti-Ro/SSA nor anti-La/SSB antibodies were found were diagnosed with SS by minor salivary gland biopsy. The anti-Ro/SSA antibody-positive group showed higher rheumatoid factor (RF) levels than the anti-Ro/SSA negative group. The anti-La/SSB antibody-positive group showed lower unstimulated whole saliva (UWS), stimulated whole saliva (SWS), higher erythrocyte sedimentation rate and RF than the anti-La/SSB-negative group. In addition, the group with both anti-Ro/SSA and anti-La/SSB antibodies showed lower UWS than the group who were positive only for anti-Ro/SSA antibodies. However, there were no significant differences in unstimulated whole saliva after taking pilocarpine, stimulated whole saliva after taking pilocarpine, and C-reactive protein. UWS and SWS were lower when anti-La/SSB was positive showing that anti-La/SSB is more likely to be involved in salivary gland hypofunction than anti-Ro/SSA in patients with pSS. Therefore, performing laboratory tests, including anti-La/SSB, is helpful in predicting the prognosis related to salivary gland function in patients with suspected pSS.

Keywords : Sjogren’s syndrome; autoantibodies; SS-A antibodies; SS-B antibodies; xerostomia

The association between autoantibody types and salivary gland hypofunction in patients with primary Sjögren's syndrome

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I. INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune rheumatoid disease characterized by lymphocytic infiltration of the salivary, lacrimal, other exocrine glands, and extra-glandular tissues (Scully, 2013). SS is most common in middle-aged and older women (Melissaropoulos et al., 2020). Its prevalence ranges from 0.22 to 1.6% (Goulabchand et al., 2021). Its etiology is not completely

understood and is characterized by chronic B and T lymphocyte infiltration in the salivary and lacrimal glands, leading to xerostomia and xerophthalmia (Baer and Walitt, 2018; Bawazir et al., 2021). SS may be primary or secondary, associated with other connective tissue autoimmnue diseases such as rheumatoid arthritis, systemic lupus erythematosus, polyarteritis, and dermatomyositis (Lopes et al., 2021; Reksten and Jonsson, 2014). Other extra-glandular features, such as pulmonary involvement and scleroderma, may also occur in secondary SS (Bowman, 2018). SS also increases the risk of lymphoma (Nocturne, 2019). Anti-Ro/SSA and anti-La/SSB autoantibodies are present in 60-70 and 50-60% of SS, respectively (Sieiro Santos et al., 2021).

SS can be diagnosed using the 2002 American European Consensus Group (AECG) classification criteria (Vitali et al., 2002). The criteria are based on six results: two subjective symptoms of xerostomia and xerophthalmia and four objective signs of Schirmer test ≤ 5 mm/5 min (or van Bijsterveld score ≥ 4); unstimulated whole salivary flow rate ≤ 0.1 ml/min; minor salivary gland biopsy (MSGB) result; and confirmation of autoantibodies such as anti-Ro/SSA and anti-La/SSB. SS is diagnosed when at least four of the six results are positive with the inclusion of at least one of the results of the MSGB or autoantibody, or when three out of four objective findings are positive. The specific criteria are listed in Table 1.

Table 1. Revised classification criteria for Sjögren's syndrome proposed by American-European Consensus Group

1. Ocular symptoms
At least one of these 3 :
1. daily persistent troublesome dry eyes > 3 months
2. recurrent sensation of sand or gravel
3. need to use teardrops > 3 times daily
2. Oral symptoms
At least one of these 3 :
1. daily feeling of dry mouth > 3 months
2. recurrent or persistently swollen salivary glands as adult
3. frequently drink liquids to aid swallowing dry foods
3. Ocular signs
At least one of these 2 :
1. Schirmer's test ≤ 5mm in 5minutes
2. Rose-Bengal score ≥ 4 according to van Bijsterveld's scoring system
4. Histopathology
Focal lymphocytic sialadenitis with a focus score ≥ 1 in minor salivary glands
5. Salivary gland involvement
A positive result for at least one of the following diagnostic tests
1. unstimulated whole salivary flow ≤ 1.5ml in 15minutes
2. parotid sialography : diffuse sialectasias
3. salivary scintigraphy : delayed uptake/reduced concentration and/or delayed excretion of tracer
6. Autoantibodies
anti-Ro/SSA and/or anti-La/SSB

As such, the autoantibody and MSGB results are important for confirming SS. In a previous study examining the relationship between autoimmune diseases, including SS and autoantibodies, Malik et al. (2007) found that the risk of lupus nephritis was significantly lower in the anti-La/SSB-positive patient group. In addition, the risk of seizures was lower in this group (Malik et al., 2007). On the other hand, when anti-Ro/SSA is positive in patients with lupus, the frequency of subacute cutaneous lupus, photosensitivity, neonatal lupus, and interstitial lung disease is high. In a similar study, Novak et al. (2017) showed that manifestations such as cutaneous and musculoskeletal diseases were mild in patients with childhood-systemic lupus erythematosus, in which both anti-Ro/SSA and anti-La/SSB are positive. Secondary SS was rarely observed in these patients (Novak et al., 2017). However, when both anti-Ro/SSA and MSGB are positive in patients with SS, anti-La/SSB-positive patients had a higher prevalence of hypergamma-globulinemia and circulating rheumatoid factor (RF) compared to those who were negative for anti-La/SSB (Cafaro et al., 2020).

Although there have been studies showing an association between severity of autoimmune diseases and autoantibodies, no studies to our knowledge, have assessed the association between anti-Ro/SSA and anti-La/SSB autoantibodies and salivary gland hypofunction in SS.

Therefore, the aim of this study was to determine the association between the presence of anti-Ro/SSA and/or anti-La/SSB antibodies with clinical and laboratory features including salivary gland hypofunction in patients with SS.

Ⅱ. SUBJECTS AND METHODS

1. Subjects

This retrospective study analyzed the charts of 1854 patients who visited the Department of Orofacial Pain and Oral Medicine at Yonsei University Dental Hospital from January 1, 2010, to May 31, 2021, and who underwent laboratory tests including anti-Ro/SSA, anti-La/SSB, and salivary flow rate tests for the diagnosis of SS. A total of 226 patients were diagnosed with SS. Among these patients, 191 patients (Females: 190, Males: 1, 60.8 ± 13.2 years) met the 2002 AECG classification criteria and were diagnosed with pSS. Of the 191 patients, 50 were positive for anti-Ro/SSA and anti-La/SSB, whereas 97 had anti-Ro/SSA but not anti-La/SSB antibodies. Forty-four patients for whom neither anti-Ro/SSA nor anti-La/SSB antibodies were found were diagnosed with SS by MSGB (Fig. 1). Clinical and laboratory characteristics of the 191 patients were compared. This study was approved by the Institutional Review Board of Yonsei University Dental Hospital (IRB. 2-2021-0085).

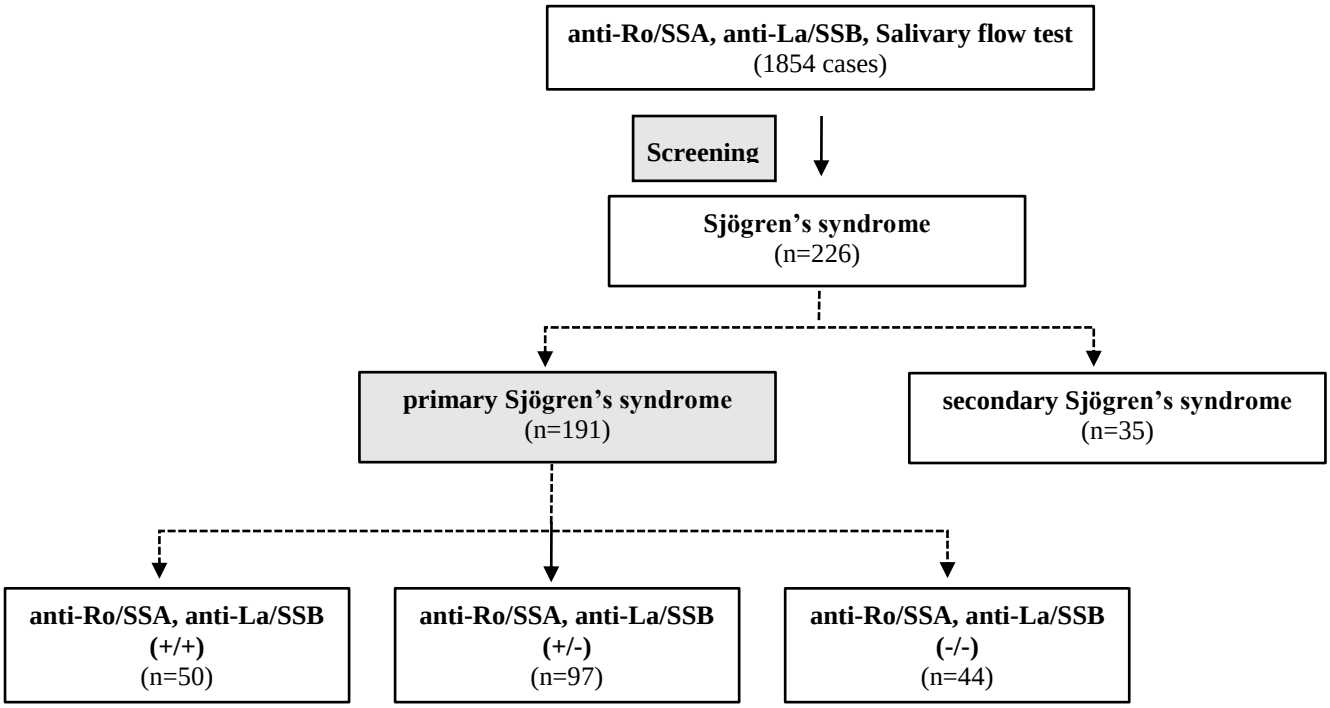

Figure 1. Flow chart of study subjects

2. Statistical Analysis

For all statistical analyses, SPSS statistics (version 26.0; IBM, Armonk, New York, USA) was used. The data were not normally distributed (Shapiro-Wilk test) and were analyzed using a nonparametric test. The Kruskal-Wallis test was performed to compare the clinical and laboratory features of patients with pSS according to the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies and was verified using the Mann-Whitney *U* test. The Chi-square test and Fisher's exact test were used for categorical variables. Descriptive statistics were presented as absolute number (frequencies) for categorical variables and medians (minimum and maximum values) for continuous variables. A p value of < 0.05 was considered statistically significant, and one asterisk denotes $p < 0.05$.

Ⅲ. RESULTS

1. Clinical and laboratory features of patients with pSS

There were 191 subjects, 190 females (99.5%) and one male (0.5%), with a mean age of 60.8. The mean values of the variables were as follows: unstimulated whole saliva (UWS) 0.093; stimulated whole saliva (SWS) 0.411; unstimulated whole saliva after taking pilocarpine (UWS-P) 0.139; stimulated whole saliva after taking pilocarpine (SWS-P) 0.468; erythrocyte sedimentation rate (ESR) 30.6; C-reactive protein (CRP) 1.6; and RF 30.1 (Table 2).

Table 2. Clinical and laboratory features of patients with pSS (n = 191)

Variables		Values*
Age (years)		60.8 ± 13.2
Sex		
	Female	190 (99.5)
	Male	1 (0.5)
Clinical features		
	[a]UWS	0.093 ± 0.103
	[b]SWS	0.411 ± 0.390
	[c]UWS-P	0.139 ± 0.140
	[d]SWS-P	0.468 ± 0.496
Laboratory features		
	[e]ESR	30.6 ± 20.5
	[f]CRP	1.6 ± 2.2
	[g]RF	30.1 ± 72.14

[a]UWS, unstimulated whole saliva; [b]SWS, stimulated whole saliva; [c]UWS-P, unstimulated whole saliva after taking pilocarpine; [d]SWS-P, stimulated whole saliva after taking pilocarpine; [e]ESR, erythrocyte sedimentation rate; [f]CRP, C-reactive protein; [g]RF, rheumatoid factor

*Values are presented as n (%) or mean ± standard deviation.

2. Clinical and laboratory features of patients with pSS according to the presence or absence of anti-Ro/SSA antibodies

There were no statistically significant differences in UWS, SWS, UWS-P, SWS-P, ESR, and CRP between anti-Ro/SSA positive and negative patients. RF was significantly different between the two groups. Anti-Ro/SSA positive patients showed higher levels of RF than anti-Ro/SSA negative patients ($p < 0.001$) (Table 3).

Table 3. Clinical and laboratory features of patients with pSS according to presence/absence of anti-Ro/SSA antibodies

	anti-Ro/SSA (+)	anti-Ro/SSA (-)	*p*-value
Clinical features			
[a]UWS (ml/min)	n = 147	n = 44	0.840
	0.061 (0.008-0.114)	0.053 (0.020-0.115)	
[b]SWS (ml/min)	n = 147	n = 44	0.357
	0.221 (0.112-0.376)	0.446 (0.154-0.608)	
[c]UWS-P (ml/min)	n = 75	n = 33	0.174
	0.090 (0.034-0.164)	0.124 (0.057-0.303)	
[d]SWS-P (ml/min)	n = 75	n = 33	0.268
	0.347 (0.122-0.670)	0.412 (0.158-0.768)	
Laboratory features			
[e]ESR	n = 143	n = 44	0.071
	30.0 (19.0-44.0)	17.0 (11.5-32.0)	
[f]CRP	n = 146	n = 44	0.446
	1.0 (0.6-1.6)	0.9 (0.5-2.3)	
[g]RF	n = 126	n = 37	<0.001*
	16.4 (7.0-49.3)	4.1 (3.0-11.3)	

n, number; [a]UWS, unstimulated whole saliva; [b]SWS, stimulated whole saliva; [c]UWS-P, unstimulated whole saliva after taking pilocarpine; [d]SWS-P, stimulated whole saliva after taking pilocarpine; [e]ESR, erythrocyte sedimentation rate; [f]CRP, C-reactive protein; [g]RF, rheumatoid factor.

* *p*-value calculated using the Mann-Whitney *U* test at α=0.05.

3. Clinical and laboratory features of patients with pSS according to the presence or absence of anti-La/SSB antibodies

UWS, SWS, ESR, and RF was significantly different between anti-La/SSB-positive and negative patients. Anti-La/SSB-positive patients showed lower UWS and SWS, and higher levels of ESR and RF compared to anti-La/SSB-negative patients. (p = 0.032, p = 0.020, p = 0.001, p < 0.001, respectively). There were no statistically significant differences in UWS-P, SWS-P, and CRP between both the two groups (Table 4, Fig. 2).

Table 4. Clinical and laboratory features of patients with pSS according to presence/absence of anti-La/SSB antibodies

	anti-La/SSB (+)	anti-La/SSB (-)	*p*-value
Clinical features			
[a]UWS (ml/min)	n = 52	n = 139	0.032*
	0.038 (0.002-0.103)	0.068 (0.020-0.117)	
[b]SWS (ml/min)	n = 52	n = 139	0.020*
	0.178 (0.078-0.346)	0.278 (0.128-0.597)	
[c]UWS-P (ml/min)	n = 30	n = 78	0.163
	0.098 (0.034-0.164)	0.153 (0.052-0.338)	
[d]SWS-P (ml/min)	n = 30	n = 78	0.104
	0.342 (0.126-0.670)	0.472 (0.164-0.818)	
Laboratory features			
[e]ESR	n = 51	n = 136	0.001*
	38.0 (23.0-55.0)	23.0 (14.5-36.5)	
[f]CRP	n = 52	n = 138	0.118
	1.2 (0.7-2.1)	0.9 (0.5-1.6)	
[g]RF	n = 44	n = 119	<0.001*
	37.0 (14.2-53.1)	7.0 (3.0-19.1)	

n, number; [a]UWS, unstimulated whole saliva; [b]SWS, stimulated whole saliva; [c]UWS-P, unstimulated whole saliva after taking pilocarpine; [d]SWS-P, stimulated whole saliva after taking pilocarpine; [e]ESR, erythrocyte sedimentation rate; [f]CRP, C-reactive protein; [g]RF, rheumatoid factor.

* *p*-value calculated using the Mann-Whitney *U* test at α=0.05.

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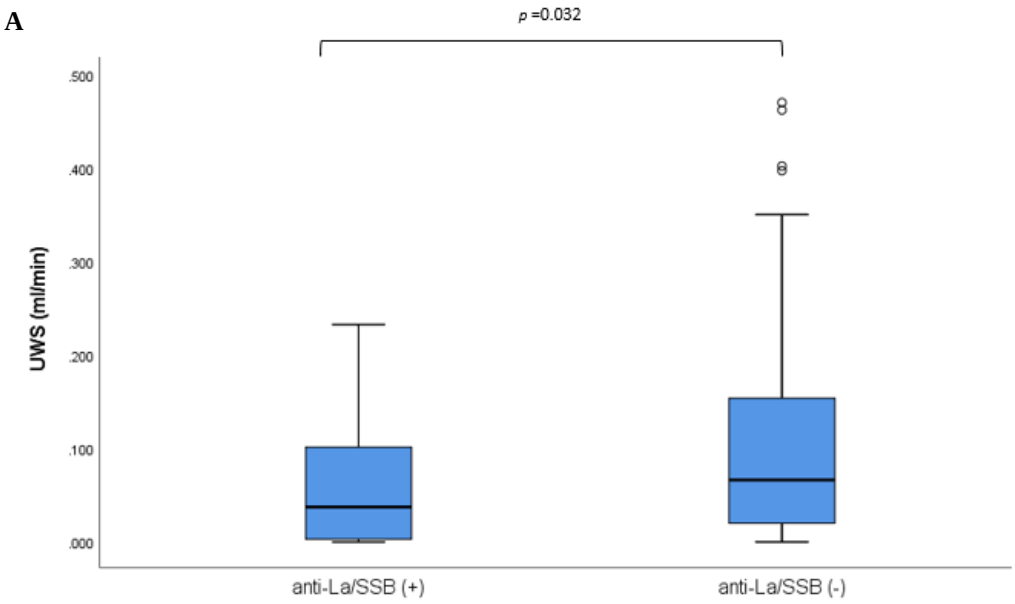

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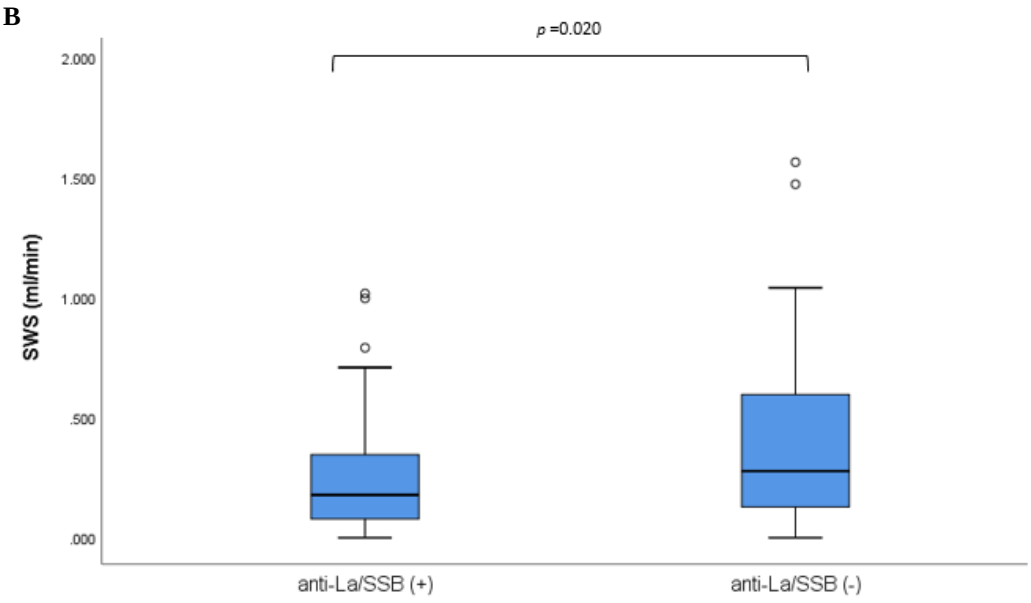

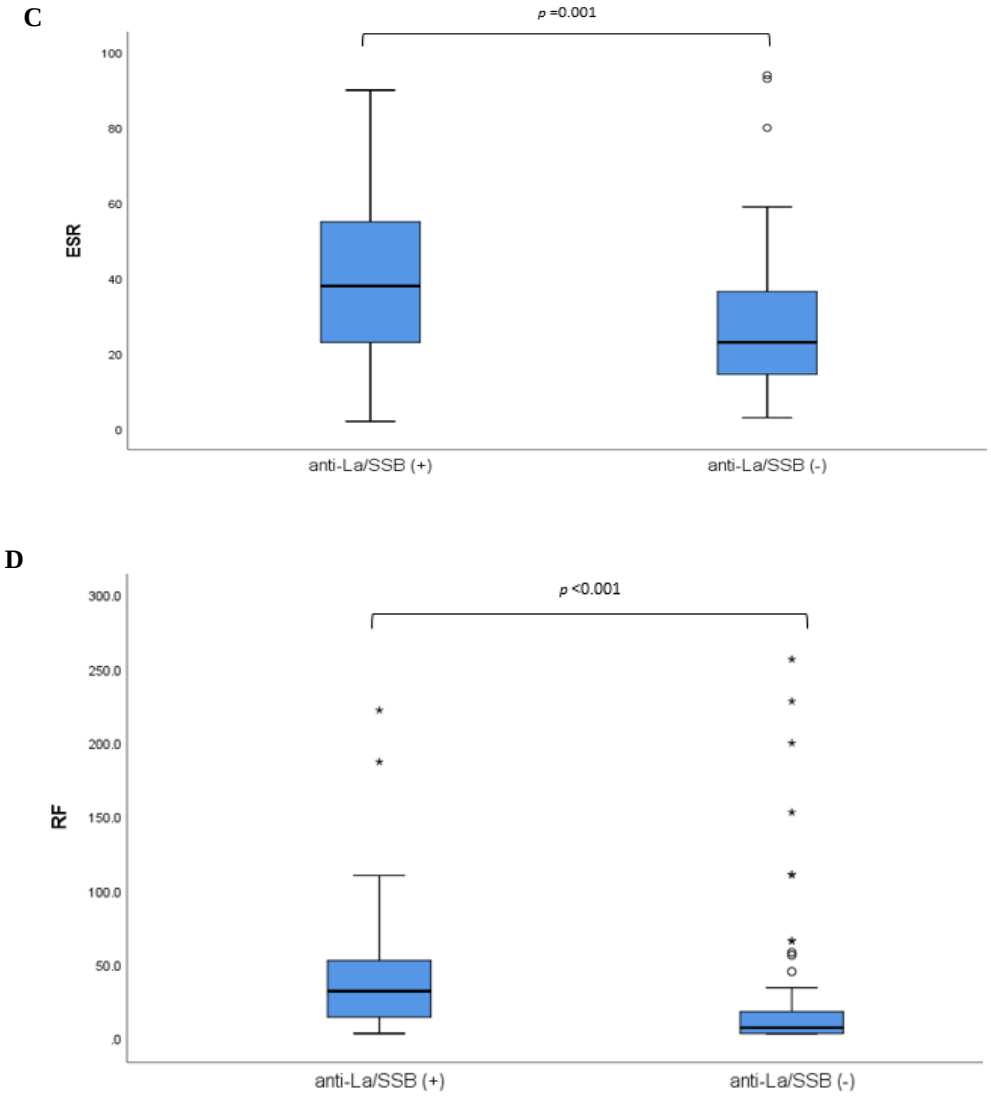

Figure 2. UWS, SWS, ESR, RF in patients with pSS according to presence/absence of anti-La/SSB antibodies

A. UWS in patients with pSS according to presence/absence of anti-La/SSB antibodies
B. SWS in patients with pSS according to presence/absence of anti-La/SSB antibodies
C. ESR in patients with pSS according to presence/absence of anti-La/SSB antibodies
D. RF in patients with pSS according to the presence/absence of anti-La/SSB antibodies

4. Clinical and laboratory features of patients with pSS according to the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies

UWS, ESR, and RF were significantly different according to the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies ($p = 0.048$, $p = 0.006$, $p < 0.001$, respectively). Patients with both anti-Ro/SSA and anti-La/SSB antibodies showed lower UWS than those with only anti-Ro/SSA antibodies ($p = 0.014$). Patients with both anti-Ro/SSA and anti-La/SSB antibodies had higher ESR and RF levels than patients with only anti-Ro/SSA antibodies or patients without any of them. There were no statistically significant differences in SWS, UWS-P, SWS-P, and CRP regardless of the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies (Table 5, Fig. 3).

Table 5. Clinical and laboratory features of patients with pSS according to presence/absence of anti-Ro/SSA and anti-La/SSB antibodies

	anti Ro/La (+/+)	anti Ro/La (+/-)	anti Ro/La (-/-)	*p*-value
Clinical features				
[a]UWS (ml/min)	n = 50	n = 97	n = 44	0.048*
	0.038 (0.002-0.105)	0.071 (0.025-0.164)	0.059 (0.020-0.121)	
[b]SWS (ml/min)	n = 50	n = 97	n = 44	0.111
	0.179 (0.066-0.361)	0.244 (0.132-0.488)	0.446 (0.154-0.608)	
[c]UWS-P (ml/min)	n = 29	n = 46	n = 33	0.238
	0.086 (0.020-0.139)	0.106 (0.039-0.190)	0.124 (0.057-0.303)	
[d]SWS-P (ml/min)	n = 29	n = 46	n = 33	0.168
	0.305 (0.050-0.425)	0.395 (0.142-0.702)	0.412 (0.158-0.768)	
Laboratory features				
[e]ESR	n = 49	n = 94	n = 44	0.006*
	40.0 (22.5-56.0)	27.5 (18.0-40.0)	17.0 (11.5-32.0)	
[f]CRP	n = 50	n = 96	n = 44	0.117
	1.2 (0.7-2.3)	0.9 (0.5-1.4)	0.9 (0.5-2.3)	
[g]RF	n = 42	n = 84	n = 37	<0.001*
	31.7 (14.2-53.1)	7.0 (4.3-20.0)	4.3 (3.0-13.9)	

n, number; [a]UWS, unstimulated whole saliva; [b]SWS, stimulated whole saliva; [c]UWS-P, unstimulated whole saliva after taking pilocarpine; [d]SWS-P, stimulated whole saliva after taking pilocarpine; [e]ESR, erythrocyte sedimentation rate; [f]CRP, C-reactive protein; [g]RF, rheumatoid factor.

* *p*-value calculated using the Kruskal-Wallis test at α=0.05.

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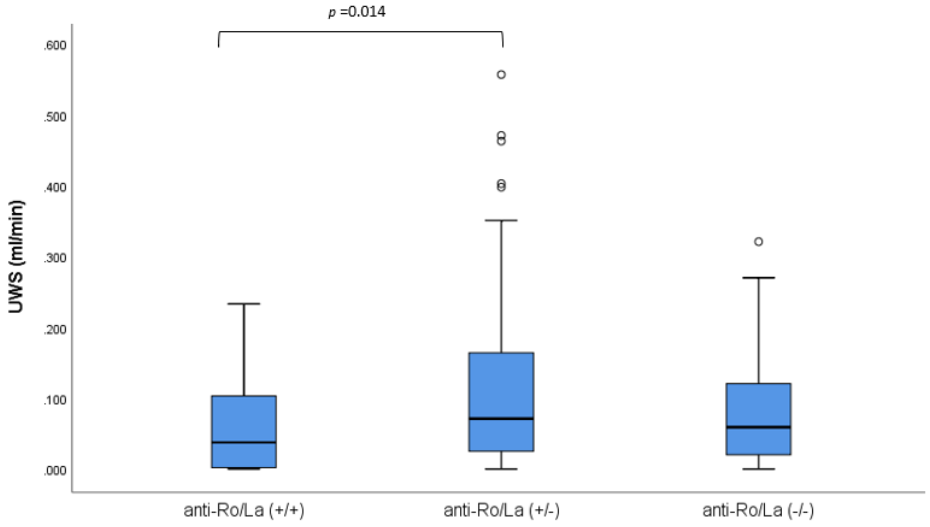

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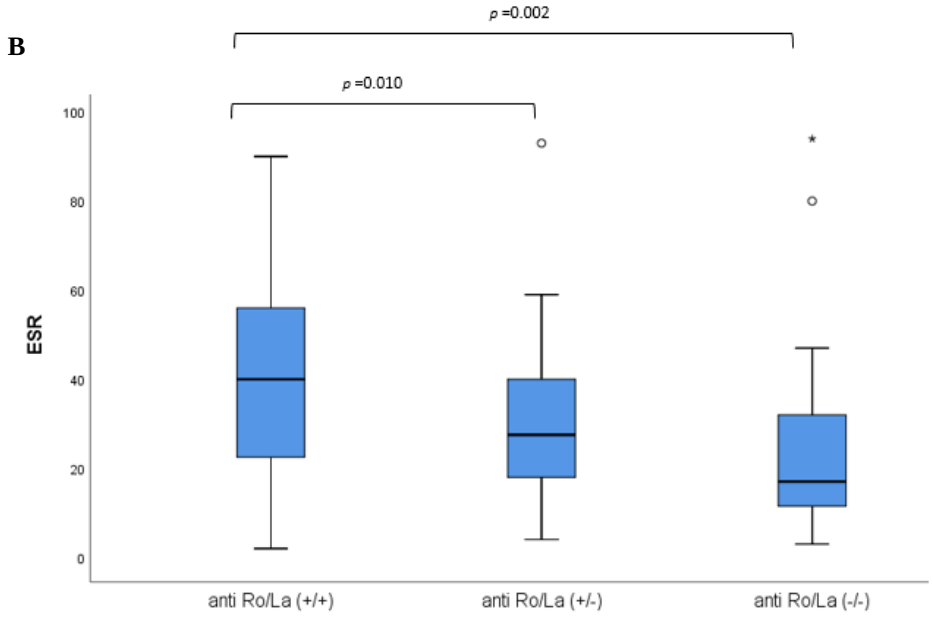

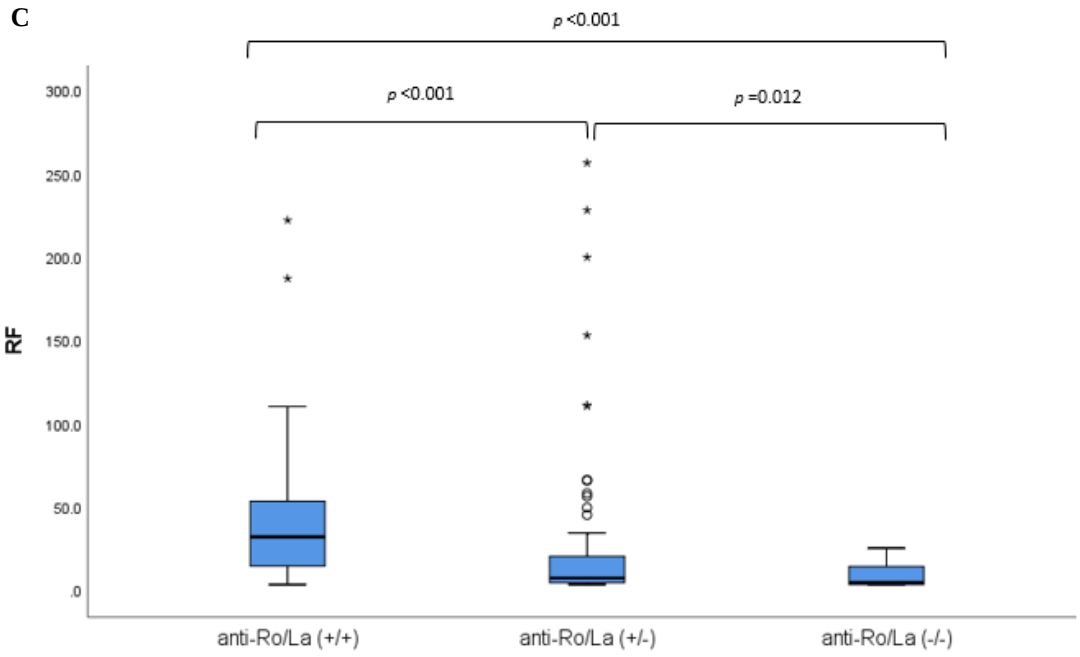

Figure 3. UWS, ESR, RF in patients with pSS according to presence/absence of anti-Ro/SSA and anti-La/SSB antibodies

A. UWS in patients with pSS according to presence/absence of anti-Ro/SSA and anti-La/SSB

B. ESR in patients with pSS according to presence/absence of anti-Ro/SSA and anti-La/SSB

C. RF in patients with pSS according to presence/absence of anti-Ro/SSA and anti-La/SSB

5. Differences in unstimulated/stimulated whole saliva according to the presence or absence of subjective improvement after taking pilocarpine in patients with pSS

There were no statistically significant differences in differences in unstimulated whole saliva before and after taking pilocarpine (UWS-P(d)), differences in stimulated whole saliva before and after taking pilocarpine (SWS-P(d)) regardless of the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies. However, objective improvement in unstimulated/stimulated whole saliva was significantly different according to the presence or absence of subjective improvement after pilocarpine administration in patients with pSS. Patients with subjective improvement after taking pilocarpine showed objective improvement in unstimulated/stimulated whole saliva compared to patients without subjective improvement after taking pilocarpine ($p = 0.001$ and $p < 0.001$, respectively) (Table 6, Fig.4).

Table 6. Differences in unstimulated/stimulated whole saliva according to presence/absence of subjective improvement after taking pilocarpine in patients with pSS

	Subjective improvement		*p-value*
	Yes (n = 62)	No (n = 43)	
Clinical features			
UWS-P(d) (ml/min)	0.050 (0.016-0.141)	0.016 (0-0.048)	0.001*
SWS-P(d) (ml/min)	0.131 (0.010-0.338)	0 (-0.064-0.112)	<0.001*

UWS-P(d), Differences in unstimulated whole saliva before and after taking pilocarpine;
SWS-P(d), Differences in stimulated whole saliva before and after taking pilocarpine
* *p*-value calculated by the Mann-Whitney *U* test at α=0.05

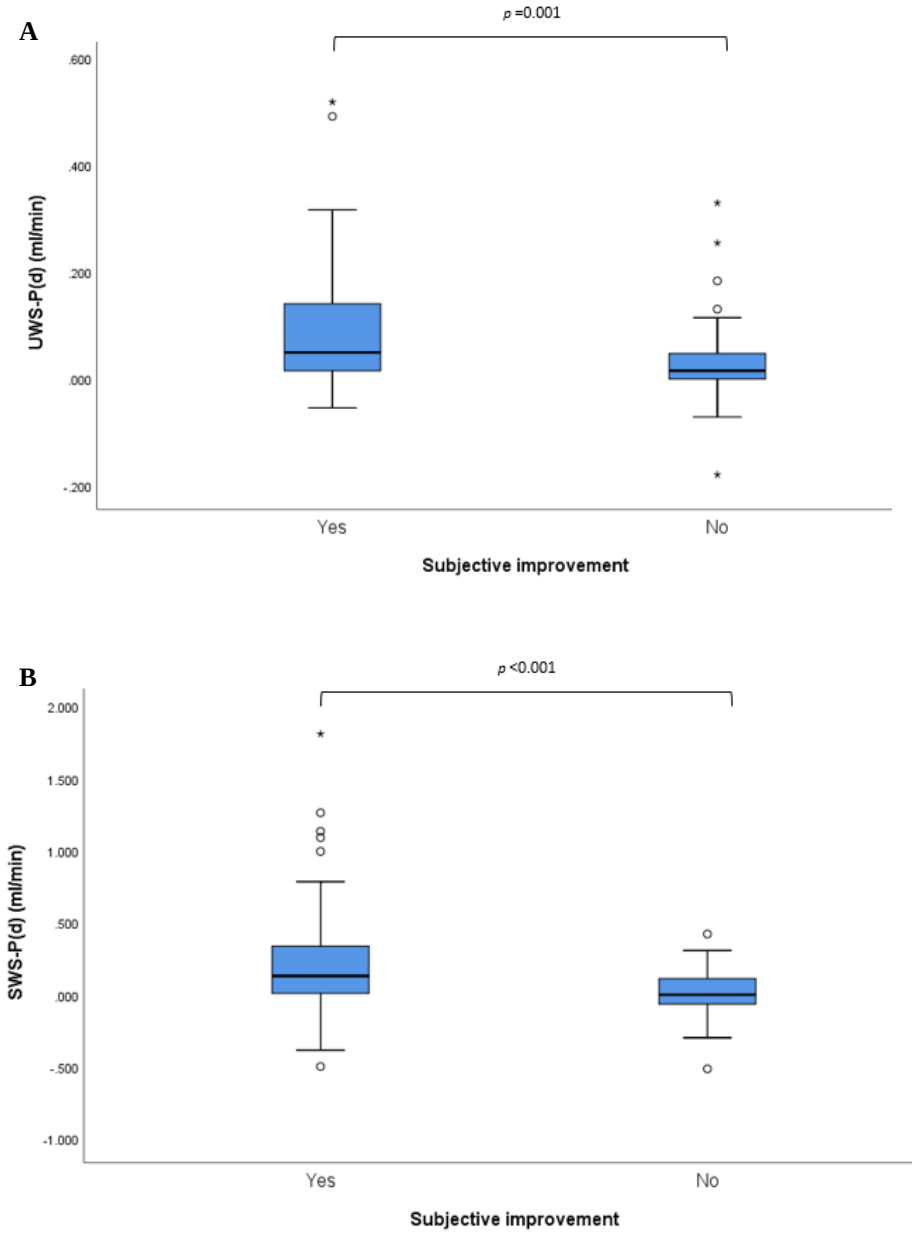

Figure 4. Differences in unstimulated/stimulated whole saliva according to presence/absence of subjective improvement after taking pilocarpine in patients with pSS

A. Differences in UWS-P(d) according to presence/absence of subjective improvement after taking pilocarpine

B. Differences in SWS-P(d) according to presence/absence of subjective improvement after taking pilocarpine

6. Clinical and laboratory features of patients with pSS according to anti-nuclear antibody pattern

UWS, UWS-P, SWS-P, ESR, and RF were significantly different according to anti-nuclear antibody (ANA) pattern. To account for type-1 error, Bonferroni correction was calculated, with an adjusted p value (α=0.05). Patients with mixed type had higher UWS than those with centromere type (p = 0.011). Patients with mixed type had higher UWS-P levels than patients with speckled, centromere, and homogeneous types (p = 0.009, p = 0.001, p = 0.005 respectively) (Table 7, Fig. 5).

Table 7. Clinical and laboratory features of patients with pSS according to ANA pattern

ANA patterns	speckled	centromere	homogeneous	nucleolar	mixed	*p*-value
Clinical features						
[a]UWS (ml/min)	n = 89	n = 25	n = 13	n = 6	n = 23	0.005*
	0.054 (0.018-0.102)	0.020 (0.000-0.052)	0.039 (0.000-0.091)	0.112 (0.066-0.173)	0.139 (0.096-0.175)	
[b]SWS (ml/min)	n = 89	n = 25	n = 13	n = 6	n = 23	0.178
	0.210 (0.084-0.367)	0.132 (0.116-0.488)	0.203 (0.118-0.286)	0.352 (0.337-0.471)	0.446 (0.356-0.645)	
[c]UWS-P (ml/min)	n = 55	n = 16	n = 8	n=3	n = 8	0.019*
	0.111 (0.040-0.217)	0.061 (0.018-0.099)	0.043 (0.001-0.087)	0.355 (0.197-0.369)	0.162 (0.085-0.368)	
[d]SWS-P (ml/min)	n = 55	n = 16	n = 8	n = 3	n = 8	0.028*
	0.321 (0.064-0.642)	0.132 (0.062-0.554)	0.172 (0.126-0.234)	0.846 (0.649-1.624)	0.354 (0.329-0.906)	
Laboratory features						
[e]ESR	n = 87	n = 25	n = 13	n = 5	n = 22	0.040*
	30.0 (19.5-43.5)	15.0 (10.0-33.0)	27.5 (11.0-40.0)	11.0 (10.0-13.0)	30.0 (19.0-48.5)	
[f]CRP	n = 89	n = 25	n = 13	n = 5	n = 23	0.209
	1.0 (0.6-1.7)	0.9 (0.6-1.2)	0.8 (0.5-1.1)	0.7 (0.6-0.7)	0.8 (0.7-1.4)	
[g]RF	n = 77	n = 21	n = 9	n = 5	n = 20	0.009*
	18.1 (8.9-47.0)	7.0 (4.1-15.0)	12.0 (7.0-17.6)	6.7 (4.9-13.4)	4.7 (3.0-39.0)	

n, number; [a]UWS, unstimulated whole saliva; [b]SWS, stimulated whole saliva; [c]UWS-P, unstimulated whole saliva after taking pilocarpine; [d]SWS-P, stimulated whole saliva after taking pilocarpine; [e]ESR, erythrocyte sedimentation rate; [f]CRP, C-reactive protein; [g]RF, rheumatoid factor.

* *p*-value calculated using the Kruskal-Wallis test at α=0.05.

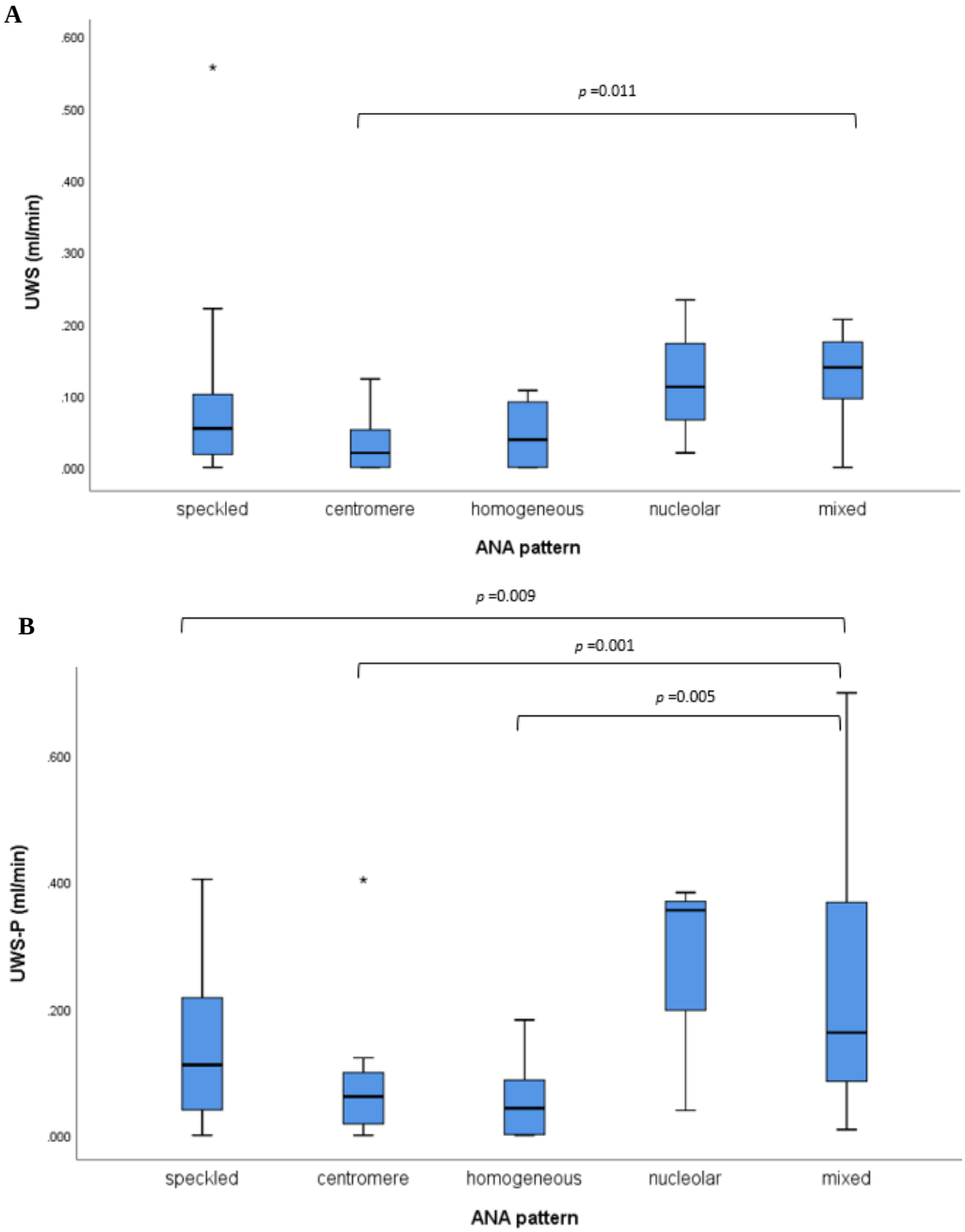

Figure 5. UWS, UWS-P in patients with pSS according to ANA pattern

A. UWS in patients with pSS according to ANA pattern

B. UWS-P in patients with pSS according to ANA pattern

Ⅳ. DISCUSSION

Previous studies on SS have mainly focused on the types, frequency, and severity of related diseases. However, there have been no studies on the autoantibody of SS and the salivary flow rate. Thus, this study was performed to examine the association between the autoantibody types of pSS and salivary gland hypofunction.

In this study, anti-Ro/SSA positive patients showed higher levels of RF than anti-Ro/SSA negative patients. Anti-La/SSB positive patients showed lower UWS, SWS, and higher levels of ESR and RF compared to anti-La/SSB-negative patients. In addition, patients with both anti-Ro/SSA and anti-La/SSB antibodies showed lower UWS compared to patients with only anti-Ro/SSA antibodies. This suggests that the presence of anti-La/SSB may decrease salivary gland function.

Meanwhile, Patients with both anti-Ro/SSA and anti-La/SSB antibodies had higher levels of ESR and RF than patients with only anti-Ro/SSA antibodies or patients without any of them. There were no statistically significant differences in SWS, UWS-P, SWS-P, and CRP regardless of the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies. In other words, the presence of anti-Ro/SSA and/or anti-La/SSB antibodies was associated with a significantly elevated ESR and RF. Specifically, when anti-Ro/SSA was present, RF levels were significantly high, and when anti-La/SSB was present, ESR and RF levels were significantly high.

Similarly, in a study by Park et al. (2019), anti-Ro/SSA negative patients showed less RF and leukopenia than patients who were positive for anti-Ro/SSA antibodies (Park et al., 2019). Malik et al. (2007) also found that patients with lupus, an autoimmune disease such as SS, who were positive for both anti-Ro/SSA and anti-La/SSB antibodies were about two times more likely to have arthritis as compared with patients with anti-Ro alone (Malik et al., 2007). In addition, Cafaro et al. (2020)

reported that anti-La/SSB-positive patients had higher levels of circulating immunoglobulins and RF (Cafaro et al., 2020).

In this study, patients with subjective improvement after taking pilocarpine also showed objective improvement in unstimulated/stimulated whole saliva compared to patients without subjective improvement after taking pilocarpine. However, there were no statistically significant differences in UWS-P(d) and SWS-P(d) regardless of the presence or absence of anti-Ro/SSA and anti-La/SSB antibodies.

Finally, UWS, UWS-P, SWS-P, ESR and RF was significantly different according to ANA pattern. Patients with mixed type had higher UWS those with centromere type. Patients with mixed type had higher UWS-P levels than patients with speckled, centromere, and homogeneous types. There were no statistically significant differences in CRP, SWS, and SWS-P.

Anti-La/SSB was not included in the 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for SS (Shiboski et al., 2017). According to our study, hyposalivation was more severe, and ESR and RF level were more elevated when anti-La/SSB was present in patients with pSS. In the case of prolonged hyposalivation, which is one of the main symptoms of SS, oral diseases such as multiple dental caries and candidiasis may frequently occur (Cartee et al., 2015; López-Pintor et al., 2015). Therefore, it is crucial to check the degree of salivation in patients with SS. As the role of anti-La/SSB has been highlighted in several studies covering autoimmune disease such as lupus and SS, it seems important to perform anti-La/SSB in laboratory test for the diagnosis of SS, even if anti-La/SSB status was excluded from the recent classification criteria for SS. Additionally, although not included in this study, there was one patient with anti Ro-negative/La-positive, who was diagnosed with SS after MSGB. From this, it can be inferred that anti-La/SSB plays an important role in the diagnostic criteria for SS.

Therefore, it is recommended that SS is diagnosed by performing MSGB in patients with suspicious SS considering the anti-La/SSB status.

Our study has several limitations. It did not include anti Ro-negative/La-positive group and did not analyze the association with MSGB results and salivary gland function because of relatively small sample size. Thus, further prospective studies are needed to compare anti-Ro-negative/La-positive group and those of both negative group to increase analytical power. Prospective studies are also needed to assess the correlation between MSGB and autoantibodies, and to analyze salivary gland hypofunction in the pSS group with both MSGB and laboratory tests, including anti-Ro/SSA and anti-La/SSB. As few studies have investigated the association between salivary gland function and ANA pattern or that have assessed the severity of pSS according to the ANA pattern, it will be helpful in predicting the prognosis of the disease if further studies are performed in larger sample sizes.

In conclusion, UWS and SWS were lower when anti-La/SSB was positive showing that anti-La/SSB is more likely to be involved in salivary gland hypofunction than anti-Ro/SSA in patients with pSS. Therefore, performing laboratory tests, including anti-La/SSB, is helpful in predicting the prognosis related to salivary gland function in patients with suspected pSS.

V. CONCLUSION

1. There were 191 subjects, 190 females (99.5%) and one male (0.5%), with a mean age of 60.8. Anti-Ro/SSA positive patients showed higher levels of RF than anti-Ro/SSA negative patients. ($p < 0.001$) Anti-La/SSB-positive patients showed lower UWS and SWS, and higher levels of ESR and RF compared to anti-La/SSB-negative patients.
($p = 0.032$, $p = 0.020$, $p = 0.001$, $p < 0.001$, respectively)

2. Patients with both anti-Ro/SSA and anti-La/SSB antibodies showed lower UWS than those with only anti-Ro/SSA antibodies ($p = 0.014$). Patients with both anti-Ro/SSA and anti-La/SSB antibodies had higher ESR and RF levels than patients with only anti-Ro/SSA antibodies or patients without any of them.

3. Patients with subjective improvement after taking pilocarpine showed objective improvement in unstimulated/stimulated whole saliva compared to patients without subjective improvement after taking pilocarpine. ($p = 0.001$ and $p < 0.001$, respectively)

4. Patients with mixed type had higher UWS those with centromere type ($p = 0.011$). Patients with mixed type had higher UWS-P levels than patients with speckled, centromere, and homogeneous type. ($p = 0.009$, $p = 0.001$, and $p = 0.005$, respectively)

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Abstract (in Korean)

일차성 쇼그렌 증후군 환자에서 자가 항체 종류와 타액선 기능 저하와의 상관관계

< 지도교수 안 형 준 >

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김 복 음

본 연구는 일차성 쇼그렌증후군 환자의 자가 항체 종류와 타액선 기능 저하와의 관련성을 확인하기 위해 시행하였다. 2010년 1월 1일부터 2021년 5월 31일까지 연세대학교 치과대학병원 구강내과를 방문한 환자 중 일차성 쇼그렌증후군으로 진단된 총 191명 (여성: 190명, 남성: 1명)의 환자를 대상으로 후향적 연구를 시행하였다. 쇼그렌증후군 진단 기준으로는 2002년 미국-유럽 공동 제안 분류를 사용하였다. 191명의 환자 중 50명은 항SSA, 항SSB가 모두 양성이었고, 97명은 항SSA는 양성, 항SSB는 음성이었다. 44명의 환자는 항SSA, 항SSB가 모두 음성이었고, 소타액선 생검을 통하여 쇼그렌증후군으로 확진하였다. 항SSA가 양성인 환자 군은 항SSA가 음성인 환자 군들에 비해 높은 류마토이드 인자(RF) 수치를 보였다. 항SSB가 양성인 환

자 군은 항SSB가 음성인 환자 군들에 비해 비자극성, 자극성 타액 분비율이 낮았고, 적혈구 침강 속도(ESR)와 류마토이드 인자(RF)는 높게 나타났다. 항SSA, 항SSB가 모두 양성인 환자 군은 항SSA만 양성인 환자 군에 비해 낮은 비자극성 타액 분비율을 보였다. 그러나 상기 환자 군에서 필로카핀 복용 후 비자극성, 자극성 타액 분비율, C-반응성 단백질(CRP)은 유의할 만한 상관관계가 확인되지 않았다. 일차성 쇼그렌증후군 환자에서 항SSB가 양성인 환자 군에서 음성인 환자 군에 비해 비자극성, 자극성 타액 분비율의 저하가 관찰되었다. 즉, 일차성 쇼그렌증후군 환자에서 항SSB가 항SSA보다 타액선 기능 저하와 관련성이 있을 것으로 보인다. 따라서 쇼그렌증후군이 의심되는 환자에서 항SSB를 포함한 자가 항체 검사를 시행하는 것이 타액선 기능과 관련된 예후를 예측하는데 도움이 될 것으로 보인다.

핵심어 : 쇼그렌증후군; 자가 항체; 항SSA; 항SSB; 구강건조증