The impact of concomitant Sjögren’s disease on rheumatoid arthritis disease activity: a systematic review and meta-analysis

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Abstract

Objective
Rheumatoid arthritis (RA) and Sjögren’s syndrome (SS) frequently co-exist but the consequence for RA disease activity of having concomitant SS (RA/SS) is not well established. We conducted a systematic review and meta-analysis to investigate the impact of SS on disease outcomes in individuals with RA.

Methods
We searched Web of Science (Core Collection, FSTA, Medline), PubMed and Cochrane databases, without language restriction. Studies reporting RA disease activity scores, joint counts, visual analogue scales (VAS), disability and joint damage, and comparing RA and RA/SS were selected. Outcomes reported in at least 3 studies in which the diagnosis of SS fulfilled classification criteria underwent meta-analysis, using a random effects model where heterogeneity was detected.

Results
The literature search identified 2991 articles and abstracts; 23 underwent full-text review and 16 were included. The studies included a total of 29722 patients (8614 with RA/SS and 21108 with RA). Using studies eligible for meta-analysis (744 patients with RA/SS and 4450 with RA), we found higher DAS-28 ESR scores (mean difference 0.50, 95% CI -0.008–1.006; p=0.05), higher swollen joint count scores (mean difference 1.05, 95% CI 0.42-1.67; p=0.001), and greater functional disability as measured by HAQ (mean difference 0.19, 95% CI 0.05–0.34; p=0.009) in RA/SS compared to RA alone. Other outcome measures (tender joint count, fatigue VAS) showed a numerical trend towards higher scores in RA/SS but were not statistically significant.

Conclusion
RA/SS patients appear to have higher disease activity and more functional disability than patients with RA alone. The aetiology and clinical implications of this are unclear and warrant further investigation.

Key word
Sjögren’s syndrome, rheumatoid arthritis, outcome assessment, health care, patient-reported outcome measures, disability evaluation, fatigue, erosive arthropathy
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Introduction
Rheumatoid arthritis (RA) is the most common rheumatic immune-mediated inflammatory disease (IMID). Poorly controlled disease activity is associated with disability and joint damage. Numerous disease-modifying treatments exist that are introduced in a trial-and-error approach with few pointers to indicate which patient may respond best to which treatment. Sjögren’s syndrome (SS) is another IMID that is characterised by focal lymphocytic infiltration of the exocrine glands, dryness, fatigue and extraglandular manifestations including non-erosive arthritis (1, 2). Estimates suggest between 3.6–31% of individuals with RA also have SS, with the differing values influenced by divergent classification criteria, methodolology, geographics and disease duration (3–6). Rather than considering SS as ‘secondary’ to RA, it is possible that SS concomitant with RA (RA/SS) might define a disease subset with differing pathophysiology and treatment response (7). The preferential SLE outcomes with epratuzumab for a SLE/SS subset in the post-hoc analysis of the EMBody trials illustrates this possibility (8). The pathogenesis of SS is strongly associated with type I interferon and B cell hyperactivity and lack of response to anti-TNF (9, 10). Type I interferon is also associated with poor outcomes in RA (11) but whether the co-existence of RA and SS is associated with worse RA outcomes is not clear. Several studies have assessed the impact of concomitant SS on RA disease activity, but these studies are often small, inconclusive or have divergent conclusions. Furthermore, SS is associated with higher ESR, due to hypergammaglobulinaemia, and high symptom burden, including limb pain and fatigue. Elevated ESR and symptom burden due to SS might impact the measurement of composite scores of RA disease activity.

Despite the prevalence of RA/SS, data remains scarce on its interaction with RA disease activity and patient outcomes. Identifying the characteristics and impact of RA/SS may help clinicians improve assessment and treatment in this population.

We conducted a systematic review and meta-analysis to understand if disease activity scores, joint damage and disability differed according to the presence or absence of SS. If composite disease activity scores differed, we aimed to understand which components were responsible for the observed differences.

Methods
Search strategy and study selection
Our systematic review was performed following an a priori described protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guideline (12). This review protocol was registered with PROSPERO (registration number CRD42022377490) (13). We searched Web of Science (Core Collection, FSTA, Medline), PubMed, Cochrane databases up to September 2022 to find studies comparing the RA clinical outcomes of RA alone with RA/SS. There were no restrictions on age, sex or duration of the study. There were no geographic or language limitations. Two authors (TT and TC) independently selected studies based on titles and abstracts. Afterward, full-text articles were acquired for those studies assumed to satisfy the inclusion criteria. The papers were independently evaluated by the 2 assessment-authors. A third assessment-author (BF) was consulted if agreement was not reached.

We included the following search terms: ‘rheumatoid arthritis’, ‘Sjögren’, ‘secondary’, ‘overlap’, ‘disease activity’, ‘erosions’, ‘disability’, ‘DAS (Disease activity score) 28’, ‘SDAI (Simplified Disease Activity Index)’ and ‘CDAI (Clinical Disease Activity Index)’. We excluded single case reports. Studies where either the 2002 American-European Consensus Group (AECG), 2012 provisional American College of Rheumatology (ACR) or 2016 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for SS could not be applied were excluded from meta-analysis.

Data extraction and quality evaluation
All data were independently extracted by two authors (TT and TC). Information on the study such as author, year of
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publication, study design, study place, sample size, diagnosis of RA and SS and classification criteria used, age and gender of patients were collected. We evaluated the quality of evidence of studies with the Newcastle-Ottawa Scale (NOS) (14, 15). The maximum NOS score is 9 points and studies achieving 0–3, 4–6 or 7–9 points were considered low, medium, and high quality, respectively.

Outcome evaluation
The primary outcome was a composite measure of RA disease activity: DAS28-ESR (Erythrocyte sedimentation rate), DAS28-CRP (C-reactive protein), SDAI or CDAI. Secondary outcomes were Swollen Joint Count (SJC), Tender Joint Count (TJC), Health Assessment Questionnaire-Disability Index (HAQ-DI) or modified Health Assessment Questionnaire (mHAQ), Visual Analogue Scale (VAS), joint damage indices and number of patients with damaged joints.

Statistical analysis
We performed a meta-analysis on observational or case control studies using a random effects model. Clinical parameters with less than 3 studies were considered inappropriate for statistical analysis. Heterogeneity of selected studies were assessed using the I² statistic; I² value of ≤25% indicates low heterogeneity, 25%–75% as moderate heterogeneity and >75% as considerable heterogeneity (16). In addition, we assessed heterogeneity of studies with the Tau-squared method (17) and using Cochran’s Q-statistics with a significance level of p<0.10. Publication bias was assessed with funnel plots (18). We did not perform meta-regression analysis because the number of obtainable studies for each analysis was less than 10. For continuous data, mean difference (MD) and 95% CI were calculated with mean value and standard deviation (SD) of RA and RA/SS patients. When data were not presented as means and standard deviations, we estimated with the median, first quartile, third quartile, and sample size (19-21). If data were skewed, we performed subgroup analyses of studies with skewed data and no skewed data for examination of the effect of skewed data on results. Statistical analyses were performed with R commander (manova; R Ver 2.7-1) (22). All statistical tests adapted a two-sided p-value of 0.05 for significance except for the Q-statistics.

Results
Study selection
We identified 3723 references through the literature search of which we removed 36 duplicates (n=36) and 696 ineligible (n=696) articles prior to screening. A further 2991 titles and abstracts were excluded after primary screening. A further 2991 titles and abstracts were excluded after primary screening. After reviewing the remaining 23 full text articles, we excluded 5 studies without enough data and 2 studies with overlapping samples from the same database. Finally, 16 full-text papers met all eligibility criteria (Fig. 1).

Characteristics of the included studies
Table I shows the characteristics of the 16 included observational papers (5 cohort studies, 5 case-control studies and 6 cross-sectional studies) with a total of 21,108 RA patients and 8,614 RA/SS patients. All papers were published between 1999 and 2022, with 6 studies in Europe, 2 studies in North America, 3 studies in South America, 5 papers in East Asia, 1 paper in South Asia. The method of SS diagnosis was described in all the studies except Uhlig et al. (23). However, this paper contained a group with low tear and saliva flow that we considered would likely meet 2002 AECG classification for SS. Harrold et al described a registry-based study where SS was a physician-reported diagnosis and the study did not capture whether SS classification criteria were
fulfilled; this study was therefore excluded from meta-analysis.

The mean age of RA and RA/SS patients were 58.5 and 61.1 years. The proportions of female patients were 68.1% and 81.6%, in the RA and RA/SS groups respectively. Disease duration did not differ between groups except in three studies (5, 24, 25). Several studies identified a higher proportion of patients in the RA/SS group as being rheumatoid factor or anti-citrullinated protein antibody positive when compared with RA alone. However, no study stratified their analysis by autoantibody status. Where available, data on comorbidities and RA treatments are included in Supplementary Tables S1 and S2. Using NOS we determined that 8 papers were of high quality (7–9 points) and 8 papers medium quality (4–6 points).

Composite measures of disease activity
There was only one paper containing data for CDAI and no papers containing data for SDAI. Therefore, we only performed meta-analysis for DAS28-ESR and DAS28-CRP.

Meta-analysis of DAS28-ESR included 7 studies (23, 26-31), with a total of 1920 RA and 320 RA/SS patients. For one paper (27), the mean DAS28-ESR and SD were calculated using the provided data. The calculated data-distribution was not significantly skewed. We adopted a random effects model due to the high heterogeneity of studies (I²=78.3%, τ²=0.38, p<0.01) (Fig. 2A). The difference between the two patient groups showed a strong trend to higher DAS28-ESR scores in RA/SS with borderline statistical significance (MD: 0.50; 95% CI [-0.008; 1.006]; p=0.05) (Fig. 2A).

For meta-analysis of DAS28-CRP we included 6 studies (3, 24, 26, 28, 32, 33) comprising 2166 RA and 330 RA/SS patients. The mean CRP in RA and RA/SS patients were 2.0 (95% CI [1.5; 2.5]) and 2.5 (95% CI [2.0; 3.0]) mg/l respectively. We performed a meta-analysis for CRP using only 3 studies, which comprised 865 RA and 215 RA/SS patients. The mean CRP in RA and RA/SS patients were 2.0 (95% CI [1.5; 2.5]) and 2.5 (95% CI [2.0; 3.0]) mg/l respectively. A significant difference was observed between the two patient groups (MD: 0.50; 95% CI [0.30; 0.70]; p=0.0003) (Fig. 2B).

ACPA: anti-citrullinated protein/peptide antibody; Duration: RA disease duration; N: number of seropositive patients; N/A: no data available; NOS: Newcastle-Ottawa Scale; NS: not significant; +ve: positive; RA: rheumatoid arthritis; SS: Sjögren’s syndrome; T: total number of patients with data available.

*Based on IgG.
*Calculated by Chi-square test when p-value was not presented in cited papers.
SS patients. We adopted a random effects model due to the high heterogeneity between studies (I²=90%, τ²=0.32, p<0.01) (Fig. 2B). There was no significant difference despite a numerical trend to higher scores in the RA/SS group (MD: 0.37; 95% CI [-0.13; 0.87], p=0.15) (Fig. 2B). We included 8 studies (3, 23, 29-31, 34-36) in the meta-analysis of SJC with a total of 1637 RA and 342 RA with SS patients. There was significant heterogeneity between studies (I²=60%, τ²=2.6923, p=0.01) (Fig. 3B). We found no significant difference between RA patients and RA/SS patients, despite a numerical trend to higher counts in the RA/SS group (MD: 0.88; 95% CI [-0.58; 2.35], p=0.24) (Fig. 3B).

Function
We found 4 papers with function data suitable for meta-analysis; 3 studies with HAQ-DI (26, 29, 34) and 1 study with mHAQ (23). Altogether, they included 693 RA and 126 RA/SS patients. There was no significant heterogeneity of studies (I²=21.9%, τ²=0.0001, p=0.28) (Fig. 4). Function was worse in the RA/SS group compared with RA alone (MD: 0.19; 95% CI [0.05; 0.34], p=0.009) (Fig. 4). We also performed subgroup analysis using papers with HAQ-DI data and studies with mHAQ data (Suppl. Fig. S2). We observed no significant differences between studies with HAQ-DI and papers with mHAQ (Q=0.01, p=0.93) (Suppl. Fig. S2).

Our literature search identified a further paper by Harrold et al. presenting data from a very large registry study in the USA (5). We did not include this in our meta-analysis as the diagnosis of SS was a physician answered question without evidence of fulfilment of SS classification criteria. Nevertheless, consistent with the data above, this study found RA/SS patients had a higher mHAQ (0.4, SD 0.5; n=7659) compared to RA alone (0.3, SD 0.4; n=16466).

VAS
Studies with groups meeting SS classification criteria and reporting VAS data included 2 papers with patient-reported pain VAS (3, 23), 3 studies with patient-reported fatigue VAS (23, 29, 34), 2 papers with patient global assessment VAS (patient’s global assessment) (23, 29), and only 1 study with physician global assessment VAS (23).

Uhlig et al. (23) reported that the RA/SS patients had worse pain VAS scores (mean=43.1, SD=22.0, n=46) than RA alone (mean=32.9, SD=22.0, n=377). Haga et al. (3) supported these findings, with their RA/SS group having worse scores (mean=39.00, SD=28.68, n=11) than those with RA alone (mean=29.13, SD=23.81, n=296).

Uhlig et al. (23) also reported that the RA/SS group (mean=2.91, SD=0.98,
n=46) had worse scores for patient global assessment (range 1–5) than the RA group (mean=2.55, SD=0.87, n=377). On the contrary, Lins et al. (29) reported that the RA/SS group had a better score using a different patient global assessment (range 0-100 mm) (mean=46.7, SD=32.9, n=39) than RA group (mean=53.2, SD=31.7, n=191).

Meta-analysis of fatigue V AS included 638 RA and 112 RA/SS (23, 29, 34). There was no significant heterogeneity of papers (I²=42.6%, τ²=29.53, p=0.18) (Suppl. Fig. S3). We found no significant difference between RA patients and RA/SS patients (MD: 3.73; 95% CI [-5.42; 12.88], p=0.42) (Supplementary Fig. S3). V AS data from the Harrold et al. registry study were excluded from the meta-analysis because they did not use classification criteria of SS (5, 37), but similarly reported that the RA/SS group had higher pain scores and patient global assessment.

Joint damage
There were only two studies which included Sharp/van der Heijde scores as a measure of radiographic joint damage (24, 32) and only one paper with a damaged joint count as a clinical measure (23).

With the Sharp/van der Heijde method, Larocque et al. demonstrated that the RA/SS group had more radiographic joint damage (n=39, median=13.9) compared with RA alone (n=39, median=15.4) (23). However, there was no statistical significance (p=0.79) (32). Brown et al. also described the same tendency; RA/SS (n=85, median=47.5) having more radiographic joint damage than RA alone (n=744, median=17.0) (24). Using a less sensitive clinical measure, Uhlig et al. reported no difference in deformed joint count (0-18) between RA alone (n=377, mean=1.8, SD=3.5) and RA/SS (n=46, mean=1.8 SD=3.4) (23).

Three papers reported the percentage of patients with at least one damaged joint. (25, 35, 38). Yang et al. used radiographic assessments, but was non-informative as all patients in both groups had at least one damaged joint (35). The other two papers assessed joint deformity clinically. He et al. reported that RA/SS patients (n=74, 60.8%) were more likely to have a clinically deformed joint than patients with RA alone (n=435, 45.3%) (25). Meanwhile, Santosh et al. demonstrated a numerically higher percentage of patients with ≥1 damaged joint in the RA/SS group (36%) compared to RA alone (32%), although this did not reach statistical significance (p=0.29) (38).

Discussion
The coexistence of more than one autoimmune disease is common (39) but the impact of one autoimmune disease on the disease activity or outcomes of a second is rarely examined. Various small studies have suggested that RA disease activity may be higher in patients with concomitant SS. Based on available data, our meta-analysis confirms that patients with RA/SS have higher DAS28-ESR scores (p=0.05). It is well-recognised that patients with SS often have raised ESR, at least in part due to higher immunoglobulin levels, however CRP is typically normal except in the presence of certain extra-glandular features that may include inflammatory arthritis. Patients with SS are also well-recognised to have a high symptom burden, including limb pain and fatigue, that negatively impacts health-related quality of life. It is therefore possible that these factors, ESR and symptoms, may be the drivers behind the observed higher DAS28-ESR scores. It is therefore of interest that we also found that patients with RA/SS had a higher swollen joint count than
those with RA alone. Further, although the DAS28-CRP meta-analysis did not reach statistical significance, it showed a similar numerical trend. Other papers we identified showed higher symptom burden, higher disability as measured by mHAQ/HAQ and higher joint erosion scores.

The papers identified in our systematic review do not identify any biological mechanisms underlying the observations of higher disease activity in RA/SS and this will need to be a subject of further research. However, a biological mechanism is not implausible as, for example, SS is strongly associated with a high type 1 interferon signature (40) that in RA is a poor prognostic factor (11).

There are potential implications related to our findings. Uncontrolled disease activity in RA is associated with joint damage, disability, and higher risk for subsequent joint replacement. Although there are numerous therapies used to control disease activity in RA, these are typically introduced in the order of their historical introduction into medicine, with no reliable predictors of response to specific therapies and primary nonresponse rates of at least 30%; both factors leading to cycling through treatments. Whether the presence of concomitant SS should influence the selection of therapy in RA is yet to be determined but is worthy of further research. Firstly, if there are pathobiological differences in RA processes between RA/SS and RA alone, there may be a differential response to certain immunomodulators depending on the presence or absence of SS. Secondly, in RA/SS there are two autoimmune processes that may have a discordant or concordant response to any potential therapy, for example, anti-TNF has not been demonstrated to be efficacious in primary SS (9, 10). Thirdly, SS-related pathobiology may influence drug-response through other means. For example, Chen et al. utilised an autoantigen microarray in adalimumab treated RA patients and identified that the presence of anti-Ro60 antibodies were associated with formation of anti-drug antibodies and poor EULAR response (41), although this finding needs further validation in larger cohorts. The presence of anti-Ro antibodies also predicts a poorer response to abatacept (42), although again this needs validation in larger cohorts.

Our study has significant limitations, meaning that we need to be cautious about our conclusions. The included studies showed statistically significant heterogeneity, although we compensated for this by selecting a conservative random effects model, as opposed to a fixed effects model, to evaluate statistical significance. Studies were mainly cross-sectional, and it was not possible to correct for factors that may have differed between groups such as disease duration, sex, co-morbidities, and therapy. We were unable to identify if our observations applied equally to RF or ACPA positive and negative patients, or if seropositivity was a confounding factor given the imbalance observed in some studies, as none of the analyses were stratified by autoantibody status. No SS-specific outcome measures were available and SS disease activity might also impact functional scores such as the HAQ.

There are also particular challenges in researching RA/SS. Studies which have carefully documented the presence of SS using recognised classification criteria are typically small well-characterised cohorts which may therefore lack statistical power to explore differences in some outcomes or to adjust for confounders, co-morbidities, disease duration and treatment. An alternative approach is to utilise large registry studies which may have the requisite statistical power to assess disease activity and treatment response in a fully adjusted analysis, but where the diagnosis of SS may not be based upon classification criteria. Whilst a physician diagnosis may be conservative and based upon objective evidence of SS, as well as reflecting ‘real-world’ clinical practice, it is very possible that the method for diagnosing SS may vary between sites. The diagnosis of SS without a full evaluation of tests typically included in classification criteria is subject to potential error as dryness symptoms are common and may be due to other causes such as meibomian gland deficiency, age or drug side effects. Thus, physician diagnosis may under or over diagnose SS relative to classification criteria. The challenges of correct classification will only be amplified further with studies attempting to utilise larger primary care databases.

Conclusion
We have identified that RA disease activity is higher in RA/SS patients. Whilst we need to be cautious in our interpretation, we believe our findings are important for raising awareness and stimulating further research to characterise the underlying biological mechanisms and clinical implications.

Take home messages
- Patients with RA/SS may have higher disease activity than RA alone.
- The pathobiology and clinical implications of this require further investigation.
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