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RAPID3 SCORE CAN PREDICT DISEASE ACTIVITY IN PRIMARY SJÖGREN'S SYNDROME

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Abstract

Aim: Sjögren's syndrome (SS) is a chronic autoimmune disease that causes salivary and lacrimal gland dysfunction, resulting in oral and ocular dryness. The European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) is a systemic disease activity index measuring disease activity in patients with SS. The ESSDAI includes 12 domains. The EULAR SS Patient-Reported Index (ESSPRI) is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease. Routine Assessment of Patient Index Data 3 (RAPID3) is used to evaluate disease activity in patients with rheumatoid arthritis, which is another inflammatory disorder. This study evaluates whether RAPID3 is useful in primary SS.

Material and Methods: In this cross-sectional study, 30 patients with primary SS were enrolled. ESSDAI, ESSPRI and RAPID3 scores were recorded. Chi-square, Mann-Whitney U test and Pearson correlation analysis was performed for the statistical analysis.

Results: Mean ESSDAI, ESSPRI, and RAPID3 scores were 3.8±3.6, 5.8±1.7, and 14.8±5.2, respectively. ESSPRI and RAPID3 scores were positively correlated ($r=0.669$, $p<0.001$). Additionally, when we set the cut-off value to 12 on the RAPID3 score (>12 accepted as active, and ≤12 accepted as inactive), ESSPRI score was significantly higher in active patients (6.4±1.4 vs 4.1±1.4, $p=0.002$). However, there was no relationship between the RAPID3 and ESSDAI scores.

Conclusion: In SS, it is difficult to detect disease activity. Comorbid psychosomatic diseases affect the set detecting global disease activity. These results suggest that RAPID3 may be useful to detecting disease activity in primary SS.

Keywords: Sjögren's syndrome, disease activity, Routine Assessment of Patient Index Data 3

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of unknown origin that causes salivary and lacrimal gland dysfunction (1). SS has a wide variety of presentations, ranging from the local involvement of exocrine glands with keratoconjunctivitis sicca and xerostomia to the systemicand extraglandular involvement of multiple organs (2). Reported symptoms such as fatigue, arthralgia and chronic process have been associated with reduced health-related quality of life. Activity indices were used to assess disease severity, progression,

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and evolution. They can help prevent or delay damage by identifying patients with active disease that could be altered by treatment and selecting subgroups with more severe disease (3). A therapeutic approach to SS compared to other autoimmune diseases is also unclear because there is little consensus on which treatment to use and when for systemic involvement (4). Treatment is decided on an individual basis according to disease activity and the presence and extent of extraglandular manifestations (5). We are trying to determine the treatment response with activity indices. Therefore, good activity indices are required in SS and other connective tissue diseases. The European League Against Rheumatism (EULAR) SS Disease Activity Index (ESSDAI) is a systemic disease activity index measuring disease activity in patients with SS (6). The ESSDAI includes 12 domains. The EULAR SS Patient-Reported Index (ESSPRI) is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease (7). Routine Assessment of Patient Index Data 3 (RAPID3) is used to evaluate disease activity in patients with rheumatoid arthritis, which is another inflammatory disorder (8).

One patient-only index, termed the RAPID3, can be scored in fewer than 10 s on a Multidimensional Health Assessment Questionnaire (MDHAQ), compared to about 42 s for a standard HAQ, and 90 s for a quantitative 28-joint count (9-11). We think that it is an index that can be used in SS as well since it provides faster and shorter results. This study evaluates whether RAPID3 is useful in primary SS.

MATERIAL AND METHODS

Thirty patients with primary SS were enrolled in this cross-sectional study. ESSDAI, ESSPRI, and RAPID3 scores were recorded. SS patients were recruited from patients who applied to the rheumatology outpatient clinic, met the diagnostic/classification criteria, and agreed to participate in the study. Those under the age of 18 and over the age of 65, pregnant women, those in the lactation period, those with active infection, poorly controlled diabetes, or heart failure, and those with malignancy were excluded from the study. The results of routine tests (fasting blood sugar, creatinine, alanine aminotransferase, blood count, sedimentation and C-reactive protein, anti-nuclear antibody, anti-Ro, anti-La) of the patients were recorded. All the cases included in the study were first informed about their diseases. Afterwards, the purpose of the study was explained verbally and in writing, and an informed consent form was signed by the participants who agreed to participate in the study. Our study was found to be ethically appropriate and approved by the Ethics Committee of Fırat University (decision no: 01, date no: 24.02.2015).

Statistical Analysis

Statistical analyses were conducted using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Chi-square, Mann-Whitney U test, and Pearson correlation analysis were performed for the statistical analysis. A p value <0.05 is accepted as statistically significant.

RESULTS

Demographic and clinical data of the patients are given in Table 1. Mean ESSDAI, ESSPRI, and RAPID3 scores were 3.8±3.6, 5.8±1.7, and 14.8±5.2, respectively. ESSPRI and RAPID3 scores were positively correlated ($r=0.669$, $p<0.001$) (Table 2). Additionally, when we set the cut-off value to 12 on the RAPID3 score (>12 accepted as active, and ≤12 accepted as inactive), ESSPRI score was significantly higher in active patients (6.4±1.4 vs 4.1±1.4, $p=0.002$). However, there was no relationship between the RAPID3 and ESSDAI scores (Table 2). The schirmer test was positively correlated with tear break-up time (BUT) ($r=0.573$,

Table 1. Demographics and clinical variables

	SS (n=30)
Mean ageand years	51.0±8.7
Disease duration, years	6.3±4.6
Sex, % females	100
WBC, 10^3/µL	5.9±1.8
Hemoglobin, g/dL	13.3±1.5
ESR, mm/h	19.5±16.4
CRP, mg/dL	7.2±13.5
ANA positivity, %	83.3
Anti-Ro positivity, %	65.5
Anti-La positivity, %	46.2
HAQ	32.4±4.9
Schirmer test, mm	11.4±6.4
BUT, sec	3.2±1.8
Lissamine green score	2.2±1.1

SS: Sjögren's syndrome, WBC: White blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody, HAQ: Health assessment questionnaire, BUT: Break-up time

Table 2. The correlation between the activity indices

		ESSPRI	ESSDAI
RAPID3	r	0.669	0.296
	p	<0.001	0.113

RAPID3: Routine Assessment of Patient Index Data 3, ESSDAI: The European League Against Rheumatism Sjögren's Syndrome Disease Activity Index, ESSPRI: The European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index

p=0.007). Lissamine green score was negatively correlated with the Schirmer test and BUT (r=-0.484, p=0.007, and r=-0.507, p=0.004, respectively). Despite there was high compliance among these three scales evaluating eye involvement, these scales did not appear to correlate with the ESSDAI, ESSPRI, and RAPID3 scores that assess the global activity of the disease. The mean age was significantly higher in patients with the Schirmer test ≤5 mm compared to the patients with >5 mm (55.6±6.9 vs 47.6±8.5 years, p=0.044).

DISCUSSION

SS is a systemic autoimmune disease that primarily affects the exocrine glands (mainly the salivary and lacrimal glands) and results in the severe dryness of mucosal surfaces, principally in the mouth and eyes. This disease predominantly affects middle-aged women, but can also be observed in children, men, and the elderly. The clinical presentation of SS is heterogeneous and can vary from sicca symptoms to systemic disease (characterized by peri-epithelial lymphocytic infiltration of the affected tissue or the deposition of the immune complex) and lymphoma. The mechanism underlying the development of SS is the destruction of the epithelium of the exocrine glands, as a consequence of abnormal B cell and T cell responses to the autoantigens Ro/SSA and La/SSB, among others. Diagnostic criteria for SS include the detection of autoantibodies in patient serum and histological analysis of biopsied salivary gland tissue (1). Therapeutic approaches for SS include both topical and systemic treatments to manage the sicca and systemic symptoms of the disease. SS is a serious disease with excess mortality, mainly related to the systemic involvement of the disease and the development of lymphomas in some patients. Knowledge of SS has progressed substantially, but this disease is still characterized by sicca symptoms, the systemic involvement of disease, lymphocytic infiltration to exocrine glands, the presence of anti-Ro/SSA and anti-La/SSB autoantibodies, and the increased risk of lymphoma in patients with SS (1). Disease activity and damage index are two different antitheses used in the follow-up and evaluation of diseases. Conceptually, activity refers to the reversibility of the process, while damage is an irreversible process associated with a permanent loss of function of the organ or system. Severity, on the other hand, means that there are increased reversible and irreversible changes caused by the disease in a particular organ or tissue (12). In SS, it is difficult to detect disease activity. Comorbid psychosomatic diseases affect the set detecting global disease activity. On the other hand, the activity of glandular involvement and global disease activity are not with compliance (6). Indices such as the SS Disease Activity Index and Sjögren's Clinical Activity Index have been used regionally to measure disease activity in patients with SS with systemic symptoms. Because to the fact that these indices have been developed in a limited number of patients and in a single country, two separate indices have been developed aimed at evaluating two different aspects of the disease. The ESSDAI index has been developed for systemic findings, and the ESSPRI index has been developed for patients' symptoms (12,13).

The ESSDAI is a systemic disease activity index measuring disease activity in patients with SS. The ESSDAI is a physician-oriented outcome measure. With the growing use of the ESSDAI, some domains appear to be more challenging to rate than others. The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure, even a primary outcome measure, in current randomized clinical trials. Therefore, ensuring an accurate and reproducible rating of each domain, by providing a more detailed definition of each domain, has emerged as an urgent need. The ESSDAI includes 12 domains (i.e., organ systems: Cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathy, and biological) (6). ESSPRI is used to evaluate dryness, fatigue, and pain symptoms, and their impact on the disease. ESSPRI is a patient-administered questionnaire that evaluates dryness, fatigue, and pain, and each component is measured with a single 0-10 numerical scale. A score of 0 indicates the lowest disease activity (7). ESSDAI and ESSRI have been used and evaluated in numerous studies. It has also been shown that both the ESSDAI and ESSRI scores improve significantly after treatment. However, it has been found in studies that the correlation between ESSPRI and ESSDAI is weak (14). Additionally, various activity parameters have been developed according to the specific area of involvement, such as drynessand fatigue. For example, indices such as the Functional Assessment of Chronic Illness Therapy or Fatigue Severity Scale are used for fatigue. Due to the extreme heterogeneity of clinical features in PSS, the search for a new index that can combine the assessment of systemic disease activity, subjective symptoms, glandular function, and serological parameters continues (15). RAPID3 is an index, which includes only the three patient-reported measures from the RA core set physical function, pain, and patient global assessment each scored 0-10, for a total of 0-30. RAPID3 was developed initially for feasibility in routine care, as the patient provides the data while in the waiting area (8). In clinical studies, RAPID3 correlates with the Disease Activity Score 28 (DAS28) and the Clinical Disease Activity Index (16,17). Furthermore, patient self-report questionnaires have higher reproducibility than physician-performed joint counts (18). The correlation of the ESSPRI index

and RAPID3 score in our study may be because both indices are patient-oriented outcome criteria. On the other hand, the lack of correlation between ESSDAI and RAPID3 may suggest that the RAPID3 score is weak in the evaluation of systemic findings.

Study Limitations

The fact that the number of patients is small and no other comparable study group is included is the limitations of our study.

CONCLUSION

ESSDAI and ESSPRI are the main activity scores used in SS. RAPID3 has previously been used in RA, and data in SS are limited. We wanted to test the usability of RAPID3 in our study. In conclusion, these results suggest that RAPID3 can be useful for detecting disease activity in primary SS.

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Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Fırat University Ethics Committee (decision no: 01, date no: 24.02.2015).

Informed Consent: Patient consent form was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S.A., Z.Ö., O.Ç., N.G., Concept: M.S.A., B.Ö., N.G., A.K., Design: M.S.A., B.Ö., A.K., Data Collection or Processing: M.S.A., Z.Ö., S.Ç., Analysis or Interpretation: M.S.A., Z.Ö., A.K., Literature Search: M.S.A., Writing: M.S.A.

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