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Original Article

Clinical characteristics of chronic sclerosing sialadenitis as a distinctive entity from primary Sjögren's syndrome

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Objective: This study aimed to elucidate the clinical and laboratory differences between chronic sclerosing sialadenitis (CSS) and primary Sjögren's syndrome (pSS), highlighting CSS as a distinct pathological entity within the spectrum of salivary gland pathology.

Methods: This retrospective, single-center study was conducted at Seoul St. Mary's Hospital between January 2000 and December 2022. Patients diagnosed with CSS via salivary gland biopsy were included, and those with IgG4-related disease (IgG4-RD) or other confounding factors were excluded. Clinical and laboratory CSS profiles were compared with those of a control group of patients with typical pSS from the Korean Initiative of Primary Sjögren's Syndrome (KISS) prospective cohort study. Twenty-one with CSS and 501 patients with pSS from Seoul St. Mary's Hospital were retrospectively analyzed.

Results: Patients with CSS were older at diagnosis, had a lower prevalence of ocular symptoms, and exhibited distinct immunological markers compared to those with pSS. Logistic regression analysis revealed that anti-Ro antibody positivity, elevated erythrocyte sedimentation rate levels, low serum complement 3 levels, and accompanying dry eye symptoms were factors distinguishing pSS from CSS.

Conclusion: Even after excluding IgG4-RD, CSS was significantly different from pSS in terms of clinical and laboratory findings. Recognition of these differences is crucial for the accurate diagnosis and management of CSS, underscoring its status as a distinct pathological entity among salivary gland pathologies.

Keywords: Chronic sclerosing sialadenitis, Küttner's tumor, Sjögren's syndrome, Immunoglobulin G4-related disease

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a chronic, progressive autoimmune disorder characterized primarily by lymphoplasmacytic infiltration of the exocrine glands, with specific emphasis on the salivary and lacrimal glands [1]. This pathological infiltration results in classic sicca symptoms due to decreased saliva and tear production. Although these symptoms are central to pSS, their clinical spectrum is broad and, includes manifestations such as salivary gland hypertrophy, cutaneous dryness, arthralgia, peripheral neuropathy, fatigue, interstitial lung disease, and myositis [2-5].

The diagnostic criteria for pSS have evolved [2,6-8]. The most current classification, introduced in 2016 by the American College of Rheumatology (ACR) in collaboration with the European Alliance of Associations for Rheumatology (EULAR), mandates either a positive result from a labial salivary gland biopsy or the presence of anti-Ro (SSA) antibodies [9]. Differen-

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tial diagnosis of pSS involves ruling out several conditions such as age-related dryness, eosinophilic sialodochitis, benign lymphoepithelial lesions, dacryoadenitis, sarcoidosis, graft-versus-host disease (GVHD), sequelae of head and neck radiation, and immunoglobulin G4 (IgG4)-related disease (IgG4-RD) [10-13].

Although the diagnostic criteria are comprehensive, certain clinical entities introduce ambiguity when establishing a diagnosis of pSS. Among these, chronic sclerosing sialadenitis (CSS), initially described by H. Küttner in 1896, stands out as a relatively rare salivary gland disorder distinguished by several specific features [14-19]. The diagnosis of CSS is indicated by its distinctive pathological characteristics, which include lymphocytic inflammation, the formation of lymphoid follicles, periductal lymphocytic infiltration leading to duct dilation and hyperplasia, and significant fibrosis of the gland. These changes result in cirrhosis and further hyperplasia, yet they occur without any malignant traits [16,20]. Although CSS is primarily known to involve major salivary glands, there are reports of CSS findings in minor salivary glands, which complicates the differentiation of Sjögren's syndrome through minor salivary gland biopsy [21-23].

Numerous studies have revealed potential correlations between CSS and IgG4-RD, with some categorizing CSS as a manifestation within the IgG4-RD continuum [24-27]. Nevertheless, there remains a faction of CSS diagnoses devoid of any evident IgG4-RD association.

The exact role of CSS in pSS pathogenesis remains controversial, often complicating the diagnostic processes, particularly in patients presenting with xerostomia. Considering these complexities, our study aimed to elucidate the clinical ramifications of CSS within the pSS landscape. Through a comparative analysis of the clinical and laboratory profiles of CSS and pSS, we aimed to accentuate the distinctiveness of CSS as a salient pathological variant in the gamut of salivary gland pathologies.

MATERIALS AND METHODS

Study population

This was a single-center, retrospective study. The included patients were confirmed to have CSS based on pathological results via salivary gland biopsy at Seoul St. Mary's Hospital between January 2000 and December 2022. Exclusion criteria were as follows: (1) patients who had a history of radiation in the head and neck area, (2) those diagnosed with GVHD, (3) those with IgG4-RD or showing positivity for IgG4 on immunohistochemistry (IHC) staining in biopsy, and (4) those who had insufficient pathologic results to distinguish IgG4-RD from CSS. The inclusion and exclusion criteria are presented in Table 1. During the data collection period, 2,606 minor salivary gland biopsies with confirmed pathologic reports were performed at the hospital. Twenty-seven patients showed CSS findings on biopsy. Of these 27 patients, 21 were eligible for inclusion in our analysis. The excluded patients comprised four with positivity for IgG4 on IHC staining, one with GVHD, and one with a history of head and neck radiation for brain tumor treatment. Thus, in the context of this study, CSS refers exclusively to diagnoses from which IgG4-RD has been excluded.

The control group, comprising patients with typical pSS, was selected from the Korean Initiative of Primary Sjögren's Syndrome (KISS) prospective cohort study. A nationwide database was established to provide the overall clinical data and samples of patients with pSS in Korea. Informed consent was obtained from all participants in the cohort, in accordance with the principles of the Declaration of Helsinki. Between October 2013 and July 2017, 501 patients with pSS were recruited from 12 university hospitals in Korea, including Seoul St. Mary's Hospital [28,29].

After examining whether the candidates met the classification criteria for other connective tissue diseases, experienced rheumatologists ruled out patients with secondary cases that might be combined with other systemic autoimmune diseases,

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Pathologic confirm of CSS via salivary gland biopsy in Seoul St. Mary's Hospital
2. Duration of retrospective chart analysis: from January 2000 to December 2022
Exclusion criteria
1. History of radiation on head and neck area
2. Diagnosed with GVHD
3. Having IgG4-RD or showing positivity in IgG4 with IHC staining in biopsy
4. Insufficient pathologic result to distinguish IgG4-RD from CSS

CSS subjects who met any exclusionary parameters upon comprehensive evaluation were omitted from the analysis. CSS: chronic sclerosing sialadenitis, GVHD: graft-versus-host disease, IgG4-RD: immunoglobulin G4-related disease, IgG4: immunoglobulin G4, IHC: immunohistochemistry.

such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. Additional exclusion criteria were a history of head and neck radiation, chronic hepatitis C or human immunodeficiency virus infection, prior lymphoproliferative disease, sarcoidosis, GVHD, amyloidosis, and IgG4-RD. Finally, 160 patients were excluded from the study [30-34].

Owing to the time of enrolment, some applicants just required to meet at least one of the following old classifications: the 2012 ACR criteria or the 2002 American-European Consensus Group categorization criteria [7,8]. Considering the inclusion criteria used to enroll the KISS cohort, we reassessed 239 of 341 patients who (1) were eligible for 2016 ACR-EULAR classification and (2) satisfied the salivary gland biopsy results [9]. Figure 1 shows the schematic process of the inclusion and exclusion of the study population. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital of the Catholic University of Korea (KC23RISI0017).

Assessment of clinical and laboratory findings of pSS and CSS

The EULAR Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient-reported index (ESSPRI) were used to evaluate the severity of pSS [35,36]. CSS were assessed as equivalent to those with pSS by reviewing their medical records. Extraglandular manifestations (EGMs) were also described [37]. The presence of anti-nuclear antibodies (ANA) and rheumatoid factor (RF) was evaluated using an indirect immunofluorescence assay on HEp-2 cells and an immunoturbidimetric assay, respectively. The positivity of ANA and RF had cut-off values of 1:320 or more and 20 IU/mL or more,

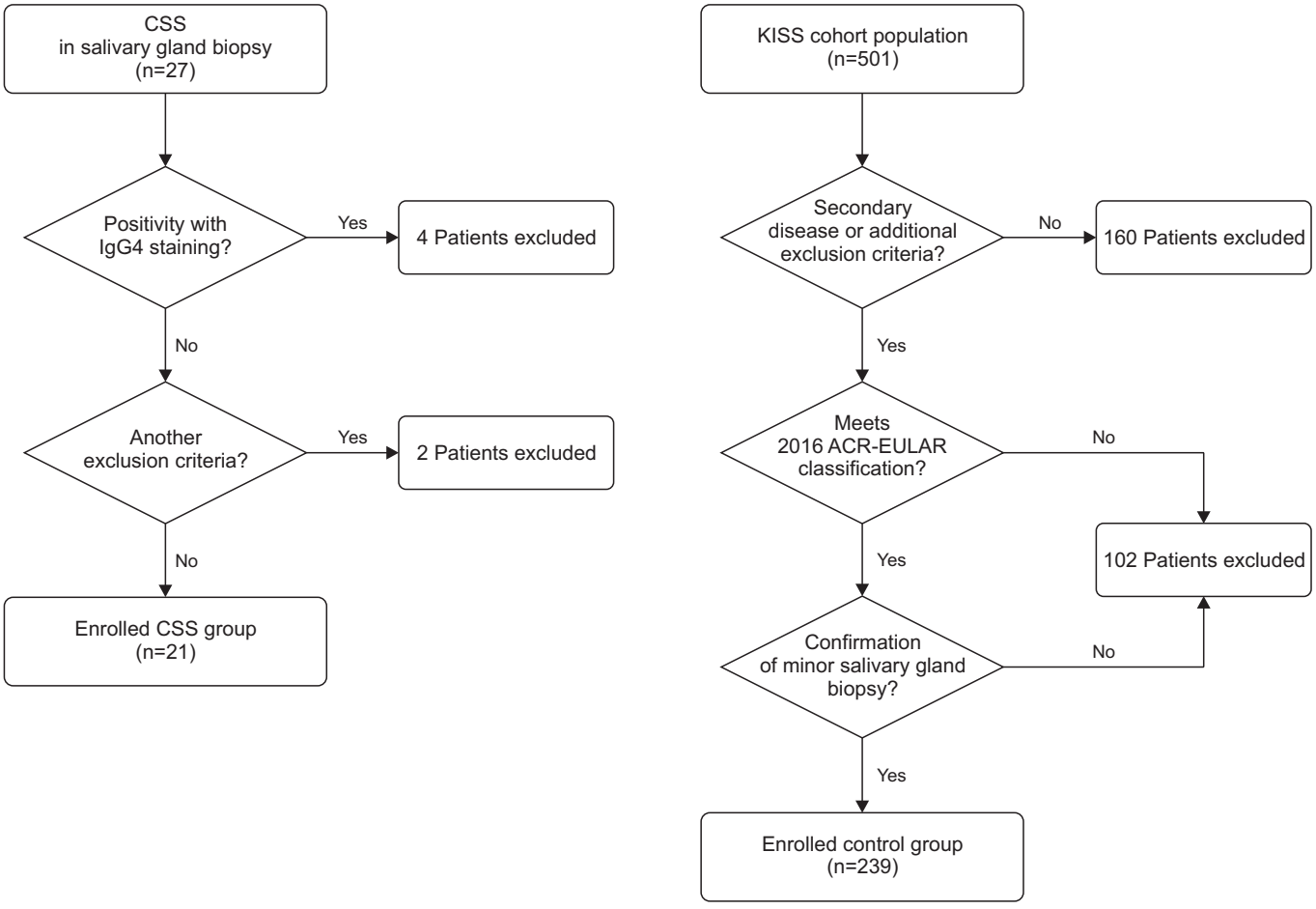

Figure 1. Schematic representation of study population composition. Total 260 patients (21 of CSS group and 239 of typical pSS group from KISS cohort) were enrolled. CSS: chronic sclerosing sialadenitis, pSS: primary Sjögren's syndrome, IgG4: immunoglobulin G4, KISS cohort: Korean Initiative of Primary Sjögren's Syndrome cohort, ACR: American College of Rheumatology, EULAR: European Alliance of Associations for Rheumatology.

Table 2. Baseline characteristics of CSS and pSS

	CSS (n=21)	pSS (n=239)	n	p-value
Female	19 (90.48%)	237 (99.16%)	260	0.034
Age at diagnosis (yr)	61.90±9.48	50.63±12.22	260	<0.001
BMI (kg/m^2)	22.06±3.70 21.76 [20.31, 23.73]	22.15±2.93 21.88 [20.00, 23.63]	260	0.843
Smoking history			211	0.222
Non-smoker	19 (90.48%)	176 (92.52%)		
Current smoker	2 (9.52%)	5 (2.69%)		
Ex-smoker	0 (0.00%)	5 (2.69%)		
Sicca symptom				
Dry eye	15 (71.43%)	223 (93.30%)	260	0.004
Dry mouth	18 (85.71%)	227 (94.98%)	260	0.110
Diagnostic items for pSS*				
Minor salivary gland biopsy	0 (0.00%)	215 (89.95%)	260	<0.001
Anti-Ro (SSA) Ab	2 (10.00%)	185 (84.09%)	240	<0.001
Schirmer test	1 (14.29%)	169 (72.22%)	241	0.003
Ocular staining score	0 (0.00%)	64 (43.24%)	155	0.042
Decreased uSFR	15 (78.95%)	78 (82.10%)	114	0.750
uSFR (mL/min)	0.08±0.10 0.04 [0.02, 0.09]	0.10±0.19 0.05 [0.00, 0.10]	107	0.856
sSFR (mL/min)	0.65±0.57 0.44 [0.28, 0.92]	0.54±1.15 0.20 [0.20, 0.20]	103	0.001
EGMs	0.38±0.67 0.00 [0.00, 1.00]	1.08±1.03 1.00 [0.00, 2.00]	260	0.001
ESSDAI	1.05±2.48 0.00 [0.00, 0.50]	3.05±3.69 1.00 [0.00, 5.00]	259	<0.001
ESSPRI	4.78±1.57	5.41±1.84	206	0.131
ANA*	9 (45.00%)	165 (89.19%)	205	<0.001
Titer	220±560 80 [0, 180]	610±670 400 [160, 800]	204	<0.001
Anti-La (SSB) Ab	1 (8.33%)	112 (51.14%)	231	0.010
RF*	4 (22.22%)	125 (65.79%)	208	0.001
Serum level (IU/mL)	11.95±18.69	98.88±206.24	208	<0.001
ACPA (IU/mL)	0.17±0.28	23.19±82.36	200	<0.001
Cryoglobulin	0 (0.00%)	7 (4.14%)	174	>0.999
β2-microglobulin (μg/mL)	1.78±0.41 1.72 [1.69, 1.72]	1.98±0.78 1.92 [1.49, 2.19]	82	0.510
Hypergammaglobulinemia*	1 (16.67%)	89 (46.84%)	196	0.221
Serum IgG (mg/dL)	1395.33±169.22 1322.50 [1280.00, 1476.00]	1756.57±708.63 1522.50 [1311.00, 2007.00]	196	0.162
Hypocomplementemia*	1 (5.00%)	91 (42.92%)	232	0.002
C3 (mg/dL)	103.25±11.98	92.87±16.60	232	0.007
C4 (mg/dL)	25.31±0.00 26.90 [20.50, 30.35]	23.78±13.57 22.35 [18.10, 26.95]	232	0.094
CH50 (U/mL)	56.35±4.31 56.35 [53.30, 59.40]	55.30±10.40 55.25 [49.05, 60.40]	190	0.811
WBC count (×10^9/L)	6.11±2.21 5.48 [4.64, 6.69]	5.10±2.08 4.61 [3.90, 5.74]	249	0.017
Leukopenia*	2 (10.00%)	61 (26.64%)	249	0.170

Table 2. Continued

	CSS (n=21)	pSS (n=239)	n	p-value
ANC count (×10^9/L)	3.57±1.51 3.21 [2.36, 4.49]	2.90±1.85 2.52 [1.90, 3.30]	247	0.010
Neutropenia*	0 (0.00%)	20 (8.81%)	247	0.384
Hb (g/dL)	13.33±0.79 13.30 [12.60, 13.90]	12.78±1.19 12.90 [12.00, 13.70]	249	0.051
Hct (%)	40.36±2.68 40.25 [38.65, 41.95]	41.33±33.75 38.60 [36.10, 40.60]	249	0.008
Anemia*	0 (0.00%)	52 (22.71%)	249	0.010
Platelet count (×10^9/L)	225.60±60.25 233.00 [185.50, 267.50]	225.39±54.23 219.00 [187.00, 260.00]	249	0.725
Thrombocytopenia*	2 (10.00%)	14 (6.11%)	249	0.375
ESR (mm/hr)	9.38±10.33 7.00 [5.00, 11.00]	28.96±21.43 24.00 [13.00, 38.50]	244	<0.001
CRP (mg/dL)	0.11±0.15 0.05 [0.03, 0.12]	0.31±1.28 0.07 [0.03, 0.28]	243	0.274
AST (IU/L)	21.85±7.23 21.00 [17.50, 23.00]	25.63±30.59 22.00 [18.00, 26.00]	247	0.333
ALT (IU/L)	23.85±8.38 23.00 [18.00, 27.50]	20.82±15.62 17.00 [13.00, 23.00]	247	0.006
BUN (mg/dL)	13.02±3.41 12.80 [10.95, 15.15]	12.99±4.14 12.20 [10.20, 15.10]	244	0.596
Cr (mg/dL)	0.73±0.11 0.71 [0.68, 0.78]	0.73±0.14 0.71 [0.65, 0.80]	245	0.887
CPK (IU/L)	76.33±29.97 70.00 [61.00, 88.00]	94.92±199.38 69.00 [51.00, 96.00]	223	0.873
LDH (IU/L)	361.11±161.37 364.00 [180.00, 444.00]	315.16±125.93 316.50 [216.00, 393.00]	230	0.195
Fasting glucose (mg/dL)	106.95±26.51 100.50 [93.00, 106.00]	96.16±24.98 92.00 [88.00, 99.00]	245	0.004
Total cholesterol (mg/dL)	189.37±37.42	172.78±33.07	238	0.039
HDL (mg/dL)	50.20±15.09 43.00 [40.00, 58.00]	53.17±15.59 52.00 [41.00, 61.00]	173	0.657
LDL (mg/dL)	103.06±34.94 104.50 [81.00, 129.00]	102.09±25.43 100.00 [82.00, 116.00]	206	0.755
Triglyceride (mg/dL)	111.53±58.64 97.00 [64.50, 161.50]	98.89±53.07 87.00 [67.00, 119.00]	212	0.439
Free T4 (ng/dL)	1.25±0.24 1.22 [1.14, 1.28]	1.17±0.30 1.10 [0.99, 1.27]	181	0.061
TSH (μIU/mL)	2.39±1.67 2.06 [1.30, 3.07]	2.52±2.08 2.70 [1.27, 3.12]	193	0.989
Albuminuria	0 (0.00%)	19 (8.64%)	232	0.606
Hematuria	3 (23.08%)	37 (16.82%)	233	0.472

In both groups, significant differences were observed in terms of sex and age at the time of diagnosis, with no consideration for interactions between these variables and others in this table. The results expressed with mean±standard deviation in continuous variable with normality. In case of non-normal variables with failure to normality test, additional median (25% quantile, 75% quantile) was also presented. Categorical variables are shown as number (percentile). P-value less than 0.05 was set to be statistically significant. CSS: chronic sclerosing sialadenitis, pSS: primary Sjögren's syndrome, N: numbers, BMI: body mass index, uSFR: unstimulated salivary flow rate, sSFR: stimulated salivary flow rate, EGMs: extraglandular manifestations, ESSDAI: EULAR Sjögren's syndrome disease activity index, ESSPRI: EULAR Sjögren's syndrome patient-reported index, EULAR: European Alliance of Associations for Rheumatology, ANA: anti-nuclear antibody, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, C3: complement 3, C4: complement 4, CH50: 50% hemolytic complement, WBC: white blood cell count, ANC: absolute neutrophil count, Hb: hemoglobin, Hct: hematocrit, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, Cr: creatinine, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone. *Only counted in case of excessing cut-off value or positivity result.

respectively. Anti-neutrophil cytoplasmic antibodies (ANCA) were measured using commercial enzyme-linked immunosorbent assays without subtyping each possible subset of autoantibodies. The profile of all extractable nuclear antigen antibodies was determined using line immunoassay (post-December 27, 2019) or fluoro-enzyme immunoassay (prior to December 27, 2019).

We assessed complete blood counts (white blood cell counts [WBC], absolute neutrophil counts, hemoglobin and hematocrit [Hct], platelet counts), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine (Cr), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), cryoglobulin, β2-microglobulin, IgG, complement 3 (C3), complement 4 (C4), and measurement of 50% hemolytic complement activity (CH50). We also obtained the patient's age at the time of pSS or CSS diagnosis, height, weight, sicca symptoms, Schirmer test results, ocular staining results, unstimulated salivary flow rate (uSFR), and stimulated salivary flow rate (sSFR). Lipid profiles, which included total cholesterol (TC), directly measured high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG) levels, as well as thyroid function tests, which included free T4 (fT4) and thyroid stimulating hormone (TSH) levels, were considered as baseline characteristics. Owing to the possibility of a gap between the calculated and measured HDL levels, the calculated HDL levels were not used in this study.

The autoimmune profiles included ANA titer, anti-cyclic citrullinated protein (CCP) antibody (ACPA), anti-Ro (SSA), anti-La (SSB), anti-centromere, anti-topoisomerase, anti-RNP, anti-Jo-1, and anti-double-stranded DNA (dsDNA) antibodies. Almost all patients were evaluated and followed up at the outpatient clinic, and the interval of effective study was set at 2 months from the time of confirmation of pSS or CSS.

Statistical analysis

Considering the limited size of the CSS group, all statistical analyses incorporated the Shapiro–Wilk normality test to confirm the normality of the data distribution. Continuous variables, represented as mean and standard deviation (SD), were assessed using the Student's t-test in cases of normality and the Wilcoxon rank-sum test in cases of non-normality. For categorical variables that were presented with additional medians and interquartile ranges (IQR), we employed Fisher's exact test and Pearson's chi-squared test with Yates's continuity correction. The statistical analysis was carried out using R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria) and R Studio (version 2021.09.2+382, "Ghost Orchid" Release for Windows; R Foundation for Statistical Computing, Vienna, Austria). A p less than 0.05 indicated of statistical significance.

Our primary aim was to identify variables that show notable differences between CSS and pSS. Nevertheless, our analysis encountered challenges owing to the scarcity of CSS cases and the retrospective study design. These difficulties included issues related to missing data and the presence of numerous variables that did not adhere to the assumptions of normality. Consequently, careful consideration of statistical methodologies is essential.

As mentioned earlier, only 27 patients have had CSS in our hospital for more than two decades because of the rarity of CSS. Therefore, data on some variables was lacking. Owing to the difficulty of statistical analysis, we opted for multiple imputations using chained equations (MICE). We set a cutoff value of less than 20% for the proportion of missing data for MICE. This approach enabled us to effectively address the missing data and enhance the quality of our analysis.

We designed a logistic regression analysis using significant variables to investigate the differences between CSS and pSS. In light of overdispersion and constraints on data quantity, we initially conducted a regression analysis employing a quasibinomial approach. The selection of variables was guided by the results of an all-subset regression analysis. The logistic model was evaluated by using the confusion matrix method.

RESULTS

Baseline characteristics

The CSS and pSS groups were distinct as shown in Table 2. The CSS group exhibited a lower proportion of female individuals (90.47% in CSS and 99.16% in pSS, p=0.034), older age at the time of diagnosis (61.90±9.48 in CSS and 50.63±12.22 in pSS, p<0.001), and a lower prevalence of ocular symptoms (71.43% in CSS and 93.30% in pSS, p=0.004) when compared to the pSS group. In the context of the 2016 ACR-EULAR classification criteria, we observed significant differences in most diagnostic items between the two groups. The pSS group displayed a higher incidence of anti-Ro antibody positivity (10.00% in CSS and 84.09% in pSS, p<0.001) and positive Schirmer test results

(14.29% in CSS and 72.22% in pSS, p=0.003), whereas the CSS group did not meet the diagnostic criteria for the ocular staining score (0.00% in CSS and 43.24% in pSS, p=0.042). Moreover, we identified a significant difference only in the sSFR (CSS: 0.44 [0.28, 0.92] mL/min; pSS: 0.20 [0.20, 0.20] mL/min; p=0.001), where the pSS exhibited markedly lower values.

Regarding EGMs (0.00 [0.00, 1.00] in CSS and 1.00 [0.00, 2.00] in pSS, p=0.001) and ESSDAI scores (0.00 [0.00, 0.50] in CSS and 1.00 [0.00, 5.00] in pSS, p<0.001), statistically significant disparities were observed between the two groups. However, statistical significance was not achieved in the case of ESSPRI scores (4.78±1.57 in CSS and 5.41±1.84 in pSS, p=0.131). In our analysis of autoimmune profiles, various variables exhibited significant differences between the groups. Notably, we found significant differences in several key factors, including the prevalence and titers of ANA positivity (45% in CSS and 89.19% in pSS, p<0.001) and titer (220±560 in CSS and 610±670 in pSS, p<0.001), the presence of anti-La (SSB) antibodies (8.33% in CSS and 51.14% in pSS, p=0.010), the positivity (22.22% in CSS and 65.79% in pSS, p=0.001) and serum levels (11.95±18.69 IU/mL in CSS and 98.88±206.24 IU/mL in pSS, p<0.001) of RF, the serum level of anti-CCP antibodies (0.17±0.28 IU/mL in CSS and 23.18±82.36 IU/mL in pSS, p<0.001), and notably, a higher proportion of hypocomplementemia in pSS (5.00% in CSS and 42.92% in pSS, p=0.002), particularly with regards to serum C3 levels (103.25±11.98 mg/dL in CSS and 92.87±16.60 mg/dL in pSS, p=0.007)

Laboratory findings revealed that WBC (6.11±2.21×10^9/L in

Table 3. Comparison of clinical and laboratory features of two groups, assuming that CSS is indicative of pSS

	CSS as pSS (n=15)	pSS (n=239)	n	p-value
Female	15 (100.0%)	237 (99.2%)	254	>0.999
Age at diagnosis (yr)	64.1±6.8	61.9±9.5	254	<0.001
BMI (kg/m^2)	21.6±3.2	22.2±2.9	254	0.873
Sicca symptom				
Dry eye	11 (73.3%)	223 (93.3%)	254	0.022
Dry mouth	13 (86.7%)	227 (95.0%)	254	0.196
Diagnostic items for pSS				
Salivary gland biopsy	None	215 (90.0%)	None	
Anti-Ro (SSA) Ab	1 (6.7%)	185 (84.1%)	235	<0.001
Schirmer test	1 (25.0%)	169 (72.2%)	238	0.072
Ocular staining score	0 (0.0%)	64 (43.2%)	152	0.139
uSFR abnormality	15 (100.0%)	78 (82.1%)	110	0.121
uSFR (ml/min)	0.035±0.033	0.10±0.19	103	0.311
EGMs	0.4±0.7	1.1±1.0	254	0.006
ESSDAI	1.3±2.8	3.1±3.7	254	0.005
ESSPRI	4.6±1.7	5.4±1.8	200	0.004
ANA	8 (53.3%)	165 (89.2%)	200	0.001
Titer	280±640	610±670	199	<0.001
Anti-La (SSB) Ab	0 (0.0%)	112 (51.1%)	228	0.003
RF	4 (28.6%)	125 (65.8%)	204	0.012
Titer	14.8±20.4	98.9±206.2	204	0.001
ACPA	0.1±0.3	23.2±82.4	199	<0.001
sSFR (ml/min)	0.50±0.41	0.54±1.15	99	0.006

Even when considering CSS as indicative of pSS, it is evident that there are differences in various clinical manifestations and autoimmune profiles between the two. The results were demonstrated as mean±standard deviation for continuous variables that exhibited a normal distribution. For non-normally distributed variables, median (25th percentile, 75th percentile) values were included. Categorical variables were represented as counts (percentages). Statistical significance was considered at a p-value below 0.05. CSS: chronic sclerosing sialadenitis, pSS: primary Sjögren's syndrome, N: numbers, BMI: body mass index, uSFR: unstimulated salivary flow rate, EGMs: extraglandular manifestations, ESSDAI: EULAR Sjögren's syndrome disease activity index, ESSPRI: EULAR Sjögren's syndrome patient-reported index, EULAR: European Alliance of Associations for Rheumatology, ANA: anti-nuclear antibody, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, sSFR: stimulated salivary flow rate.

CSS and 5.10±2.08×10^9/L in pSS, p=0.017) and absolute neutrophil (ANC) counts (3.21 [2.36, 4.49]×10^9/L in CSS and 2.52 [1.90, 3.30]×10^9/L in pSS, p=0.008) were significantly lower in the pSS group. Nevertheless, the prevalence of leukopenia (CSS: 10.00%, pSS: 26.64%; p=0.170) and neutropenia (CSS: 0.00%, pSS: 8.81%; p=0.384) did not differ significantly between the two groups. Although no significant differences were observed in hemoglobin levels (13.30 [12.60, 13.90] g/dL in CSS and 12.90 [12.00, 13.70] g/dL in pSS, p=0.051), Hct values were lower in the pSS cohort (40.25 [38.65, 41.95]% in CSS and 38.60 [36.10, 40.60]% in pSS, p=0.008), and the prevalence of anemia was higher (0.00% in CSS and 22.71% in pSS, p=0.010). The ESR was also higher in the pSS group (7.00 [5.00, 11.00] mm/h in the CSS group and 24.00 [13.00, 38.50] mm/h in the pSS group; p<0.001) than that in the CSS group. However, the statistical values for Hct and ESR did not account for potential interactions with sex or age. Furthermore, we identified significant distinctions in serum ALT levels (23.00 [18.00, 27.50] IU/L in CSS and 17.00 [13.00, 23.00] IU/L in pSS, p=0.006), fasting glucose (100.50 [93.00, 106.00] mg/dL in CSS and 92.00 [88.00, 99.00] mg/dL in pSS, p=0.004), and TC levels (189.37±37.42 mg/dL in CSS and 172.78±33.07 mg/dL in pSS, p=0.039) between the two cohorts.

For further analysis, we selectively reanalyzed patients in the pSS group with a focus score of less than 1 on minor salivary gland biopsy and conducted a subgroup analysis. The results are presented in Appendix 1. While most variables continued to show significant differences, significant disparities in female sex, ocular staining score, serum C3 levels, anemia, serum ALT levels, and WBC were lost. However, leukopenia emerged as a new statistically significant variable. To date, no adjustments have been made for interactions between variables, and statistical adjustments for these interactions will be addressed in the subsequent regression analysis stage when interpreting the table.

Distinguishing CSS from pSS

Assuming that CSS qualifies for inclusion in the salivary gland biopsy component of the 2016 ACR-EULAR classification criteria with a score of 3 points, we also explored distinctions in other factors between pSS and CSS. Under this assumption, among the 21 CSS cases re-evaluated, 15 individuals were eligible for classification under the 2016 ACR-EULAR classification criteria. We proceeded to investigate whether there were any significant differences between pSS and CSS cases, focusing not only on pathological differences but also on other aspects.

The two groups exhibited similar baseline clinical characteristics, as shown in Table 3. Importantly, statistically significant differences were observed in terms of age at diagnosis (64.1±6.8 in CSS and 61.9±9.5 in pSS, p<0.001); ocular dryness symptoms (73.3% in CSS and 93.3% in pSS, p=0.022); Anti-Ro antibody positivity (6.7% in CSS and 84.1% in pSS, p<0.001); EGMs (0.4±0.7 in CSS and 1.1±1.0 in pSS, p<0.001); ESSDAI (1.3±2.8 in CSS and 3.1±3.7 in pSS, p=0.005); ESSPRI (4.6±1.7 in CSS and 5.4±1.8 in pSS, p=0.004); ANA positivity (53.3% in CSS and 89.2% in pSS, p=0.001) and titers (280±640 in CSS and 610±670 in pSS, p<0.001); RF positivity (28.6% in CSS and 65.8% in pSS, p=0.012) and titers (14.8±20.4 IU/mL in CSS and 98.9±206.2 IU/mL in pSS, p=0.001); ACPA titer (0.1±0.3 IU/mL in CSS

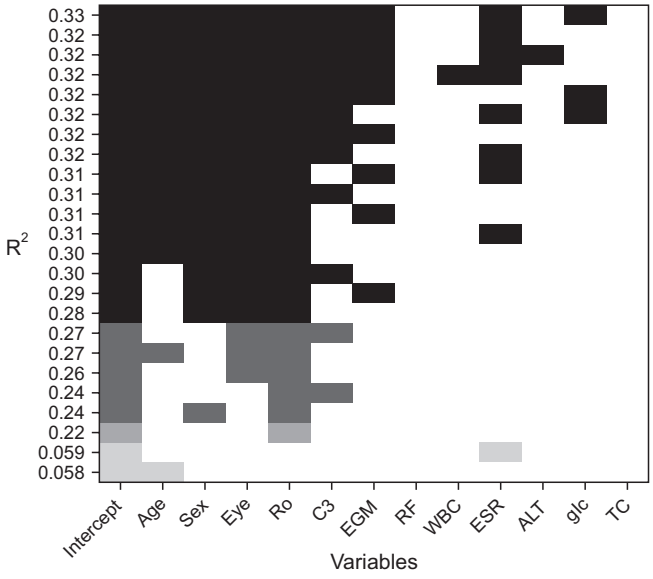

Figure 2. Result of all-subset regression. Utilizing the imputed dataset, an all-subset regression analysis was conducted to identify variables with the highest explanatory power. The horizontal line represents the variables in all-subset regression. The vertical line indicates the value of R square. Known interactions between ESR and hematocrit, as well as between WBC count and absolute neutrophil count, were taken into consideration within the framework of the all-subset regression analysis. In the context of the all-subset regression, ESR and ANC were chosen as variables for analysis, while acknowledging their interactions with Hct and WBC, respectively. Additionally, during the all-subset regression analysis, the interaction between ESR and age at diagnosis was also incorporated into the analysis. Age: age at diagnosis, Eye: ocular symptoms, Ro: anti-Ro antibody positivity, C3: low serum C3, EGM: extraglandular manifestation, RF: rheumatoid factor, WBC: leukopenia, ESR: erythrocyte sedimentation rate, glc: serum fasting glucose level, TC: serum total cholesterol.

and 23.2±82.4 IU/mL in pSS, p<0.001); and sSFR (0.50±0.41 mL/min in CSS and 0.54±1.15 mL/min in pSS, p=0.006). These findings suggest that CSS exhibits distinct clinical and laboratory features compared with pSS.

We conducted additional regression analyses based on the results from Table 2 to confirm the significant differences between CSS and pSS. Owing to the rarity of CSS, managing missing data is challenging because of small sample sizes. Thus, we employed MICE for variables with missing values below 20%. Variables not suitable for MICE were removed, and associations such as ESR with Hct and WBC count with ANC were incorporated. All-subset regression analysis of the imputed dataset identified several key variables that distinguish CSS from pSS. These variables include age at diagnosis, sex, anti-Ro antibody positivity, ocular symptoms, low serum C3 levels, EGMs, high ESR levels, high serum glucose levels, leukopenia, and high ALT levels. The explanatory power of the model reached a maximum of 0.33. The results of this regression analysis are presented in Figure 2.

Based on the outcomes of the all-subset regression, multivariate logistic regression analysis was conducted, selecting variables such as age at diagnosis, sex, ocular symptoms, anti-Ro positivity, serum C3 levels, ESR, EGMs, serum glucose levels, serum ALT levels and WBC. Nonsignificant variables identified from the regression results were excluded by step-backward method, leading to the formulation of the final regression equation presented in Table 4.

In the logistic regression analysis, odds ratios (ORs) were calculated based on the regression equation for the final logistic equation: anti-Ro positivity, high plasma ESR levels, low serum C3 levels, dry eye symptom. The ORs for each variable, along with their corresponding 95% confidence intervals (CI) and p-values, were as follows: anti-Ro positivity, 0.03 (95% CI: 0.01~0.17, p<0.001); ESR levels, 0.87 (95% CI: 0.80~0.95, p=0.002); serum C3, 1.06 (95% CI: 1.02~1.11, p=0.004); and dry eye symptom, 0.06 (95% CI: 0.01~0.52, p=0.011). The detailed results are shown in Table 4.

To assess the effectiveness of the final regression equation derived from logistic regression analysis, a confusion matrix was used for evaluation. The confusion matrix showed a sensitivity of 0.71, specificity of 0.98, positive predictive value (PPV) of 0.78, and negative predictive value (NPV) of 0.95. The confusion matrix achieved the statistical significance (p=0.005 for accuracy over the no information rate [NIR]). However, the McNemar's test and Kappa value were not statistically significant (p for McNemar's test=0.75, kappa=0.73).

DISCUSSION

The pSS presents with a spectrum of clinical manifestations ranging from sicca symptoms to systemic involvement. However, the diagnosis of pSS can be challenging because of its heterogeneous presentation and overlapping features with those of other autoimmune conditions. In this study, we aimed to elucidate the clinical and laboratory differences between CSS and pSS to enhance our understanding of CSS within the landscape of salivary gland pathology.

The evolution of the classification criteria for pSS, particularly the 2016 ACR-EULAR classification criteria, has facilitated a more accurate diagnosis and classification of patients with sicca symptoms. However, our study highlights the diagnostic challenges associated with CSS, particularly especially in differentiating it from pSS. Despite the exclusion criteria, including IgG4-RD and other confounding factors, CSS remains a diagnostic dilemma because of its overlapping features and histopathological similarities to pSS.

Immunological markers, such as anti-Ro antibodies and serum complement levels have emerged as potential biomarkers for distinguishing CSS from pSS. Our study corroborates previ-

Table 4. The result of logistic regression

	Estimate	SE	z	p>|z|	OR	LCL	UCL	p-value	VIF
(Intercept)	−2.322	2.323	−1.000	0.318	0.10	0.00	9.31	0.318	None
Dry eye	−2.860	1.128	−2.535	0.011	0.06	0.01	0.52	0.011	1.289
Anti-Ro positivity	−3.388	0.834	−4.065	<0.001	0.03	0.01	0.17	<0.001	1.308
Serum C3 levels	0.061	0.021	2.895	0.004	1.06	1.02	1.11	0.004	1.197
ESR levels	−0.135	0.044	−3.070	0.002	0.87	0.80	0.95	0.002	1.171

The final logistic regression analysis present significant differences in characteristics of CSS from pSS. CSS: chronic sclerosing sialadenitis, pSS: primary Sjögren's syndrome, SE: standard error, z: z-score, OR: odd ratio, LCL: lower confidence limit, UCL: upper confidence limit, VIF: variation inflation factor, C3: complement 3, ESR: erythrocyte sedimentation rate.

ous findings indicating a lower prevalence of anti-Ro antibodies and hypocomplementemia in patients with CSS than those in patients with pSS. These markers not only aid in the differential diagnosis but also provide insights into the underlying immunopathogenesis of CSS.

In this study, significant differences between CSS and pSS were elucidated through clinical evidence using rigorous statistical methods. The findings notably highlighted that the following factors were more strongly associated with CSS compared to pSS: (1) absence of anti-Ro antibodies, (2) normal ESR levels, (3) normal serum C3 levels, and (4) absence of ocular manifestations.

While our study provides valuable insights into the clinical distinctions between CSS and pSS, this retrospective, single-center study based on a medical record review has several limitations that warrant consideration. The retrospective design may have influenced the generalizability of our findings. Additionally, the exclusion of IgG4-RD and other confounding factors may have inadvertently biased the results.

The small sample size of patients with CSS, stemming from the extreme rarity of CSS with only 27 cases identified over 20 years, significantly limited the available data for statistical analysis [14]. Despite minor salivary gland biopsies uncovering only 2,606 confirmed instances of CSS in suspected pSS cases over more than 20 years, the utilization of MICE was introduced to address this limitation. Although the use of MICE in clinical data may be a subject of debate, recent studies have demonstrated its validity even in the context of more prevalent diseases [38,39]. Given the challenges posed by exceedingly rare diseases, such as CSS, and the lack of alternative methodological approaches, the application of MICE was justified to enable meaningful statistical analysis.

Certain variables, including Schirmer test positivity, OSS, ANA, ACPA, anti-La, and decreased sSFR, were omitted from the statistical analysis. Nevertheless, these clinical parameters showed statistically significant differences between CSS and pSS in the baseline study, underscoring the importance of accounting for their influence. Comprehensive data acquisition is imperative to fully address this issue.

While this single-center study design may introduce bias, its significance lies in its execution within one of Korea's premier tertiary hospitals, exemplifying the apex of the medical delivery system and the leading tier among university-affiliated hospitals. Nonetheless, discernible disparities between pSS and CSS persist, necessitating additional multicenter studies to develop a larger CSS cohort and mitigate potential biases.

Our findings underscore the importance of recognizing CSS as a pathological entity distinct from pSS. Despite previous associations between CSS and pSS, our study revealed notable differences in the clinical and laboratory profiles between these conditions. Notably, CSS patients exhibited older at diagnosis and had a lower prevalence of ocular symptoms than those with pSS. These findings suggest that CSS represents a distinct subset within the spectrum of salivary gland disorders, warranting careful consideration during clinical evaluation and management.

Effectiveness analysis of the regression equation, including the confusion matrix and McNemar's test, did not show any statistical significance. However, there was an extremely limited number of patients with CSS, and the p-value for NIR were showed statistical significance, which is required to meet the 95% CI. This is likely owing to the small size of the data in patients with CSS, which weakened the statistical power [40].

Importantly, failure to confirm the regression equation does not imply a lack of distinction between pSS and CSS. Assuming that CSS corresponds with the pathological findings of pSS, many laboratory and clinical differences exist between the two conditions, indicating that they cannot be regarded as the same disease.

Future research should focus on elucidating the underlying pathophysiology of CSS, exploring novel diagnostic modalities, and refining diagnostic criteria to improve the accuracy of CSS diagnosis. Our study underscores the clinical and laboratory differences between CSS and pSS, emphasizing the importance of recognizing CSS as a distinct pathological entity within the spectrum of salivary gland pathologies. By enhancing our understanding of CSS, we can improve diagnostic accuracy, optimize patient management, and pave the way for targeted therapeutic interventions for this understudied condition.

CONCLUSION

Even when IgG4-RD is excluded, CSS exhibits pathophysiological characteristics that are distinct from those of pSS across various clinical and laboratory findings. These differences are particularly significant in terms of anti-Ro antibody positivity, ESR levels, serum C3 levels, ocular manifestations, and other parameters.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

E.J.K. and J.H.J. devised the project, the main conceptual ideas and proof outline. E.J.K. worked out all the technical details and performed the numerical suggested statistical analysis. Y.P. refined the KISS cohort data for analysis. E.J.K. and S.K.K. wrote the manuscript. All of authors reviewed the manuscript and agreed the content.

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Appendix 1. Subgroup analysis of CSS and pSS cases with a focus score less than 1

	CSS (n=21)	pSS with FS<1 (n=24)	n	p-value
Female	19 (90.48%)	24 (100.00%)	45	0.210
Age at diagnosis (yr)	62.00 [56.00, 59.00]	56.00 [46.50, 63.00]	45	0.020
BMI (kg/m^2)	21.76 [20.31, 23.73]	22.86 [21.66, 23.39]	45	0.590
Smoking history				
Non-smoker	19 (90.48%)	24 (100.00%)		
Current smoker	2 (9.52%)	0 (0.00%)	45	0.210
Ex-smoker	0 (0.00%)	0 (0.00%)		
Sicca symptom				
Dry eye	15 (71.49%)	23 (95.83%)	45	0.039
Dry mouth	18 (85.71%)	24 (100.00%)	45	0.094
Diagnostic items for pSS*				
Anti-Ro (SSA) Ab	2 (10.00%)	24 (100.00%)	44	<0.001
Schirmer test	1 (14.29%)	23 (95.83%)	31	<0.001
Ocular staining score	0 (0.00%)	9 (40.91%)	29	0.066
Decreased uSFR	15 (78.95%)	12 (85.71%)	33	>0.999
uSFR (mL/min)	0.08±0.10 0.04 [0.02, 0.09]	0.04 [0.00, 0.08]	33	0.645
sSFR (mL/min)	0.65±0.57 0.44 [0.28, 0.92]	0.20 [0.20, 0.20]	32	0.001
EGMs	0.38±0.67 0.00 [0.00, 1.00]	1.08±1.04 1.00 [0.00, 2.00]	45	0.004
ESSDAI	1.05±2.48 0.00 [0.00, 0.50]	2.00 [0.00, 5.50]	44	0.018
ESSPRI	4.78±1.57	5.43±1.53	45	0.165
ANA*	9 (45.00%)	17 (78.48%)	39	0.009
Titer	220±560 80 [0, 180]	400 [150, 1200]	39	0.001
Anti-La (SSB) Ab	1 (8.33%)	15 (62.50%)	36	0.006
RF*	4 (22.22%)	14 (60.87%)	41	0.031
Serum level (IU/mL)	11.95±18.69 4.15 [2.00, 12.10]	98.88±206.24 30.30 [10.00, 61.95]	41	0.002
ACPA (IU/mL)	0.17±0.28 0.00 [0.00, 0.50]	2.00 [1.20, 5.00]	32	<0.001
Cryoglobulin	0 (0.00%)	1 (5.00%)	25	>0.999
β2-microglobulin (μg/mL)	1.78±0.41	1.79±0.39	11	0.949
Hypergammaglobulinemia*	1 (16.67%)	9 (39.13%)	29	0.633
Serum IgG (mg/dL)	1395.33±169.22 1322.50 [1280.00, 1476.00]	1756.57±708.63 1360.00 [1147.50, 2075.50]	29	0.813
Hypocomplementemia*	1 (5.00%)	8 (33.33%)	44	0.027
C3 (mg/dL)	103.25±11.98	96.52±14.08	44	0.099
C4 (mg/dL)	25.31±0.00 26.90 [20.50, 30.35]	23.78±13.57 27.60 [22.40, 31.30]	44	0.311
CH50 (U/mL)	56.35±4.31 56.35 [53.30, 59.40]	55.30±10.40 56.80 [51.00, 62.50]	23	0.956
WBC count (×10^9/L)	6.11±2.21 5.48 [4.64, 6.69]	5.10±2.08 4.58 [3.72, 5.62]	44	0.077
Leukopenia*	2 (10.00%)	10 (41.67%)	44	0.045
ANC count (×10^9/L)	3.57±1.51 3.21 [2.36, 4.49]	3.11±2.52 2.32 [1.89, 3.12]	43	0.030
Neutropenia*	0 (0.00%)	0 (0.00%)	43	
Hb (g/dL)	13.33±0.79 13.30 [12.60, 13.90]	12.78±1.19 12.90 [12.00, 13.80]	44	0.273

Appendix 1. Continued

	CSS (n=21)	pSS with FS<1 (n=24)	n	p-value
Hct (%)	40.36±2.68	38.10±4.12	44	0.041
Anemia*	0 (0.00%)	5 (20.83%)	44	0.053
Platelet count (×10^9/L)	225.60±60.25	236.75±69.23	44	0.576
Thrombocytopenia*	2 (10.00%)	2 (8.33%)	44	>0.999
ESR (mm/hr)	9.38±10.33 7.00 [5.00, 11.00]	28.96±21.43 26.00 [13.50, 45.00]	44	<0.001
CRP (mg/dL)	0.11±0.15 0.05 [0.03, 0.12]	0.31±1.28 0.05 [0.03, 0.13]	45	0.795
AST (IU/L)	21.85±7.23 21.00 [17.50, 23.00]	25.63±30.59 23.000 [19.50, 25.50]	44	0.167
ALT (IU/L)	23.85±8.38 23.00 [18.00, 27.50]	20.82±15.62 18.00 [15.00, 26.00]	44	0.233
BUN (mg/dL)	13.02±3.41 12.80 [10.95, 15.15]	12.99±4.14 12.30 [10.85, 14.60]	43	0.961
Cr (mg/dL)	0.73±0.11	0.72±0.12	44	0.613
CPK (IU/L)	76.33±29.97	88.60±40.39	40	0.091
LDH (IU/L)	361.11±161.37 364.00 [180.00, 444.00]	315.16±125.93 365.50 [266.00, 441.00]	42	>0.999
Fasting glucose (mg/dL)	106.95±26.51 100.50 [93.00, 106.00]	96.16±24.98 92.00 [88.00, 99.00]	44	0.021
Total cholesterol (mg/dL)	189.37±37.42	171.06±38.18	41	0.130
HDL (mg/dL)	50.20±15.09 43.00 [40.00, 58.00]	53.17±15.59 53.50 [40.50, 60.50]	21	0.772
LDL (mg/dL)	103.06±34.94	100.11±35.62	37	0.436
Triglyceride (mg/dL)	111.53±58.64	108.20±46.77	39	0.845
Free T4 (ng/dL)	1.25±0.24 1.22 [1.14, 1.28]	1.17±0.30 1.15 [1.05, 1.32]	35	0.377
TSH (μIU/mL)	2.39±1.67	2.17±1.54	38	0.671
Albuminuria	0 (0.00%)	1 (4.17%)	36	>0.999
Hematuria	3 (23.08%)	4 (16.67%)	37	0.678

The result of subgroup analysis with no consideration for interactions between these variables and others was demonstrated in this table. The results expressed with mean±standard deviation in continuous variable with normality. In case of non-normal variables with failure to normality test, additional median (25% quantile, 75% quantile) was also presented. Categorical variables are shown as number (percentile). P-value less than 0.05 was set to be statistically significant. CSS: chronic sclerosing sialadenitis, pSS: primary Sjögren's syndrome, N: numbers, BMI: body mass index, uSFR: unstimulated salivary flow rate, sSFR: stimulated salivary flow rate, EGMs: extraglandular manifestations, ESSDAI: EULAR Sjögren's syndrome disease activity index, ESSPRI: EULAR Sjögren's syndrome patient-reported index, EULAR: European Alliance of Associations for Rheumatology, ANA: anti-nuclear antibody, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, C3: complement 3, C4: complement 4, CH50: 50% hemolytic complement, WBC: white blood cell count, ANC: absolute neutrophil count, Hb: hemoglobin, Hct: hematocrit, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, ALT: alanine transaminase, BUN: blood urea nitrogen, Cr: creatinine, CPK: creatine phosphokinase, LDH: lactate dehydrogenase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone.*Only counted in case of excessing cut-off value or positivity result.