

Original Article
Immunology, Allergic
Disorders & Rheumatology



The Prevalence of Sjögren's Syndrome in Rheumatoid Arthritis Patients and Their Clinical Features

Hyoungyoung Kim ,¹ Soo-Kyung Cho ,¹ Hye Won Kim ,¹ Jungyong Han ,¹ Yujeong Kim ,² Kyung-Gyun Hwang ,³ and Yoon-Kyoung Sung ¹

¹Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea

²Department of Ophthalmology, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea

³Division of Oral & Maxillofacial Surgery, Department of Dentistry, Hanyang University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: May 30, 2020

Accepted: Sep 1, 2020

Address for Correspondence:

Yoon-Kyoung Sung, MD, PhD, MPH

Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, 222-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea.

E-mail: sungyk@hanyang.ac.kr

© 2020 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Hyoungyoung Kim

<https://orcid.org/0000-0003-1415-461X>

Soo-Kyung Cho

<https://orcid.org/0000-0003-4493-8837>

Hye Won Kim

<https://orcid.org/0000-0001-9270-3800>

Jungyong Han

<https://orcid.org/0000-0002-0196-9038>

Yujeong Kim

<https://orcid.org/0000-0003-4375-1472>

Kyung-Gyun Hwang

<https://orcid.org/0000-0002-8713-660X>

Yoon-Kyoung Sung

<https://orcid.org/0000-0001-6691-8939>

ABSTRACT

Background: To estimate the prevalence of Sjögren's syndrome (SS) in patients with rheumatoid arthritis (RA) and to compare the clinical features of RA patients with and without SS.

Methods: We conducted a retrospective study of RA patients who visited a rheumatology clinic in a tertiary referral hospital in Korea between May 20 and July 22, 2016. All patients fulfilled the classification criteria for RA, and the diagnosis of SS was made clinically by rheumatologists and according to the 2002 American-European Consensus Group (AECG), 2012 American College of Rheumatology (ACR), and 2016 ACR/European League Against Rheumatism (EULAR) classification criteria. The prevalence was estimated as the number of SS patients within the total number of RA patients. The disease activity and treatment pattern of RA were compared between patients with and without SS.

Results: Among 827 RA patients, 72 patients (8.7%) were diagnosed with SS by a rheumatologist, though only 60 patients (7.3%) satisfied the 2002 AECG classification criteria for SS. Fifty-two patients (6.3%) and 56 patients (6.8%) fulfilled the 2012 ACR and 2016 ACR/EULAR classification criteria, respectively. The prevalence of SS in RA patients was 10.5%, 17.0%, and 67.6% in rheumatoid factor, antinuclear antibody ($\geq 1:80$), and anti-Ro antibody positive patients, respectively.

Conclusion: The prevalence of SS among RA patients was 8.7% according to rheumatologists' diagnosis. The presence of SS did not affect the treatment patterns of RA patients. However, the autoantibody profiles and demographics of RA patients with SS differed from those of patients without SS.

Keywords: Epidemiology; Prevalence; Sjögren's Syndrome; Rheumatoid Arthritis

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease that involves exocrine glands with inflammatory infiltrates and leads to hypo-function of the salivary and lacrimal glands. One third of patients present with fatigue, arthralgia, myalgia, depression, or systemic extra-

Funding

This study was funded by Eisai Korea Inc. (2016).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Sung YK. Data curation: Kim HY, Cho SK, Kim HW, Han JW, Kim Y, Hwang KG, Sung YK. Formal analysis: Kim HY, Kim HW. Methodology: Cho SK, Sung YK. Writing - original draft: Kim HY. Writing - review & editing: Cho SK, Sung YK.

glandular inflammatory involvement of the lung, musculoskeletal, or neurologic system.¹ SS patients also have a higher risk of other comorbidities, including non-Hodgkin lymphoma, compared with the general population.²

SS is closely associated with other autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). In previous studies, the prevalence of SS in SLE patients ranged from 9% and 19%.³⁻⁵ The prevalence of SS among RA patients has been reported to be as high as 55%.⁶ Those reports estimated prevalence using rheumatologists' diagnoses, the 1993 European Classification criteria, and the 2002 American-European Consensus Group (AECG) classification criteria for SS. Discrepancies in the prevalence of SS among RA patients were caused by the use of different classification criteria for diagnosis.

Previous studies indicated that the coexistence of RA and SS could result in more severe arthritis with worse joint damage than is typical with RA alone,⁷ as well as a higher rate of systemic involvement through anemia and lung function changes.⁸ Other studies have shown that having both SS and RA increased the risk of non-Hodgkin's lymphoma and higher mortality compared to those with RA alone.^{9,10} However, no research has adequately examined the prevalence and clinical effects of SS on RA disease activity and treatment. Indeed, there have been insufficient studies on the prevalence of disease-specific autoantibodies among RA patients with SS, even though the positivity of autoantibody profiles of primary SS patients were already investigated in other studies.^{11,12}

Therefore, we aimed to estimate the prevalence of SS in RA patients according to various classification criteria for SS as well as specific autoantibodies and to compare the clinical features and treatment patterns of RA patients with and without SS.

METHODS

Study population

We conducted a retrospective study of RA patients who visited a rheumatology clinic in a tertiary referral hospital in Korea between May 20 and July 22, 2016. They were all adult patients aged over 20 and met the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA. In addition, all RA patients who visited the clinic during the study period had previously been screened for SS by asking about the presence of any sicca symptoms. If they agreed, patients who reported sicca symptoms received diagnostic tests for SS (a screen for autoantibodies, labial salivary gland biopsy, salivary scintigraphy, Schirmer's test, or ocular staining) prior to the registration period. Subject medical records were reviewed retrospectively to determine the presence of SS as judged by clinical impressions, clinical symptoms, and diagnostic tests.

Prevalence of SS in RA patients

The prevalence of SS among RA patients was first estimated using rheumatologists' clinical diagnoses. Rheumatologists diagnosed SS in patients with compatible symptoms or signs of SS and results from SS diagnostic tests. Then, the patients the rheumatologists diagnosed with SS were reassessed to determine whether they fulfilled the 2002 AECG,¹ 2012 ACR,¹³ or 2016 ACR/EULAR classification criteria.¹⁴ We also estimated the prevalence of SS in RA patients who reported any sicca symptoms.

As subgroup analyses, we estimated the prevalence of SS in RA patients with rheumatoid factor (RF) antibodies, anti-nuclear antibodies (ANAs), or anti-Ro antibodies.

Clinical characteristics of RA patients with SS

The clinical characteristics and treatment patterns of RA patients with and without SS were compared. RA disease activity was assessed using the Disease Activity Score 28 (DAS28)-erythrocyte sedimentation rate (ESR), and laboratory findings for RF, anti-cyclic citrullinated peptide antibody, ESR, and C-reactive protein. The treatment patterns for RA were investigated in terms of the medications prescribed to control disease activity, including conventional synthetic and biologic disease modifying antirheumatic drugs (DMARDs).

Statistical analysis

The prevalence of SS was estimated as the number of RA patients who were diagnosed with SS within the total number of RA patients. We present the clinical characteristics of patients as the median with interquartile range (IQR) for continuous variables and as numbers with percentages (%) for categorical variables. We compared the clinical characteristics of RA between patients with and without SS using independent *t*-tests or χ^2 tests. Any *P* value less than 0.05 was regarded as statistically significant. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

Ethics statement

This study was approved by the Institutional Review Board of Hanyang University Hospital (HYUH 2016-03-040-021), and the need for informed consent was waived because the data were de-identified and collected retrospectively.

RESULTS

Baseline characteristics of the study population

We included 827 RA patients in this study (Fig. 1), and their overall clinical characteristics are provided in Table 1. Most RA patients were female (88.5%) and their median age was 52 years old, and the median duration of RA was 8.0 years (IQR 4.0–13.0). Their RA disease activity, estimated by median DAS28-ESR, was 2.6 (IQR 2.0–3.1). In terms of their treatments, methotrexate was the most frequently used DMARD (73.2%), followed by leflunomide (28.7%) and hydroxychloroquine (22.2%). Biologic DMARDs (bDMARDs) were used in 11.6% of RA patients, and most of them (86.5%) were tumor necrosis factor inhibitors.

Prevalence of SS in RA patients

Among the 827 RA patients, 72 patients (8.7%) were diagnosed with SS by rheumatologists (Fig. 2). Diagnostic tests for SS were suggested to all 72 patients, but they were only performed with patient agreement; minor salivary gland biopsy and salivary gland scintigraphy were performed in 57 and 66 patients, respectively (Table 2). Ocular staining, Schirmer's test, and the tear breakup test were performed in 58, 57, and 49 patients, respectively, with ocular symptoms. Sixty of the 827 RA patients (7.3%) satisfied the 2002 AECG classification criteria for SS. Fifty-two patients (6.3%) met the 2012 ACR classification criteria, and 56 patients (6.8%) fulfilled the 2016 ACR/EULAR classification criteria. The prevalence of SS tended to be higher among RA patients with sicca symptoms (Fig. 2). All the patients who received a salivary gland biopsy (*n* = 57) presented histologic findings

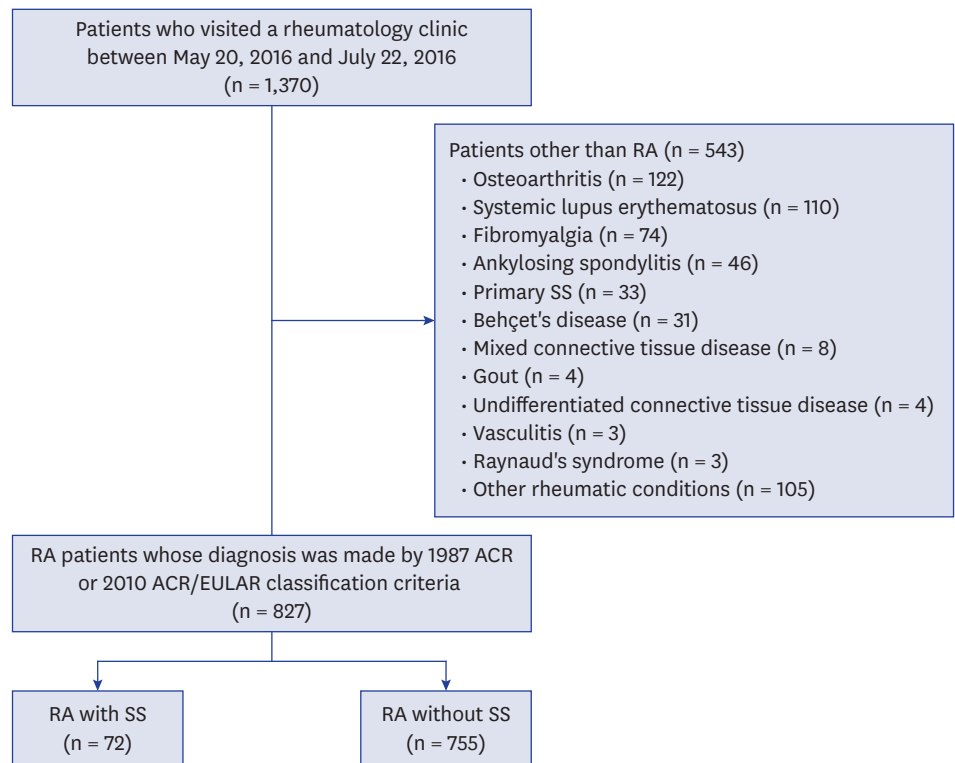


Fig. 1. Patient selection flow for patients with RA and coexisting SS.

RA = rheumatoid arthritis, SS = Sjögren's syndrome, ACR = American College of Rheumatology, EULAR = European League Against Rheumatism.

Table 1. Baseline characteristics of all RA patients in this study

Variables	Total RA patients (n = 827)
Sex, female	732 (88.5)
Age, yr	57.0 (46.0–66.0)
Disease duration of RA, yr (n = 773)	8.0 (4.0–13.0)
DAS28-ESR (n = 804)	2.6 (2.0–3.1)
Laboratory findings ^a	
RF positivity (n = 820)	581 (70.9)
Anti-CCP positivity (n = 802)	672 (83.8)
ANA titer ≥ 1: 80 (n = 827)	353 (42.7)
ESR, mm/hr (n = 816)	24.0 (11.0–43.0)
CRP, mg/dL (n = 816)	0.2 (0.2–0.6)
Medications	
Conventional synthetic DMARDs	
Methotrexate	605 (73.2)
Leflunomide	237 (28.7)
Hydroxychloroquine	184 (22.2)
Sulfasalazine	150 (18.1)
Tacrolimus	34 (4.1)
Biologic DMARDs	
TNF inhibitors	96 (11.6)
Non-TNF inhibitors	13 (1.6)
NSAIDs	510 (61.7)
Oral corticosteroids	365 (44.1)

Values are presented as number (%) or medians (interquartile ranges).

RA = rheumatoid arthritis, DAS28 = Disease Activity Score 28, ESR = erythrocyte sedimentation rate, anti-CCP = anti-cyclic citrullinated peptide antibody, ANA = anti-nuclear antibody, CRP = C-reactive protein, DMARDs = disease-modifying anti-rheumatic drugs, NSAIDs = non-steroidal anti-inflammatory drugs, TNF = tumor necrosis factor.

^aAutoantibody profiles were assessed close to the time of enrollment, and the levels of inflammatory markers were checked during the study period.

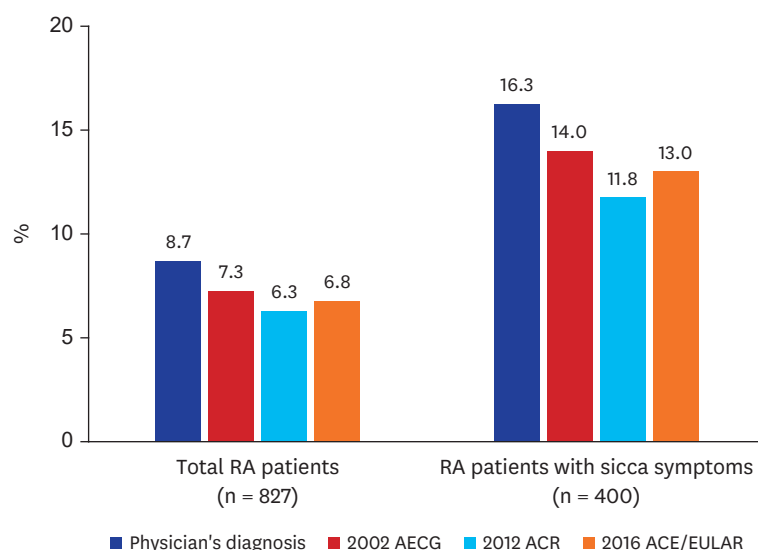


Fig. 2. Prevalence of Sjögren's syndrome in RA patients, overall and with sicca symptoms. RA = rheumatoid arthritis, AECG = American-European Consensus Group, ACR = American College of Rheumatology, EULAR = European League Against Rheumatism.

Table 2. Clinical characteristics of RA patients with SS

Variables	RA with SS (n = 72)
No. of patients satisfying diagnostic criteria for SS	
Rheumatologists' clinical diagnosis	72 (100.0)
2002 AECG criteria	60 (83.3)
2012 ACR classification criteria	52 (72.2)
2016 ACR/EULAR criteria	56 (77.8)
Glandular features	
Dry eye	56 (77.8)
Foreign body sensation in eye	12 (16.7)
Dry mouth	49 (68.1)
Objective gland functions	
No. of patients with ocular staining score ≥ 5 (n = 58) ^a	22 (37.9)
No. of patients with abnormal Schirmer's test (n = 57) ^a	24 (42.1)
No. of patients with abnormal TBUT (n = 49) ^a	47 (95.9)
TBUT, right	3.0 (2.0–3.5)
TBUT, left	3.0 (2.0–4.0)
No. of patients with focus score ≥ 1 in salivary gland biopsy (n = 57) ^a	57 (100)
No. of patients with abnormal salivary gland scintigraphy (n = 66) ^a	57 (86.4)

Values are presented as number (%) or median (interquartile ranges).

RA = rheumatoid arthritis, SS = Sjögren's syndrome, AECG = American-European Consensus Group, ACR = American College of Rheumatology, EULAR = European League Against Rheumatism, TBUT = tear breakup time.

^aThe number of patients whose lacrimal or salivary gland function was evaluated by specific test modalities.

compatible with SS (Table 2). Functional impairment of the salivary glands was found in 57 of the 66 patients who received the salivary gland scintigraphy test (86.4%).

Prevalence of SS in RA patients with specific antibodies

RF-positive RA patients

Most of the 820 RA patients were tested for RF, and 581 patients showed a positive result. Among the RF-positive RA patients (n = 581), 61 patients (10.5%) had rheumatologist-diagnosed SS (Fig. 3). Among the RF-negative RA patients (n = 239), only 11 patients (4.6%) had rheumatologist-diagnosed SS. According to the 2002 AECG classification criteria, 52 RF-positive patients (9.0%) had SS, and 48 (8.3%) and 47 RF-positive patients (8.1%) were diagnosed with SS based on the 2012 ACR and 2016 ACR/EULAR classification criteria, respectively.

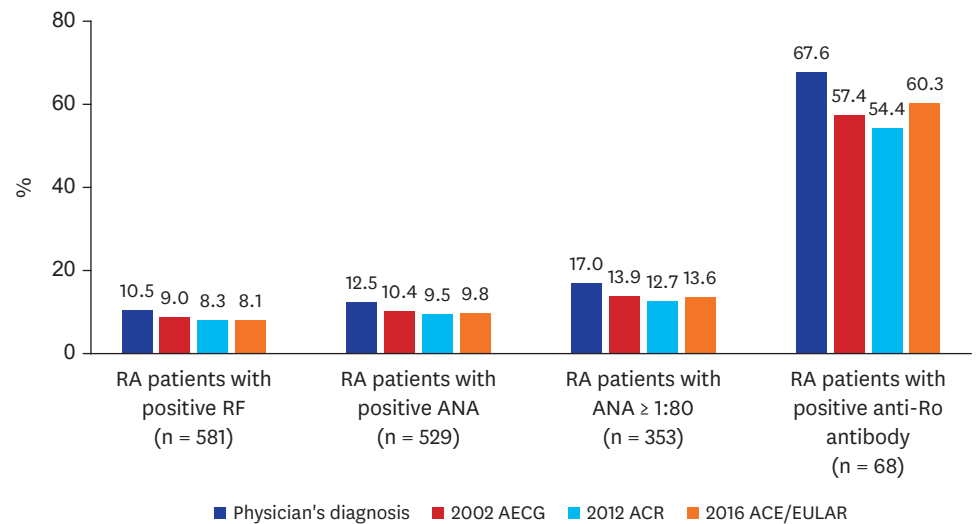


Fig. 3. Prevalence of Sjögren's syndrome in RA patients positive for specific autoantibodies. RA = rheumatoid arthritis, AECG = American-European Consensus Group, ACR = American College of Rheumatology, EULAR = European League Against Rheumatism, RF = rheumatoid factor, ANA = anti-nuclear antibody.

ANA-positive RA patients

Of the 827 RA patients, 686 received the ANA serologic test, and positive results were documented in 529 of them (77.1%) (Table 3). Among the 353 RA patients with ANA titers greater than or equal to 1:80, 60 (17.0%) had rheumatologist-diagnosed SS, and 49 (13.9%), 45 (12.7%), and 48 ANA-positive RA patients (13.6%) met the 2002 AECG, 2012 ACR, and 2016 ACR/EULAR classification criteria for SS, respectively (Fig. 3).

Anti-Ro antibody-positive RA patients

Among the 529 patients with positive ANA test results, 497 RA patients were tested for the anti-Ro antibody, and 68 (13.7%) patients tested positive. Among them, 46 (67.6%), 39 (57.4%), 37 (54.4%), and 41 (60.3%) patients (19.2%) were diagnosed with SS by a rheumatologist or the 2002 AECG, 2012 ACR, and 2016 ACR/EULAR classification criteria, respectively (Fig. 2). The other 22 RA patients who were positive for the anti-Ro antibody were not diagnosed with SS by rheumatologists.

Clinical characteristics of RA according to the presence of SS

Most RA patients were female, and the proportion of female patients did not differ among those with and without SS. Patients who had both RA and SS were younger than those without SS (median 52.0 [IQR 43.0–60.8] vs. 57.0 [IQR 46.0–66.0], $P = 0.005$). With regards to comorbidities, the prevalence of hypertension and diabetes mellitus was lower in the RA patients with SS than in those without SS (12.5% vs. 24.2%, $P = 0.024$ and 1.4% vs. 9.3%, $P = 0.023$, respectively).

RF-positivity was more common in RA patients with SS than in those without SS (84.7% vs. 69.5%, $P = 0.007$), and the prevalence of ANA (titers greater than or equal to 1:80) was also higher in RA patients with SS than in those without SS (83.3% vs. 47.7%, $P < 0.001$). Autoantibodies, the anti-Ro antibody (63.9% vs. 5.2%, $P < 0.001$) and anti-La antibody (33.3% vs. 1.6%, $P = 0.023$), were more frequently detected in RA patients with SS than in those without SS.

Sicca symptoms were more prevalent in RA patients with SS (90.3% vs. 46.3%, $P < 0.001$), and the most frequent sicca symptom was dry eye (77.8% vs. 34.1%, $P < 0.001$), followed by

Table 3. Comparison of clinical characteristics and treatment patterns of RA according to the presence of SS

Variables	RA with SS (n = 72)	RA without SS (n = 755)	P value
Sex, female	69 (95.8)	553 (80.2)	0.410
Age, yr	52.0 (43.0–60.8)	57.0 (46.0–66.0)	0.005
Comorbidity			
Hypertension	9 (12.5)	183 (24.2)	0.024
Diabetes mellitus without complication	1 (1.4)	70 (9.3)	0.023
Interstitial lung disease	1 (1.4)	33 (4.4)	0.352
Cancer	3 (4.2)	16 (2.1)	0.268
Lymphoma	0 (0.0)	1 (0.1)	NC
Other	19 (26.4)	244 (29.5)	0.302
Sicca symptoms			
Dry mouth (n = 72, 724) ^a	49 (68.1)	179 (24.7)	< 0.001
Dry eye (n = 72, 724) ^a	56 (77.8)	247 (34.1)	< 0.001
Foreign body sensation in eye (n = 72, 724) ^a	12 (16.7)	42 (5.8)	< 0.001
Disease duration of RA, yr (n = 70, 703) ^a	7.5 (3.0–14.0)	8.0 (4.0–13.0)	0.448
DAS28-ESR (n = 72, 732) ^a	2.8 (2.3–3.2)	2.6 (2.0–3.1)	0.050
Laboratory findings			
ANA positivity (n = 72, 614) ^a	66 (91.7)	463 (75.4)	0.002
ANA titer ≥ 1:80 (n = 72, 614) ^a	60 (83.3)	293 (47.7)	< 0.001
Anti-Ro antibody positivity (n = 72, 425) ^a	46 (63.9)	22 (5.2)	< 0.001
Anti-La antibody positivity (n = 72, 425) ^a	24 (33.3)	7 (1.6)	< 0.001
RF positivity (n = 72, 748) ^a	61 (84.7)	520 (69.5)	0.007
Anti-CCP positivity (n = 72, 730) ^a	66 (91.7)	606 (83.0)	0.057
ESR, mm/hr (n = 72, 744) ^a	31.0 (16.0–49.0)	23.0 (11.0–42.0)	0.030
CRP, mg/dL (n = 72, 744) ^a	0.2 (0.2–0.7)	0.2 (0.2–0.6)	0.966
Medications			
Conventional synthetic DMARDs	58 (80.6)	547 (72.5)	0.138
Methotrexate	23 (31.9)	214 (28.3)	0.519
Leflunomide	21 (29.2)	163 (21.6)	0.140
Hydroxychloroquine	15 (20.8)	135 (17.9)	0.535
Sulfasalazine	3 (4.2)	31 (4.1)	0.980
Tacrolimus	4 (5.6)	92 (12.2)	0.093
Biologic DMARDs			
TNF inhibitors	4 (5.6)	79 (10.5)	0.185
Non-TNF inhibitors	0 (0)	13 (1.7)	NC
NSAIDs	46 (63.9)	464 (61.5)	0.685
Oral corticosteroids	37 (51.4)	328 (43.4)	0.195

Values are presented as number (%) or median (interquartile ranges).

RA = rheumatoid arthritis, SS = Sjögren's syndrome, DAS28 = Disease Activity Score 28, ESR = erythrocyte sedimentation rate, ANA = anti-nuclear antibody, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide antibody, CRP = C-reactive protein, DMARDs = disease-modifying anti-rheumatic drugs, TNF = tumor necrosis factor, NSAIDs = non-steroidal anti-inflammatory drugs, NC = not calculated.

^aThe number of patients whose sicca symptoms or laboratory tests was evaluated according to the presence of SS.

dry mouth (68.1% vs. 24.7%, $P < 0.001$), and foreign body sensation in the eye (16.7% vs. 5.8%, $P < 0.001$). The use of bDMARDs was more frequent in patients without SS, whereas the use of conventional synthetic DMARDs, oral corticosteroids, and non-steroidal anti-inflammatory drugs was more frequent in those with SS. However, the overall treatment patterns for RA did not differ according to the presence of SS.

DISCUSSION

We estimated the prevalence of SS among 827 RA patients and found it to be 8.7% by rheumatologist diagnosis. Among those diagnosed by a rheumatologist, 60 patients (7.3%) satisfied the 2002 AECG classification criteria for SS, and 52 (6.3%) and 56 patients (6.8%) fulfilled the 2012 ACR and 2016 ACR/EULAR classification criteria, respectively. RA patients with SS had a higher rate of disease-specific autoantibodies (RF, ANA, and anti-

Ro antibodies) than those without SS. Their mean age was younger, and they had a lower prevalence of hypertension and diabetes mellitus than RA patients without SS. However, the presence of SS did not affect the treatment patterns or autoantibody profiles of RA patients.

The prevalence of SS among Korean RA patients was higher than reported in previous studies conducted in Denmark (3.6%) and Turkey (5.3%) and lower than reported for the USA (10.3%), China (14.5%), and Italy (17.5%).^{7,8,15-17} Study designs and definitions of SS could have affected previous estimates of SS prevalence among RA patients. The previous studies conducted in Denmark, USA, and Italy were cross-sectional, whereas those in Turkey and China were retrospective. For disease definition, the 2002 AECG criteria were used in the US and Chinese studies, whereas the studies in Denmark, Italy, and Turkey used clinical diagnoses. In Korea, another retrospective study reported that the sicca syndrome was the second most frequent extra-articular manifestation, with prevalence of 7.4% in RA patients.¹⁸ The results of that study were quite similar to ours, but we used a different definition of SS based on objective evidence of glandular dysfunction. In addition, we described the specific serologic profiles and detailed clinical features of SS.

Applying different classification criteria for SS affects the prevalence reported because each set of classification criteria uses distinct objective components, including serologic tests, glandular function tests, and histopathologic confirmation on salivary glands. The most current classification system (the 2016 ACR/EULAR criteria) includes anti-Ro antibody as an independent criterion of the highest weight, so it could be the crucial criterion for diagnosing SS because the summed weights must be \geq four.¹⁴ In our study, 16 patients did not meet the 2016 ACR/EULAR classification criteria despite having rheumatologist-diagnosed SS (**Supplementary Table 1**). All 16 of them underwent the anti-Ro antibody test, and 11 patients had negative results. Among those 11 anti-Ro antibody-negative patients, a minor salivary gland biopsy was not conducted in six patients, and the ocular staining test was not performed in two patients due to patient unwillingness. Thus, the low performance rate of an invasive procedure such a salivary gland biopsy might cause underestimation of SS prevalence according to the 2016 ACR/EULAR classification criteria.

The previous 2002 AECG classification criteria classified SS into primary and secondary, whereas the more recent 2012 ACR and 2016 ACR/EULAR classification criteria focus on primary SS. The 2016 ACR/EULAR classification criteria can also be used to classify secondary SS,¹⁴ and a population-based study supports its performance in defining secondary SS.¹⁹ However, recent criteria might be another hurdle to diagnosing SS among RA patients. The newer classification criteria regard sicca symptoms as the entry criterion for diagnosing SS, and they require RA patients to perform numerous examinations to confirm ocular or salivary gland involvement. In our study, seven of the 60 RA patients who met the 2002 AECG classification criteria did not meet the 2016 ACR/EULAR classification criteria. Among them, four patients did not consent to any testing (ocular staining, Schirmer's test, labial salivary gland biopsy, or unstimulated whole saliva flow). The current criteria might thus delay the diagnosis of SS in RA patients and affect the determination of treatment strategies for RA patients with SS.

As previously noted,⁸ RA patients with SS are characterized by a higher frequency of positive serologic tests than found in those without SS. In other words, if a specific autoantibody is positive, the probability that SS will accompany the RA increases; the prevalence of SS increased to 10.5% in RF-positive patients and 17% in patients with ANA titers greater than

or equal to 1:80. The anti-Ro antibody has the highest specificity for SS, and 67.6% of the RA patients that were positive for the anti-Ro antibody had SS. Therefore, positive ANA and RF test results, in addition to positivity for the anti-Ro antibody, may be regarded as clues for the diagnosis of SS among RA patients with dryness symptoms. However, the higher rate of positive ANA in this study may have been affected by patients' age, and performance of the ANA test in up to 100% of the patients in the referral hospital. The clinical implications of such autoantibodies should be considered when assessing the various factors that can affect the positivity of autoantibody profiles.

We found no differences in RA manifestations or treatment patterns according to the presence of SS. Because the RA patients with SS were younger than those without SS, they had a lower prevalence of hypertension and diabetes mellitus as comorbidities. In the use of medications, 12.2% of RA patients without SS and 5.6% of RA patients with SS used bDMARDs. However, it is uncertain whether the early use of bDMARDs can delay the development of SS in RA patients. A well-designed prospective study will provide evidence about whether the use of bDMARDs can lower the incidence of SS in RA patients.

This study has several strengths, including our study design. We included all RA patients who visited our rheumatologic clinic within two months to prevent selection bias and confirmation bias. Although the data were collected retrospectively, the diagnostic tests for SS had already been done because our clinic has a well-organized multidisciplinary approach to SS that involves dentists, ophthalmologists, and rheumatologists. Second, we classified SS patients using rheumatologists' diagnoses and the 2002 AECG, 2012 ACR, and 2016 ACR/EULAR classification criteria for SS to show differences in the prevalence of SS among RA patients according to each set of criteria. We thereby clarified potential discrepancies among the criteria and showed the limitations of diagnosing SS in RA patients caused by the insufficient implementation of diagnostic tests in a real-world setting. Third, we provided the prevalence of SS in RA patients according to the presence of sicca symptoms and the presences of RF, ANA, and anti-Ro antibodies. Changes in the prevalence of SS according to the presence of sicca symptoms or autoantibodies implies that they could be potential risk factors for the presence of SS in RA patients.

Our study also has some limitations. First, we might have underestimated the prevalence of SS among RA patients because this was a retrospective observational study from a single tertiary hospital. We could not conduct the invasive studies required to make a final diagnosis of SS unless patients consented to them in that real clinical setting. In the consideration of routine care, we set rheumatologists' diagnostic tests as the gold standard, which resulted in a higher prevalence of SS among RA patients than found in previous studies. Second, we did not collect clinical information about quality of life, fatigue, or sleep quality. In fact, most SS patients suffer from constitutional symptoms, so in further prospective studies, we need to focus not only on dryness but also on patient-reported outcomes (PROs) to better understand RA patients with SS.

In conclusion, we found that the prevalence of SS among RA patients was 8.7%, 7.3%, 6.3%, and 6.8% according to rheumatologists' diagnoses and the 2002 AECG, 2012 ACR, and 2016 ACR/EULAR classification criteria, respectively. Patients with both RA and SS showed a higher rate of positive ANA and anti-Ro antibody tests, and they had a lower prevalence of hypertension and diabetes mellitus than those without SS. However, the clinical characteristics and disease activity of RA did not differ according to the presence of SS.

Further prospective observational studies are required to collect PROs from RA patients with SS and to understand how SS affects the clinical course and treatment patterns of RA.

ACKNOWLEDGMENTS

The manuscript was proofread by eWorldEditing, Inc.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Performance of diagnostic tests on those who did not satisfy the particular classification criteria among RA patients with Sjögren's syndrome (n = 72)

[Click here to view](#)

REFERENCES

- Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61(6):554-8.
[PUBMED](#) | [CROSSREF](#)
- Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. *Arthritis Rheum* 1999;42(8):1765-72.
[PUBMED](#) | [CROSSREF](#)
- Manoussakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, et al. Sjögren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjögren's syndrome. *Arthritis Rheum* 2004;50(3):882-91.
[PUBMED](#) | [CROSSREF](#)
- Gilboe IM, Kvien TK, Uhlig T, Husby G. Sicca symptoms and secondary Sjögren's syndrome in systemic lupus erythematosus: comparison with rheumatoid arthritis and correlation with disease variables. *Ann Rheum Dis* 2001;60(12):1103-9.
[PUBMED](#) | [CROSSREF](#)
- Nossent JC, Swaak AJ. Systemic lupus erythematosus VII: frequency and impact of secondary Sjögren's syndrome. *Lupus* 1998;7(4):231-4.
[PUBMED](#) | [CROSSREF](#)
- Alani H, Henty JR, Thompson NL, Jury E, Ciurtin C. Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. *Scand J Rheumatol* 2018;47(2):141-54.
[PUBMED](#) | [CROSSREF](#)
- Brown LE, Frits ML, Iannaccone CK, Weinblatt ME, Shadick NA, Liao KP. Clinical characteristics of RA patients with secondary SS and association with joint damage. *Rheumatology (Oxford)* 2015;54(5):816-20.
[PUBMED](#) | [CROSSREF](#)
- He J, Ding Y, Feng M, Guo J, Sun X, Zhao J, et al. Characteristics of Sjögren's syndrome in rheumatoid arthritis. *Rheumatology (Oxford)* 2013;52(6):1084-9.
[PUBMED](#) | [CROSSREF](#)
- Martens PB, Pillemer SR, Jacobsson LT, O'Fallon WM, Matteson EL. Survivorship in a population based cohort of patients with Sjögren's syndrome, 1976-1992. *J Rheumatol* 1999;26(6):1296-300.
[PUBMED](#)
- Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. *J Rheumatol* 2002;29(1):62-7.
[PUBMED](#)

11. Kim SM, Park E, Lee JH, Lee SH, Kim HR. The clinical significance of anti-cyclic citrullinated peptide antibody in primary Sjögren syndrome. *Rheumatol Int* 2012;32(12):3963-7.
[PUBMED](#) | [CROSSREF](#)
12. Lee J, Koh JH, Kim JW, Sung YK, Lee SS, Choe JY, et al. Performance of the 2016 ACR-EULAR classification criteria for primary Sjögren's syndrome in a Korean cohort. *Rheumatol Int* 2018;38(9):1651-60.
[PUBMED](#) | [CROSSREF](#)
13. Shiboski SC, Shiboski CH, Criswell L, Baer A, Challacombe S, Lanfranchi H, et al. American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort. *Arthritis Care Res (Hoboken)* 2012;64(4):475-87.
[PUBMED](#) | [CROSSREF](#)
14. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017;76(1):9-16.
[PUBMED](#) | [CROSSREF](#)
15. Haga HJ, Naderi Y, Moreno AM, Peen E. A study of the prevalence of sicca symptoms and secondary Sjögren's syndrome in patients with rheumatoid arthritis, and its association to disease activity and treatment profile. *Int J Rheum Dis* 2012;15(3):284-8.
[PUBMED](#) | [CROSSREF](#)
16. Calgüneri M, Ureten K, Akif Oztürk M, Onat AM, Ertenli I, Kiraz S, et al. Extra-articular manifestations of rheumatoid arthritis: results of a university hospital of 526 patients in Turkey. *Clin Exp Rheumatol* 2006;24(3):305-8.
[PUBMED](#)
17. Cimmino MA, Salvarani C, Macchioni P, Montecucco C, Fossaluzza V, Mascia MT, et al. Extra-articular manifestations in 587 Italian patients with rheumatoid arthritis. *Rheumatol Int* 2000;19(6):213-7.
[PUBMED](#) | [CROSSREF](#)
18. Kim SK, Park SH, Shin IH, Choe JY. Anti-cyclic citrullinated peptide antibody, smoking, alcohol consumption, and disease duration as risk factors for extraarticular manifestations in Korean patients with rheumatoid arthritis. *J Rheumatol* 2008;35(6):995-1001.
[PUBMED](#)
19. Billings M, Amin Hadavand M, Alevizos I. Comparative analysis of the 2016 ACR-EULAR and the 2002 AECG classification criteria for Sjögren's syndrome: Findings from the NIH cohort. *Oral Dis* 2018;24(1-2):184-90.
[PUBMED](#) | [CROSSREF](#)