SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Clinical and Laboratory Analysis of Polyarthritis with Different Origins in Sjögren's Syndrome, with a Focus on Rheumatoid Factor Isotopes

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The PhD Defense takes place at the Lecture Hall of Building A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 13:00, on 17th of March, 2026.

1. Introduction

Sjögren's disease (SS), formerly known as Sjögren's syndrome, is one of the most common systemic autoimmune diseases, primarily affecting the exocrine glands but potentially involving multiple other organs as well. Its incidence is approximately 6.92 per 100,000, and its prevalence is around 60.82 per 100,000. Two forms are distinguished: the primary form (a combination of glandular and/or extraglandular manifestations, pSS) and the associated — formerly called secondary — form (when it occurs in association with another systemic autoimmune disorder, sSS). The most prominent symptoms that are present in the vast majority of patients include dry eyes, dry mouth, fatigue, and joint pain. The clinical presentation and severity of symptoms can vary widely between individuals, ranging from few or mild symptoms to unbearable dryness, pain, or disabling fatigue. In approximately 30–40% of Sjögren's patients, the disease is accompanied by systemic manifestations and can cause the dysfunction of various organs, such as the lungs, liver, kidneys, gastrointestinal tract, joints, muscles, and peripheral or central nervous system. Patients also have a higher risk of developing B cell lymphoma. The risk of B cell lymphoma is 15 to 20 times higher among adult patients with SS compared to the general population (lifetime risk: 5–10%). The disease affects mainly women, with a female/male ratio of 9:1, and the onset may occur at any age, but it is most commonly diagnosed in women of perimenopausal age. Antibodies characteristic for the disease are anti-Ro/Sjögren's syndrome-A (anti-Ro/SS-A) and anti-La/Sjögren's syndrome-B (anti-La/SS-B). Articular involvement is the most common extraglandular manifestation (EGM). According to some data, approximately 30–60% of primary SS patients suffered from articular manifestations, which were associated with multisystem involvement. Joint manifestations can be grouped as arthrosis (referred to as osteoarthritis in the Anglo-Saxon literature), being predominantly age-related and, therefore, not requiring immunomodulant medications, despite the pain, as a common feature; non-erosive polyarthritis as an extraglandular manifestation of SS; and rheumatoid arthritis (RA) as another systemic autoimmune disease associated with SS. The absence of joint destruction and bone erosions distinguishes SS-polyarthritis from RA, where joint damage more frequently occurs and is a disease hallmark. It is of great importance to differentiate between the two types of inflammatory joint manifestations in a single patient, since the association with RA requires an earlier and more aggressive disease-modifying antirheumatic drug (DMARD) or even further escalated, targeted treatment to prevent the development of irreversible erosions.

In our study, we aimed to compare the characteristic demographic, clinical, and laboratory parameters of SS patients with different kinds of inflammatory joint manifestations in order to search for potential factors that help in distinguishing them. In the second part of our study, we examined rheumatoid factor (RF) isotypes among SS patients to find out whether differences between RF isotype patterns of the groups could be potentially useful in everyday practice.

2. Objectives

A significant proportion of patients with Sjögren's disease suffer from joint complaints, which may be of inflammatory or non-inflammatory origin. One of the most common extraglandular manifestations is non-erosive polyarthritis, which is crucial to distinguish from concomitant rheumatoid arthritis in order to select the optimal therapy.

In the first part of our study, we aimed to compare the characteristic demographic, clinical, and laboratory parameters of SS patients with inflammatory joint manifestations of different origins, in order to identify potential factors that may help distinguish between these groups.

In the second part of our study, we examined rheumatoid factor isotypes in patients with SS alone, SS complicated with polyarthritis as an EGM, and SS associated with rheumatoid arthritis as a second autoimmune disorder to find out whether differences between RF isotype patterns of the groups could be potentially useful in everyday practice. We also investigated whether there is a correlation between immunoglobulin (Ig) isotypes and RF isotypes.

3. Patients and Methods

3.1. Selection and Grouping of Patients

In our study, we systematically analyzed data from patients with Sjögren's disease being regularly followed up at the Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Hungary. For the first part of our investigation (hereafter referred to as „characterization of inflammatory joint manifestations"), we included patients who had attended the outpatient clinic at least once in 2019, identifying a total of 355 patients with

Sjögren's disease. The data of these patients were processed retrospectively using our computerized databases, specifically the e-Medsolution and UDMed systems. Among them, 128 patients (36.0%) had no recorded mention of inflammatory joint complaints; they served as control group (SS-C). In total, 227 (63.9%) patients were identified to have some kind of inflammatory joint involvement. They were further divided into two groups according to having polyarthritis complicating Sjögren's disease as an extraglandular manifestation (SS-pa, n = 159; 47.4%) or having rheumatoid arthritis associated with Sjögren's disease (SS-RA, n = 68; 19.15%). The patients were classified according to the American College of Rheumatology (ACR) - European League Against Rheumatism (EULAR) criteria for Sjögren's disease - and for rheumatoid arthritis, keeping in mind that the latter criteria set was developed to recognize early rheumatoid arthritis. Therefore, and because of the overlapping features of the two systemic autoimmune diseases potentially resulting in differential diagnostic issues, the erosive nature of joint involvement was proved with imaging procedures. A comparative X-ray examination of the hands was performed in all cases, while, in some patients, the small joints of the feet were imaged, too. In cases where no erosive lesions were found, but they were suspected by clinical symptoms, MR was performed to detect potential abnormalities for which X-ray is not feasible. Since we aimed to characterize inflammatory joint manifestations, the patients with osteoarthritis were merged into the control group, where patients might have had any other glandular or extraglandular features except for inflammatory joint manifestations. The patient groups were compared according to their demographic data, laboratory parameters, associated diseases, and treatment modalities. Organic manifestations (such as lung, kidney, cutaneous involvement, and lymphadenopathy) were defined according to the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) domains.

In the second part of our study (hereafter referred to as „Examination of RF isotypes"), we reviewed the data of a total of 164 SS patients. As described above, we also divided patients into three groups based on the presence and type of joint involvement. In total, 119 (72.5%) patients were identified to have some kind of inflammatory joint involvement, of whom 73 (44.5%) had polyarthritis as an extraglandular manifestation (SS+PA), while 46 cases (28%) were associated with rheumatoid arthritis (SS+RA). The control group consisted of 45 patients (27.4%) without joint involvement (SS). The patient groups were compared according to their demographic data, rheumatoid factor isotype levels, further laboratory parameters, disease duration, disease activity, extraglandular manifestations, and associated diseases. To further characterize the connection between immunoglobulin and rheumatoid factor isotypes, patients

were re-grouped depending on whether they presented normal or high Ig G, A, and M levels, regardless of the aforementioned subsets.

3.2. Laboratory Methods

Laboratory parameters were determined as part of the general routine investigation and follow-up of the involved patients at the Department of Laboratory Medicine. C-reactive protein, rheumatoid factor IgM, and total immunoglobulin G concentrations were measured using turbidimetry (Cobas c503 clinical chemistry analyzer, Roche Diagnostics, Basel, Switzerland). Antinuclear antibodies were tested using HEp-2 indirect immunofluorescence assay (FC 1522–1010 ANA HEp 20–10 EUROPattern, Euroimmun, Lübeck, Germany), while enzyme-linked immunosorbent assay (ELISA) kits were used for anti-cyclic citrullinated peptide (anti-CCP) (RA96Plus Immunoscan RA anti-CCP IgG, Svar Life Science, Malmö, Sweden), anti-Ro/SS-A, and anti-La/SS-B (EA 1595–9601G SS-A(Ro) IgG and EA 1597–9601G SSB(La) IgG, Euroimmun, Lübeck, Germany) measurement. The levels of IgG, IgA, and IgM rheumatoid factor were determined using ELISA reagents from Orgentec Diagnostika GmbH (Mainz, Germany; cat. No.: ORG522G, ORG522M, ORG522A).

3.3. Statistical Analysis

3.3.1. Characterization of Inflammatory Joint Manifestations

SPSS software (version 24.0) was used for statistical analysis. The Kolmogorov–Smirnov test was used for the evaluation of normality. For continuous parameters not showing a normal distribution, Kruskal–Wallis and Mann–Whitney tests were carried out, whereas, for those with normal distribution, analysis of variance (ANOVA) and two-sample T tests were used. For discrete parameters, the Fisher's exact test was used when the expected count was 5. p values < 0.05 were considered statistically significant. For a more detailed analysis, a binary logistic regression model was created to show which parameters are independent predictors. Where necessary, continuous parameters were converted into dichotomous groups using cut-off values respecting the normal laboratory values. Receiver operating characteristic (ROC) analysis was performed to detect differential diagnostic accuracy in distinguishing between the three patient groups. The area under the curve (AUC) and its confidence interval are reported, where a higher AUC means better discrimination and a diagonal line (AUC = 0.5) indicates no differentiation.

3.3.2. Examination of Rheumatoid Factor Isotypes

Values are expressed as the mean and standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and frequency is presented as a percentage for categorical variables. Continuous variables were compared with a parametric twosample t-test or nonparametric Mann–Whitney U test for two samples and a Kruskal–Wallis test with an uncorrected Dunn-test for three samples. The effect size was calculated using Cohen's d (d), r, and η^2, respectively [22]. Categorical variables were compared with Pearson's chi-squared test or Fisher's exact test, and the effect size is reported as Cramér's V (V). Correlations between variables were calculated using Spearman's correlation coefficient (r_s). Sensitivity and specificity were calculated. All statistical tests were two-sided; differences were considered statistically significant at a <0.05 level and were reported using p-values and/or 95% confidence intervals (95% CI). Statistical analysis was performed using SPSS Statistics for Windows, version 28.0 (IBM Corp.; Armonk, NY, USA) and GraphPad Prism for Windows, version 10.3.1 (GraphPad Software, Boston, MA, USA).

4. Results

4.1. Characterization of Inflammatory Joint Manifestations

4.1.1. Demographic Data

The male/female ratio was 13/116 in the SS-C group, 8/151 in SS-pa, and 3/65 in the SS-RA subset. The median age of the patients was highest in the SS-C group (68 years), and the difference was significant compared to the SS-pa group, where patients were the youngest (63 years). In the SS-RA group, the median age was 65.5 years, and the difference was not significant compared to the other groups.

4.1.2. Laboratory Parameters

No significant differences were found between the three patient groups regarding C-reactive protein, leukocyte count, or erythrocyte sedimentation rate. Considering the immunological parameters, there was no significant difference regarding the IgG levels, occurrence of ANA, anti-Ro/SS-A, or anti-La/SS-B levels or frequency. Both anti-CCP and

rheumatoid factor levels were significantly higher in the SS-RA group than in SS-pa or SS-C patients, while the differences between the latter groups were not significant.

4.1.3. Extraglandular Manifestations and Associated Diseases

Reviewing the time passed from the diagnosis of SS until the onset of joint complaints, we found that joint complaints evolved significantly earlier in the SS-RA group (-1.18 ± 6.11 years, where a negative value means an onset before the diagnosis of SS) than in the SS-pa group (1.3 ± 5.8 years) ($p = 0.004$). The occurrence of lymphadenopathy did not show significant differences between the three patient groups. Raynaud's phenomenon was significantly more frequent in the patients with polyarthritis compared to the control group. Lung involvement was most frequent in the SS-RA patients, and the difference was significant compared to the SS-C group. Moreover, the SS-pa patients had lung manifestations significantly more often than the SS-C group, as well, however, there was no significant difference between the SS-RA and SS-pa patients. Kidney involvement occurred in a significantly smaller proportion of the SS-C group than in the SS-RA group. The occurrence of cutaneous manifestations defined as palpable purpura, recurrent urticaria, and photosensitivity, as well as the frequency of Hashimoto's thyroiditis, did not differ among the three patient groups. Regarding the association of further systemic and organ-specific autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome, celiac disease, and primary biliary cholangitis) and the occurrence of non-immune diseases (hypertension, type 2 diabetes mellitus, and chronic obstructive pulmonary disorder), the patient groups did not differ.

4.1.4. Treatment

Among the therapies used, sulfasalazine and antimalarial use was significantly more frequent in the SS-pa patients when compared to the SS-C group, but no significant difference was detected between the SS-pa and SS-RA groups or the SS-RA and SS-C groups. The SS-RA patients required glucocorticoids significantly more often during their disease course than any other patient group. Methotrexate use was gradually significantly less common in the control group than in the two groups with inflammatory joint manifestations, while this therapy was more frequent in the SS-RA patients than in the SS-pa group. Leflunomide was used exclusively at patients with rheumatoid arthritis.

4.1.5. Binary Multiparametric Logistic Regression Model and ROC Curve Analysis

After developing subsets based on having low-positive (≤3 × upper limit of normal - ULN) or high-positive (≥3 × ULN) anti-CCP and rheumatoid factor levels, a binary multiparametric logistic regression model was created. This model provided further diagnostic value in differentiating the three patient groups. It became clear that only high-positive anti-CCP and RF levels can increase the accuracy of the model, whereas - unlike anti-Ro/SS-A - anti-La/SS-B positivity decreases the chance of having SS-RA. A high IgG level is another laboratory parameter associated with lower odds for RA when compared to control patients. Among the organic manifestations, kidney involvement was able to improve the diagnostic accuracy of differentiating SS-RA from SS-pa. Raynaud's syndrome and lung involvement were proved to be independent factors related to joint disease by this multiparametric approach.

Using ROC analysis, the diagnostic accuracy of the binary multiparametric logistic regression model was weakest in the SS-C vs. SS-pa patients (AUC = 0.6741), best at distinguishing between the SS-C and SS-RA groups (AUC = 0.9331). Regarding the most crucial issue from a physician's perspective, differentiating SS-pa patients from SS-RA patients, the diagnostic accuracy was good (AUC = 0.8836), and, what is even more important, it was better than that of the anti-CCP test alone (AUC = 0.8083).

4.2. Examination of Rheumatoid Factor Isotypes

4.2.1. Demographic Data

The male/female ratio was 3/42 in the SS group, 2/71 in the SS+pa subset, and 1/45 in the SS+RA subset. The mean age of the patients was the highest in the SS+RA group and the lowest in the SS group, but the difference was not significant among the three groups. No significant difference was observed in disease duration.

4.2.2. Laboratory Parameters

4.2.2.1. Basic Laboratory Parameters

No significant difference was found between the three patient groups regarding IgA, IgM, C-reactive protein, and rheumatoid factor levels. Remarkably, the highest IgG levels were

measured in the SS group and the lowest levels in the SS+RA group, and the difference was significant between the three subsets.

4.2.2.2. Rheumatoid Factor Isotypes

Among RF isotypes, the most notable difference between the three patient groups was found for IgA RF, with the highest levels in the SS group and the lowest in the SS+RA subgroup; however, the difference was not statistically significant. No significant difference was found between the patient groups when comparing IgG RF and IgM RF levels either.

4.2.2.3. Correlations Between Patient Groups, Rheumatoid Factor Isotypes, and Disease-Specific Parameters

Examining the relationship between the RF Ig subclasses and disease-specific parameters in the different patient subsets, significant negative correlations were found between age and each RF isotype in each patient group. Regarding disease duration, only IgG and IgM RF isotypes correlated significantly and negatively in control SS patients. Both the initial and the latest anti-cyclic citrullinated peptide (CCP) levels showed significant positive correlation with IgM RF results, but only in SS+RA patients. Lastly, anti-CCP levels and IgG RF levels showed a significant positive correlation in SS and SS+RA patients. As expected, all RF isotypes showed significant positive correlation with rheumatoid factor concentrations in each patient group. Unlike in SS+RA patients, the other two subsets showed a significant positive correlation between all RF isotypes and anti-Ro/SS-A and between anti-La/SS-B and total IgA and IgG levels. IgM levels correlated only with the IgG RF and IgM RF levels of SS+RA patients. Regarding erythrocyte sedimentation rate (ESR) values, significant positive correlation was observed in the SS group with each RF isotype, while SS+pa patients had a positive correlation with IgM RF and SS+RA patients with IgA RF levels. Interestingly, white blood cell count correlated negatively with all RF isotypes in SS+pa patients. The disease activity score obtained in 28 joints (DAS28) was calculated only in the SS+RA group; however, it correlated with IgA RF levels. Regarding the ESSDAI, the most pronounced positive correlations were found with IgA RF; however, the IgG RF values correlated with the ESSDAI values in SS+RA patients as well.

4.2.2.4. Differences Among Patient Groups According to the Negative or Positive Rheumatoid Factor Isotype Results

When grouped based on whether IgA, IgM, and IgG RF levels were below or above the cut-off value (denoted as negative or positive accordingly), there was no significant difference in any patient subsets (SS vs. SS-pa vs. SS+RA). However, regarding all isotypes, seropositive patients were significantly younger. Moreover, disease duration of positive IgA RF patients was significantly shorter than that of negative ones. ESSDAI was higher in each seropositive patient group regardless of RF isotype. We also noticed that positive testing for initial anti-CCP, RF, anti-Ro/SS-A, anti-La/SS-B, antinuclear antibody (ANA) and high ESR values were significantly more frequent in all positive IgA, IgM, and IgG RF patients than in the negative ones. In addition, IgG and IgM RF seropositive patients tested positive for anti-CCP significantly more often. Except for total IgM levels in positive IgA RF patients, all other immunoglobulin levels in all other positive RF isotype groups were significantly higher than in seronegative patients.

Regarding the effect of ongoing immunomodulant or immunosuppressive medications on rheumatoid factor isotype levels, no significant difference was found among the frequency of drugs used and the occurrence of RF isotypes, with the only exception being sulfasalazine, used significantly less frequent in positive IgG RF patients compared to negative ones.

4.2.2.5. Rheumatoid Factor Isotype Levels According to the Occurrence of Extraglandular Manifestations and Associated Autoimmune Diseases

If Sjögren's disease-associated skin manifestations (purpura and cutaneous vasculitis) were present, significantly higher RF levels were observed regarding each isotype. In the case of further extraglandular manifestations or associated organospecific (Hashimoto's thyroiditis, primary biliary cholangitis, and autoimmune hepatitis) or systemic (systemic lupus erythematosus and antiphospholipid syndrome) autoimmune diseases, there was no significant difference in RF isotypes.

4.2.2.6. Rheumatoid Factor Isotypes in the Case of Low/Normal or Elevated Immunoglobulin Levels

The patients were also grouped according to whether their total IgA, IgM, and IgG levels were low/normal or high, and then, their RF isotypes were compared. In patients with high total

IgG levels, all RF isotypes were significantly higher. IgA RF levels were significantly higher in patients with high total IgA levels. Such a phenomenon was not observed in the total IgM levels.

4.2.2.7. Combination of Immunoglobulin and Rheumatoid Factor Isotype Qualitative Results and Their Occurrence in Patient Groups

Taking the above-mentioned findings together, the IgG results and certain RF isotypes were paired to see whether these combinations might help differentiate between the three groups. High total IgG levels, together with high IgA RF levels, occur most frequently in SS patients ($p = 0.05$), whereas the combination of normal IgG and high IgM RF is significantly more frequent in the SS+RA group. The co-occurrence of high total IgG and normal IgM RF did not differ significantly between the patient subsets; however, this was the combination with the highest specificity (94.5%) for SS+pa patients.

5. Discussion

Sjögren's disease is diagnosed nine times more often in women than in men, as supported by our cohort.

Arthralgia and non-erosive polyarthritis affecting small joints are frequent extraglandular symptoms of Sjögren's disease. It has long been a debate as to how to distinguish these non-aggressive, non-erosive manifestations from early rheumatoid arthritis. According to a recent paper by Gao and colleagues, the most common cause of joint pain is either osteoarthritis, especially knee osteoarthritis, or joint involvement due to the disease itself: SS-polyarthritis. They also proved that primary SS patients with advanced age and more pronounced metabolic characteristics, such as elevated blood lipid and uric acid levels, are at risk for osteoarthritis. Moreover, SS-polyarthritis patients had higher disease activity and more organs involved. Another study showed that almost half of the anti-citrullinated protein antibody (ACPA)-positive patients with SS developed RA during their disease course. Rheumatoid factor often does not help us to differentiate between the two diseases, as it is not specific enough for rheumatoid arthritis and is often found in patients with Sjögren's disease. According to researches, a parallel examination of anti-CCP and rheumatoid factor is recommended, since

higher anti-CCP levels have been detected more often in Sjögren's disease associated with rheumatoid arthritis than in primary Sjögren's disease.

In the first part of our study, we retrospectively analyzed the data of a total of 355 SS patients, of whom 227 had inflammatory joint involvement. When examining their ages, we found that SS patients without joint complaints were significantly older than those with non-erosive polyarthritis. It is noteworthy that in young SS patients with polyarthritis, close monitoring is essential due to the increased risk of progression toward rheumatoid arthritis.

We found a significant difference regarding the time until the onset of the joint complaints between the SS-pa and SS-RA patients (15.6 vs. −14.16 months, respectively), meaning that, in the latter group, joint pain might precede the diagnosis of SS. In a follow-up examination by Ryu et al., the mean duration of progression of anti-CCP positive primary SS patients to RA was 60 months. Our results suggest that high anti-CCP levels in SS patients with inflammatory joint pain indicate progression towards rheumatoid arthritis. This finding corresponds to the observation of the abovementioned study, since they found that the anti-CCP antibody titer was independently associated with the progression to RA.

Based on our results, the occurrence of certain organ manifestations differs in the three groups. Pulmonary involvement occurred significantly more often in the groups with inflammatory joint manifestations than in the SS-C patients. In another study, where ACPA-negative and ACPA-positive SS patients were compared, pulmonary involvement presented significantly more frequently in the ACPA-positive than in ACPA-negative SS patients, as well (4/16 vs. 22/278, respectively). Similar results were found in another cohort, where SS-RA patients were compared to SS patients, regardless of having polyarthritis or not. In another study, lung involvement was more frequent, and the RF and anti-CCP levels were higher in the cohort of SS-RA patients compared to SS, however, this paper focused on the distinction of RA, SS, and SS-RA. They found that the SS-RA patients had more severe arthritis than the RA patients; moreover, rash, fever, and hematological abnormalities were also more frequent. Based on these findings, in SS patients presenting with polyarthritis as an extraglandular manifestation or concomitant rheumatoid arthritis, intensified monitoring is recommended due to the higher risk of potential lung involvement. This should include targeted medical history, more frequent screening with imaging tests, and pulmonary function tests. These complications can significantly impair the quality of life of patients, making early diagnosis and timely initiation of appropriate treatment crucial.

Raynaud's phenomenon was significantly more frequent among patients with non-erosive polyarthritis compared to the control group. This observation is consistent with the findings of García-Carrasco et al., who reported a higher prevalence of joint involvement and cutaneous vasculitis in SS patients with Raynaud's phenomenon. According to another study, the detection of Raynaud's phenomenon may help identify a subgroup of SS patients in whom pSS presents at a younger age and with more severe clinical manifestations, including complications such as lung involvement (ILD, PAH).

Regarding organ-specific autoimmune diseases, Hashimoto's thyroiditis was present at a considerable rate in patients of each group, without any significant difference. Our findings correspond to others, concluding that Hashimoto's thyroiditis is significantly more common in both primary SS and RA patients than in the general population.

Renal involvement occurred significantly more often in the SS-RA group than in the SS-C patients. Based on the literature data, kidney involvement in Sjögren's disease is rather infrequent, affecting less than 10% of patients, and presents mainly as tubulointerstitial nephritis, or, even less frequently, as membranoproliferative glomerulonephritis, whereas renal manifestations in RA have gradually evolved parallelly with the improvement of the management of the disease.

There was no significant difference regarding the occurrence of cutaneous manifestations between the individual groups. Our data correspond with the findings of Soy et al., reporting that almost half of Sjögren's disease patients manifest various skin symptoms during their disease course.

A significantly larger proportion of SS-RA patients require glucocorticoid treatment than either of the other two groups. This can be explained by the fact that glandular symptoms (SS-C group) usually do not need systemic treatment, while pain and inflammation in non-erosive polyarthritis are usually less severe than those observed in rheumatoid arthritis. Sulfasalazine and antimalarials are significantly more often used in SS-pa patients than in the SS-C group, whereas no significant difference was found between either the SS-RA and SS-pa patients or between the SS-RA and SS-C groups, meaning that these immunomodulant agents were predominantly used to manage mild forms of polyarthritis complicating SS. Unsurprisingly, methotrexate use was gradually and significantly more frequent in the SS-C, SS-pa, and SS-RA patients, respectively.

Our results draw attention to the importance of the regular and systematic follow-up of patients with Sjögren's disease, since polyarthritis, as a symptom, may suggest the progression to rheumatoid arthritis, especially when inflammatory joint complaints precede the diagnosis of SS or even sicca symptoms. Yang et al. found that the presence of arthritis, RF, and anti-CCP were independent risk factors for SS overlapping with RA. The distinction between patients with SS-pa and SS-RA is of highest importance, since it outlines the therapeutic consequences. Since there is no significant difference between these two patient groups regarding the occurrence of either extraglandular manifestations or associated organ-specific autoimmune diseases, it is difficult for clinicians to decide the exact origin of arthritis in these patients.

From a different point of view, recognizing the association of SS in patients with RA is also important. The prevalence of SS in RA patients was found to be 8.7–10% by different groups. According to a recent paper, even the responsiveness to targeted treatments is different in RA patients when associated with Sjögren's disease, as follows: anti-tumor-necrosis factor (TNF)-alpha agents are less effective, whereas rituximab is more effective than in RA alone. Furthermore, joint damage is worse in SS-RA patients than in RA patients without the association of SS. Several authors highlight the importance of recognizing erosive arthritis during the disease course of SS, being most beneficial before the emergence of irreversible radiological manifestations. Our ROC curve analysis could achieve an acceptable differential diagnostic accuracy, yet it cannot be easily used in everyday practice for individual cases. Thus, laboratory examinations must take priority. As supported by our results, rheumatoid factor assessment is not enough to distinguish between early rheumatoid arthritis and Sjögren's disease complicated by polyarthritis. If clinical suspicion is high, the measurement of anti-citrullinated protein antibodies is highly recommended. In both cases, high-positive ($\geq 3 \times$ ULN) values improve diagnostic accuracy. Nevertheless, in patients with Sjögren's disease complicated by polyarthritis, awareness justifies regular anti-CCP screening, until a more suitable biomarker appears on the horizon.

This study has the following limitations: the data were collected retrospectively, and no disease activity scores were calculated, due to the overlapping features of SS and RA.

As we know, B-cell hyperactivation is a hallmark of pSS, including polyclonal hypergammaglobulinemia, including the rheumatoid factor, antinuclear autoantibodies, and other autoantibodies, which are essential players in the development of systemic manifestations.

Rheumatoid factor (RF) is among the first biomarkers associated with rheumatoid arthritis; however, its significance has been reevaluated, as it is not specific to RA and is frequently found in other conditions such as Sjögren's disease, systemic lupus erythematosus (SLE), chronic infectious diseases (e.g., syphilis), tuberculosis, certain liver diseases, and even in healthy elderly individuals. Therefore, examining RF isotypes may be important, as studies suggest they can provide additional diagnostic information and may be useful in specific patient populations, such as those with seronegative arthritis.

In the second part of our study, we analyzed the data of a total of 164 SS patients, of whom 119 had inflammatory joint involvement. Upon reviewing their laboratory parameters, we found no significant differences in most measured values; however, it was observed that the total IgG levels were highest in the SS group, significantly higher than in any of the other two patient groups, and still higher among polyarthritis patients than in the RA-associated group. Based on these results, we can see that higher IgG levels are inherent in Sjögren's disease, and they are not caused by rheumatoid arthritis.

In search of a potential biomarker, we examined RF isotypes in this patient population. According to our results, we noticed that the IgA-RF were the highest in the SS group and the lowest in the SS+RA subgroup, although the difference was not significant. This suggests that IgA isotype RF is more a marker of Sjögren's disease than of rheumatoid arthritis. According to another study, serum concentration of IgA RF in patients with SS without EGMs was significantly higher than in patients with SS associated with RA, while in the latter, the IgM-RF isotype was more dominant. These findings correspond to our results. In that paper, IgG-RF and IgA-RF presented higher concentrations in SS patients without EGM than in SS with EGM. Our cohort presented similar results, although the differences were not significant. Lee et al. published even more comparable results as follows: the presence of IgA RF in patients with SS was associated with a significantly worse exocrine function and active serologic profile, and there was no association between IgA RF and EGM. Regarding the active serologic profile, we found the same association. That said, in EGMs, although we did not find a significant difference in IgA RF, IgG RF, and IgM RF levels in most extraglandular manifestations, all RF isotypes were significantly higher if skin manifestations occurred. According to another study that investigated RA patients, IgA RF was associated with the early development of bone erosions and with extra-articular manifestations, particularly sicca symptoms.

Based on our results, RF levels have a strong positive correlation with each RF isotype, and so did IgG, anti-Ro/SS-A, and anti-La/SS-B levels, except for the SS+RA group. Our data correspond with the findings of Maślińska et al., who reported that RF-IgA showed the best diagnostic accuracy for SS and it correlated with anti-Ro/SS-A and anti-La/SS-B antibodies, even more closely than IgM RF. IgA RF may be considered an additional marker of immunological activity in SS, as its presence correlated with level of antibodies, which are characteristic for a serologic profile of SS.

The numerous shared features of all RF isotypes, especially for SS patients without RA-positive correlations with IgA, IgG, anti-Ro/SS-A, and anti-La/SS-B levels, lead us to the conclusion that these parameters are common indications of the polyclonal B-cell activation typical in SS, and they become less pronounced when RA co-occurs.

In a paper with the purpose of defining the diagnostic accuracy of RF isotypes in the clinical scenario of inflammatory arthralgia, where the differential diagnoses included lupus, SS, and osteoarthritis, RF IgM isotype and anti-citrullinated protein antibodies were more useful in confirming RA diagnosis than other RF isotypes. Others found that the combined presence of IgG, IgA, and IgM isotype RF is characteristic of RA, while the presence of IgG and IgA isotype RF, in addition to the absence of the IgM isotype, is characteristic of other autoimmune diseases. Van Hoovels et al. noticed that the combined positivity of RF IgM, IgA, and ACPA IgG had the highest specificity for RA diagnosis and classification. In our cohort too, IgM RF alone was not enough to differentiate between patient groups. However, when combined with normal total IgG levels, high IgM RF could better define SS+RA patients.

As highlighted in a review paper, the presence of the IgA isotype of not only RF but also anti-modified protein antibodies indicates the key role of these antibodies in the inflammatory and destructive processes of RA. Furthermore, this isotype supports the mucosal origin hypothesis of the disease. Our research revealed that the higher the IgA isotype RF, the more active the disease is based on the ESSDAI and DAS28, both for RA and Sjögren's disease with or without polyarthritis. Based on these results, elevated IgA RF levels predict a more active disease and might serve as an unfavorable prognostic factor.

Our results revealed that in the presence of any RF isotype, patients tend to be younger, and in case of IgA RF, disease duration is significantly shorter as well. The correlation analysis depicts a significant negative correlation with age in SS and SS+pa patients as well. These

findings can be at least partially explained by the immune senescence, as highlighted by a recent paper where RF levels were significantly lower in older age groups; however, those patients had RA, while in our SS+RA group, we did not find any significant negative correlation with age. Moreover, when disease activity is higher, the presence of other autoantibodies and inflammatory markers is more frequent in these seropositive cases, which indicate a more severe disease course. Our findings are confirmed by the similar results of a recent study which compared seropositive and seronegative SS patients. These findings emphasize the significance of immunological markers in risk stratification, and they might pave the way towards personalized therapy.

In our correlation matrix, both the initial and the most recent anti-cyclic citrullinated peptide (anti-CCP) levels showed a significant positive correlation with IgM RF levels, but only in the SS+RA patients. This pattern is more characteristic of rheumatoid arthritis rather than Sjögren's disease. It is well known that in RA, the IgM RF isotype is the most dominant; however, the other two isotypes are also frequently present in this systemic autoimmune disease.

When examining the effect of patients' ongoing immunomodulatory or immunosuppressive therapy on RF isotypes, we found that sulfasalazine use was significantly less frequent among IgG RF–positive patients compared to isotype-negative ones, while no other significant differences were observed for the remaining drugs. This may suggest that sulfasalazine reduces IgG RF concentrations. In another study, Kanerud et al. investigated the effect of sulfasalazine on the systemic and mucosal humoral immune system in patients with rheumatoid arthritis. They reported a significant decrease in total IgA and total IgG levels, as well as in circulating IgA RF and IgM RF levels after treatment, whereas immunoglobulin levels in saliva and jejunal fluid remained unchanged. These findings indicate that sulfasalazine exerts a strong but selective inhibitory effect on systemic immunoglobulin production, without affecting mucosal immunoglobulin synthesis. Other studies have shown that IgM RF and IgA RF levels also decrease during methotrexate therapy; however, changes in these autoantibody levels did not correlate with disease activity but rather reflected the degree of immunosuppression. This suggests that while current therapies can modulate autoantibody levels, such changes have limited clinical relevance on their own—though these observations were made in a rheumatoid arthritis patient population.

The retrospective nature of the study is one of its limitations. A multi-center design with even more patients could have shown more significant data. Furthermore, repeated measurements of RF isotypes would have allowed us to track longitudinal changes in RF isotypes and further characterize their relation to disease-specific parameters, e.g., the ESSDAI, ESSPRI.

6. Summary of new observations

1. In cases of Sjögren's disease associated with rheumatoid arthritis, joint pain may precede the diagnosis of SS.
2. In SS patients with inflammatory joint pain, elevated anti-CCP levels indicate a higher risk of progression toward rheumatoid arthritis.
3. Using a binary multiparametric logistic regression model with high-positive (≥3 × ULN) RF and anti-CCP levels, we achieved acceptable differential diagnostic accuracy. The presence of renal involvement and anti-Ro/SS-A positivity further increased the likelihood of developing SS-RA, whereas anti-La/SS-B positivity reduced it.
4. Elevated IgG levels are primarily a feature of Sjögren's disease rather than a consequence of rheumatoid arthritis.
5. The presence of any RF isotype is generally associated with younger age, more severe disease course, and in the case of IgA RF, a significantly shorter disease duration.
6. IgA RF may serve as a potential early biomarker for unfavorable prognosis in SS.
7. High total IgG levels combined with high IgA RF suggest Sjögren's disease, whereas normal total IgG combined with high IgM RF points toward an association with rheumatoid arthritis.

7. Summary

During the follow-up of patients with Sjögren's disease, the recognition of associated rheumatoid arthritis at the right time helps to provide an appropriate treatment and thereby slow down or prevent the progression of bone erosions. However, in everyday practice, it is not always simple to recognize the exact background of recent-onset polyarthritis in a patient with

long-standing SS. In our binary multiparametric logistic regression model, using high-positive (≥3 × ULN) RF and anti-CCP levels, an acceptable level of differential diagnostic accuracy was achieved, where kidney involvement and anti-Ro/SS-A positivity further increased the chance of having SS-RA, while, on the contrary, anti-La/SS-B positivity decreased it. However, this model still does not perfectly predict the co-existence of RA in the background of inflammatory arthritis in an SS patient. Therefore, further biomarkers should be found for an easier distinction between the different origins of inflammatory joint manifestations during the disease course of individuals with SS.

In our oppinion, rheumatoid factor isotypes could serve as such biomarkers. IgA and IgM RF isotypes have an additive diagnostic value when the goal is to distinguish between SS+pa and SS+RA; however, they must be combined with total IgG levels. High total IgG levels together with high IgA RF suggest SS, and normal total IgG levels combined with high IgM RF are suggestive of SS+RA. In SS+pa, the most sensitive combination is a high total IgG and normal IgM RF. Notably, the presence of RF of any isotype predicts a more severe disease course. Finally, the positive correlation between IgA RF and ESSDAI, the several markers of serological activity of SS, and its negative correlation with age make IgA RF a potential biomarker for early, poor prognosis of SS. Based on our results, we recommend using IgA RF levels as a complementary marker, especially upon diagnosis or upon the development of joint complaints during the disease course of SS patients.

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9. List of publications

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Candidate: Zsófia Aradi
Doctoral School: Gyula Petrányi Doctoral School of Allergy and Clinical Immunology
MTMT ID: 10094569

List of publications related to the dissertation

1. **Aradi, Z.**, Bói, B., Nagy, G., Antal-Szalmás, P., Mezei, K., Horváth, I. F., Szántó, A.: Additive Value of Rheumatoid Factor Isotypes in Sjögren's Syndrome Patients with Joint Complaints of Different Etiologies: Can Rheumatoid Factor IgA Serve as an Early, Poor Prognostic Biomarker Candidate?
   Int. J. Mol. Sci. 26 (10), 1-13, 2025.
   DOI: http://dx.doi.org/10.3390/ijms26104797
   IF: 4.9 (2024)
2. **Aradi, Z.**, Nagy, G., Horváth, I. F., Antal-Szalmás, P., Szántó, A.: Polyarthritis in Sjögren's Syndrome: Difficulties in Distinguishing Extraglandular Manifestation and Associated Rheumatoid Arthritis.
   Diagnostics. 14 (14), 1-12, 2024.
   DOI: http://dx.doi.org/10.3390/diagnostics14141494
   IF: 3.3

List of other publications

3. Módis, L., Matuz, A., **Aradi, Z.**, Horváth, I. F., Szántó, A., Bugán, A.: Unveiling psychobiological correlates in primary Sjögren's syndrome: a machine learning approach to determinants of disease burden.
   Front. Psychiatry. 16, 1-11, 2025.
   DOI: http://dx.doi.org/10.3389/fpsyt.2025.1549756
   IF: 3.2 (2024)
4. Mezei, K., Nagy, L., Orosz, V., **Aradi, Z.**, Bói, B., Szántó, A.: Obesity: Friend or Foe in Sjögren's Syndrome Patients?
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5. Módis, L., **Aradi, Z.**, Horváth, I. F., Pikó, P., Papp, G., Osváth, M., Szántó, A., Bugán, A.: Spirituality is associated with immune parameters and disease activity in primary Sjögren's syndrome: a cross-sectional study.
Sci. Rep. 14 (1), 1-9, 2024.
DOI: http://dx.doi.org/10.1038/s41598-024-62801-w
IF: 3.9

6. Módis, L., **Aradi, Z.**, Horváth, I. F., Bencze, J., Papp, T., Emri, M., Berényi, E., Bugán, A., Szántó, A.: Central Nervous System Involvement in Primary Sjögren's Syndrome: Narrative Review of MRI Findings.
Diagnostics. 13 (1), 1-18, 2023.
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