Compromised ultrasound remission, functional ability and clinical decision associated with overlapping Sjögren's syndrome in rheumatoid arthritis patients: results from a propensity-score matched cohort from 2009 to 2019

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Received on June 1, 2020; accepted in revised form on July 27, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 126): S73-S77.

Key words: rheumatoid arthritis, overlapping Sjögren's syndrome, ultrasound remission, HAQ, propensity-score matching

ABSTRACT

Objective. *Rheumatoid arthritis (RA) patients with Sjögren's syndrome (SS) often present with more severe synovitis. We intended to clarify the impact of overlapping SS on ultrasound remission, functional ability and clinical decision-making in RA patients in a real-world cohort from 2009 to 2019.*

Methods. *The medical records of RA patients in our medical centre from 2009 to 2019 were reviewed. Cox proportional hazards models of ultrasound remission and no disability (by health assessment questionnaire [HAQ]) were conducted in both the 1-to-1 nearest propensity score matched (PSM) and unmatched cohorts between RA patients with SS (RA-SS) and without (RA-noSS) to correct critical confounders. Four kinds of PSM methods were used and the corresponding average treatment effect on the treated (ATT) was calculated to clarify the effect of overlapping SS on distinguishable characteristics or drug prescription in RA patients.*

Results. *A total of 1100 RA patients were included in the study, of which 133 (12.1%) overlapped with SS. Among 256 patients consisting of 128 RA-SS and 128 RA-noSS after 1-to-1 nearest PSM, overlapping SS was associated with a 44%, 32% lower probability of reaching ultrasound remission, no disability in RA patients, respectively. More hydroxychloroquine (HCQ) usage, less biologic disease-modifying anti-rheumatic drugs (bDMARDs) prescription were confirmed to be correlated with overlapping SS by the robust PSM.*

Conclusion. *Overlapping SS is associated with a lower probability of reaching ultrasound remission and no disability in RA patients. HCQ may still be the mainstream of clinical decision making in RA-SS patients.*

Funding: this work was supported by the National Natural Science Foundation of China (no. 81801604, 81771740, 81971524).

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that mainly affects the joints, resulting in severe joint damage and physical disability if improperly treated. Over the past decade, the implementation of treat-to-target (T2T) has brought unprecedented innovation to the management of RA. Clinical assessment of joints, together with serological acute phase reactants (APRs) and patient-reported outcomes (PROs), are the most common for practicing T2T.

Inflammation is at the apex of joint destruction and functional disability in RA (1). When APRs and PROs are significantly disturbed, musculoskeletal ultrasound provides a simple, objective and feasible way to evaluate the inflammation in the joint. Besides, the presence of subclinical synovitis has been confirmed to be associated with radiological progression and subsequent clinical flare, which is detrimental to RA patients with the aim of achieving good long-term outcomes (2-4).

Overlapping SS is common in RA patients. The coexistence with Sjögren's syndrome (SS) is reported in 5.5% to 38.7% RA patients worldwide (5-9). Cross-sectional studies have demonstrated that RA-SS patients are more likely to suffer from severe arthritis (9, 10). Besides, we have verified that overlapping SS reduces the probability of reaching target in RA patients (11). However, the effect of overlapping SS per se on the subclinical synovitis, functional ability and clinical decision keeps a riddle, making the clarification of the correlation important.

To correct known confounding factors, propensity score matching (PSM) was used to clarify the aforementioned outcomes of interest (12, 13).

Methods

Study subjects

Between January 2009 and September 2019, 1100 patients were included from our hospital with RA according to the 1987 American college of Rheumatology (ACR) criteria or 2010 ACR/European League Against Rheumatism (EULAR) classification criteria, ages 16 years or older, without other definite connective tissue diseases except SS (14, 15). The diagnosis of SS was based on the 2016 ACR/EULAR classification criteria (16).

General demographic data, ultrasound grey-scale (GS) and power Doppler (PD) score based on scan of bilateral wrists and hand joints, health assessment questionnaire (HAQ) scores, ILD confirmed by chest CT, laboratory findings and drug prescription were retrospectively collected. Chest CT was only applied in patients with symptoms or positive signs suggestive of ILD on physical examination or chest x-ray. The diagnosis of ILD was based on the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (17). Anti-SSA was detected by immunoblotting assay, and positive labial salivary gland biopsy was defined as focal lymphocytic sialadenitis with focus score ≥1 foci/4 mm^2. The study was approved by the institutional Research Ethics Committee and all patients received informed consent for data collection of their medical records.

Propensity score matching

Propensity score methods have long been verified as a reliable approach to reduce the effects of confounding in the observational studies (13). In the current study, propensity score matching (PSM) was applied to correct possible confounding factors including age, gender, RA duration, rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) status, disease activity at first visit. Besides, "whether T2T or not" was used to control the confounding effect caused by treatment differences, which was defined according to the year of first visit after or prior to 2011, since when the T2T concept has been generally adopted in our medical centre, causing a dramatically decline in disease activity (18).

Ultrasonography was routinely performed by 2 experienced rheumatologists who were blinded to all clinical data with interobserver reliability of 0.986 for GS and 0.988 for PD (19). 22 joints (bilateral wrists, metacarpophalangeal joints and proximal interphalangeal joints) were scanned from dorsal aspect on transverse and longitudinal planes. The LOGIQ E9 ultrasound machine (General Electric) with a corresponding linear transducer ML 6–15 was used in our study. The synovitis was measured and semi-quantitatively graded using the 2001 Szkudlarek method (20). PD total score (0–66) and GS total score (0–66) were the sum of PD scores and GS scores at each joint, respectively. Ultrasound remission was referred to the state of total GS≤1 and PD=0.

To explore the effects of overlapping SS on ultrasound remission and functional ability improvement, we identified 1 propensity score matched RA-noSS patient using a 1:1 greedy matching algorithm for each RA-SS patient (13). While in the clarification of other scenarios of interest, mainly visceral involvement and decision-making, four kinds of matching strategies, consisting of one-to-one matching, 3-nearest neighbours matching, radius matching and local linear regression matching, were conducted to estimate the average treatment effect on the treated (ATT), defined as the average impact of overlapping SS on RA compared with those without SS (21).

Statistical analysis

As primary outcomes, ultrasound remission of RA was defined as GS≤1 and PD=0, no-functional disability was defined as HAQ<1 (22, 23). Given that the primary outcomes could be reached or lost more than once during follow-up, we adopted Cox proportional hazard model with multiple-failure data and conducted the analysis in both the matched and unmatched cohorts.

In the sensitivity analysis, we repeated subgroup analyses stratified by gender, age (≤40 yrs, 41-60 yrs, ≥61 yrs), RF/ACPA status (++, +-, -+, --), RF status, ACPA status, RA duration (<6 months, ≥6 months), DAS28-CRP at first visit (<2.6, 2.6-3.2, 3.2-5.1, ≥5.1) and HCQ, methotrexate (MTX), biologic disease-modifying anti-rheumatic drugs (bDMARDs), glucocorticoids prescription. Furthermore, we re-performed the same regression in the cohort with either trimmed at the 5^{th}-95^{th} percentiles of the matched one.

For secondary outcomes, visceral involvement and clinical decision-making including ILD, haematological abnormalities such as hypergammaglobulinaemia, leukopenia, positive RF, higher ESR, prescription of HCQ, MTX, glucocorticoids and bDMARDs, the ATTs based on the aforementioned four kinds of PSM strategies were estimated. To ensure the robustness of results, bootstrapping of the standard error of the estimate with a 200-reps was conducted.

The results of Cox regressions were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Continuous variables were depicted as medians and interquartile ranges (IQRs). *p*-values were set two-sided with a 0.05 or less considered statistically significant. All statistical analyses were performed using Stata version 14.0.

Results

Critical characteristics of the cohort

Among the 1100 RA patients, the median follow-up time was 20 (IQR 8-39) months, 133 (12.1%) patients were overlapped with SS. 104 (78.2%) of these patients were positive with anti-SSA antibody and 30 (22.6%) patients showed positive histological picture suggestive of SS on labial salivary gland biopsy. 118 (88.7%) of them were RF positive and 120 (90.2%) were ACPA positive. Before PSM, a significantly higher proportion of female and younger median age at first visit were observed in RA-SS patients than RA-noSS (99.2% *vs*. 75.7%, $p<0.001$; 51 *vs*. 55 yrs, $p=0.003$) (Table I).

128 of 133 RA-SS and 128 of 967 RA-noSS patients were statistically extracted into the propensity score matched cohort, where the aforementioned critical characteristics were well balanced between the two groups. After PSM, RA-SS patients remained at moderate disease activity (DAS28-CRP at

Table I. Critical characteristics in the unmatched and propensity-score matched cohorts.

	Unmatched cohort			Mached cohort		
	RA with SS (n=133)	RA without SS (n=967)	*p*-value	RA with SS (n=128)	RA without SS (n=128)	*p*-value
Female, n (%)	132 (99.2)	732 (75.7)	<0.001	127 (99.2)	127 (99.2)	0.250
Seropositive, n (%)	127 (95.5)	839 (86.8)	0.127	125 (97.7)	125 (97.7)	0.225
T2T therapy, n (%)	110 (82.7)	849 (87.8)	0.115	106 (82.8)	112 (87.5)	0.423
Age, median (IQR) yrs	51 (45-61)	55 (45-64)	0.003	51 (44.5-61)	60.5 (49-71)	0.408
RA duration, median (IQR) months	24 (7-120)	24 (6-84)	0.075	24 (6.5-120)	12 (3.5-48)	0.659
DAS28-CRP at first visit, median (IQR)	3.85 (2.71-4.73)	3.81 (2.92-4.92)	0.858	3.85 (2.76-4.73)	3.58 (2.48-4.57)	0.998

Values are presented as n (%) for binary variables or median (IQR) for continuous variables. Unmatched cohort refers to whole sample (n=1100), matched cohort refers to propensity score matched (PSM) patients (n=256). Seropositive refers to positive for RF or ACPA; T2T refers to treat-to-target approach; IQR refers to interquartile ranges.

Table II. Hazard ratios for ultrasound remission/no functional disability associated with overlapping SS.

	Unmatched cohort		Matched cohort		Trimmed cohort	
	US remission	No functional disability	US remission	No functional disability	US remission	No functional disability
Unstratified	0.63 (0.51, 0.79)	0.60 (0.52, 0.70)	0.56 (0.42, 0.74)	0.68 (0.55, 0.83)	0.58 (0.44, 0.77)	0.69 (0.56, 0.84)
Stratified						
Gender	0.62 (0.50, 0.77)	0.63 (0.54, 0.74)	0.53 (0.40, 0.71)	0.66 (0.54, 0.80)	0.59 (0.45, 0.78)	0.69 (0.56, 0.84)
Age	0.63 (0.51, 0.78)	0.60 (0.52, 0.70)	0.54 (0.40, 0.72)	0.62 (0.50, 0.76)	0.55 (0.41, 0.74)	0.63 (0.51, 0.78)
RF	0.64 (0.52, 0.80)	0.63 (0.54, 0.73)	0.56 (0.42, 0.74)	0.68 (0.55, 0.83)	0.58 (0.44, 0.77)	0.74 (0.60, 0.91)
ACPA	0.63 (0.51, 0.79)	0.59 (0.50, 0.68)	0.57 (0.43, 0.76)	0.63 (0.51, 0.78)	0.57 (0.43, 0.77)	0.61 (0.50, 0.75)
Seropositivity	0.64 (0.52, 0.80)	0.63 (0.54, 0.74)	0.59 (0.45, 0.79)	0.75 (0.61, 0.92)	0.59 (0.44, 0.79)	0.72 (0.58, 0.89)
RA duration	0.64 (0.51, 0.79)	0.61 (0.52, 0.71)	0.58 (0.44, 0.77)	0.70 (0.57, 0.86)	0.59 (0.44, 0.79)	0.70 (0.57, 0.86)
BLDAS28CRP	0.64 (0.51, 0.80)	0.62 (0.53, 0.72)	0.54 (0.41, 0.72)	0.66 (0.54, 0.81)	0.57 (0.42, 0.75)	0.68 (0.55, 0.84)
HCQ	0.61 (0.49, 0.76)	0.56 (0.48, 0.66)	0.55 (0.41, 0.73)	0.67 (0.55, 0.82)	0.56 (0.42, 0.75)	0.67 (0.54, 0.82)
MTX	0.64 (0.52, 0.80)	0.61 (0.52, 0.71)	0.54 (0.41, 0.71)	0.64 (0.52, 0.78)	0.56 (0.42, 0.75)	0.65 (0.53, 0.80)
bDMARDs	0.61 (0.49, 0.76)	0.59 (0.51, 0.69)	0.58 (0.44, 0.77)	0.66 (0.54, 0.81)	0.60 (0.45, 0.80)	0.67 (0.55, 0.83)
Glucocorticoids	0.65 (0.53, 0.81)	0.60 (0.52, 0.70)	0.57 (0.43, 0.76)	0.70 (0.57, 0.86)	0.57 (0.43, 0.77)	0.61 (0.50, 0.75)

Values are presented as total and stratified hazard ratio (95% CI) for no-synovitis/functional disability associated with overlapping SS in RA patients according to gender, age, RF/ACPA status, RA duration, DAS28-CRP at 1st visit and HCQ, bDMARDs, glucocorticoids usage. GS refers to gray scale, PD refers to power Doppler. Unmatched cohort refers to whole sample (n=1100), matched cohort refers to propensity score matched (PSM) patients (n=256), trimmed cohort refers to cohort with either trimmed at the 5th-95th percentiles of the PSM (n=246). The values are statistically significant at the level of 0.01.

the first visit 3.85 [IQR 2.76–4.73]), with RA duration of 24 (IQR 6.5–120) months and a median age of 51 (IQR 44.5-61) years (Table I).

Impacts of overlapping SS on primary outcomes

After correcting the influence of critical confounding characteristics, the total hazard ratios (HRs) of overlapping SS for the probability of attaining ultrasound remission and no disability in RA patients were 0.56 (95% CI 0.42–0.74) and 0.68 (95% CI 0.55–0.83), respectively (Table II).

As for the sensitivity analyses, the adverse impact of overlapping SS on the ultrasound remission and functional ability improvement persisted in the repeated verification of the trimmed PS-matched cohort and Cox proportional hazard model stratified by the aforementioned critical characteristics and concomitant use of HCQ, MTX, bDMARDs and glucocorticoids (Table II).

Effects of overlapping SS on secondary outcomes

As illustrated in Table III, the trend of ATTs obtained from the four PSM methods was consistent and mostly of statistical significance for each secondary outcome except for MTX. Independent of RA itself, overlapping SS was associated with more prevalent ILD, leukopenia, hypergammaglobulinaemia, serological RF positivity and higher ESR in RA patients. In terms of therapeutic drugs, the existence of overlapping SS led to more frequent administration of HCQ and less prescription of bDMARDs. Furthermore, increased prescription of glucocorticoids was associated with overlapping SS, yet statistically significant only at the 10% level.

Discussion

Our current study estimated the association of overlapping SS with ultrasound remission, functional ability and clinical decision-making in RA patients in the setting of real medical practice by PSM.

Independent of known RA components including gender, age, RA duration, RF/ACPA status and DAS28-CRP at first visit, overlapping SS itself could reduce the probability of reaching ultrasound remission or avoidance of functional disability by nearly 30-40%. It seems that the coexistence of the two diseases makes the synovial inflammation more severe and persistent, which is exactly the initiator and aggravator of forthcoming joint damage and func-

Table III. ATT associated with overlapping SS for comorbidity/laboratory indices/ therapeutic preference of RA.

Matching method		Nt	Nc	ATT (95%CI)
Interstitial lung disease	One-to-one matching	128	128	0.07 (-0.00, 0.15)*
	3-Nearest neighbours matching	128	716	0.07 (0.01, 0.14)**
	Radius matching	128	629	0.07 (0.00, 0.14)**
	Local linear regression matching	128	716	0.06 (0.01, 0.12)**
Positive RF	One-to-one matching	124	124	0.09 (0.00, 0.18)**
	3-Nearest neighbours matching	125	698	0.07 (-0.01, 0.16)*
	Radius matching	122	539	0.09 (0.01, 0.16)**
	Local linear regression matching	125	698	0.10 (0.04, 0.16)***
Leukopenia	One-to-one matching	127	127	0.13 (0.05, 0.21)***
	3-Nearest neighbours matching	128	713	0.15 (0.06, 0.23)***
	Radius matching	126	613	0.14 (0.06, 0.22)***
	Local linear regression matching	128	713	0.15 (0.08, 0.22)***
ESR	One-to-one matching	128	128	2.95 (-3.41, 9.32)
	3-Nearest neighbours matching	129	727	5.06 (-0.72, 10.84)*
	Radius matching	128	600	5.43 (-0.33, 11.19)*
	Local linear regression matching	129	727	5.57 (0.63, 10.50)**
Hypergammaglobulinaemia	One-to-one matching	127	127	0.44 (0.33, 0.55)***
	3-Nearest neighbours matching	128	713	0.43 (0.31, 0.56)***
	Radius matching	126	613	0.43 (0.32, 0.53)***
	Local linear regression matching	128	713	0.42 (0.32, 0.51)***
Hydroxychloroquine	One-to-one matching	128	128	0.22 (0.08, 0.36)***
	3-Nearest neighbours matching	128	716	0.18 (0.05, 0.31)***
	Radius matching	128	629	0.19 (0.08, 0.30)***
	Local linear regression matching	128	716	0.18 (0.09, 0.27)***
Methotrexate	One-to-one matching	128	128	-0.06 (-0.17, 0.04)
	3-Nearest neighbours matching	128	716	-0.06 (-0.17, 0.04)
	Radius matching	128	629	-0.06 (-0.16, 0.03)
	Local linear regression matching	128	716	-0.03 (-0.11, 0.05)
Glucocorticoids	One-to-one matching	128	128	0.13 (-0.00, 0.25)*
	3-Nearest neighbours matching	128	716	0.11 (-0.01, 0.22)*
	Radius matching	128	629	0.06 (-0.05, 0.18)
	Local linear regression matching	128	716	0.05 (-0.05, 0.14)
bDMARDs	One-to-one matching	128	128	-0.08 (-0.14, -0.02)**
	3-Nearest neighbours matching	128	716	-0.08 (-0.14, -0.03)***
	Radius matching	128	629	-0.06 (-0.11, -0.01)**
	Local linear regression matching	128	716	-0.07 (-0.10, -0.03)***

Nt: number of patients treated; Nc: number of controls, referring to the number of matched RA-SS and RA-no SS patients respectively; ATT: average treatment effect of treated, referring to the effect associated with overlapping SS on scenarios of interest.
*Statistically significant at the level of 0.10. **Statistically significant at the level of 0.05.
***Statistically significant at the level of 0.01.

tional disability (24). In the setting of overlapping SS, both the elevated B-cell activating factor (BAFF) levels and receptor activator of nuclear factor ϰB ligand (RANKL) expressed on the autoreactive B cells could exacerbate natural evolution of RA (25-27). Therefore, close attention should be paid to RA patients with overlapping SS.

RA-SS accounted for 12.1% in the total 1100 RA patients, which was consistent with the results of previous studies. Four main characteristics of RA-SS patients in contrast to RA-noSS patients were revealed, namely coexisting ILD, positive RF, leukopenia and hypergammaglobulinaemia. That is, overlapping SS brings more characteristics of SS extra-glandular involvement to RA. In turn, it would be worthwhile for clinicians to stay alert against RA patients with one or more above features and make timely diagnoses.

Over the past decades, RA treatments have sprung up and greatly improved the clinical outcomes of RA patients. Nevertheless, there has been no encouraging progress in the treatment of SS so far (28). Commonly used HCQ has failed in the JOQUER study (29). Meanwhile, almost all the new drugs were annihilated on the way to the desired primary endpoints, therefore they are considered only when there is life-threatening or severe organ involvement (30, 31).

For a detailed portray of the impact of overlapping SS on RA management, three compromises should be taken into consideration. First, despite the aforementioned unsatisfactory performance of HCQ, its extensive prescription might partly originate from some studies and the good wishes of physicians (32-36). Second, bDMARDs used in our cohort are mainly TNF-α inhibitors, which has been proved to be ineffective against primary SS. None of the various bDMARDs was verified to effectively eliminate the persistent inflammation due to overlapping SS. Third, given the current predicament, more preferences are being placed on glucocorticoids.

This study provided the true encounter of overlapping SS in the real clinical practice of RA, but there were some limitations due to the nature of single-centre retrospective cohort. First, the insufficient systemic assessment of outpatients made the analysis of comorbidities other than ILD such as thyroid involvement and osteoporosis unavailable. Second, the incomplete radiographic archives led to the difficulty in evaluation of radiographic progression. Third, ultrasound scan confined to the hands and wrists is not comprehensive for evaluation of RA.

In conclusion, overlapping SS per se was associated with 30-40% reduction in reaching ultrasound remission and avoidance of functional disability, yet less aggressive clinical intervention independent of RA. Hence, it will be of great significance to improve the vigilance of timely identification and clinical decision-making of overlapping SS.

Acknowledgements

This study is based on the contributions of all colleagues in our department during the outpatient visits over the past decade. We would like to thank Dr Peicai Wu (Chinese Academy of Social Sciences, China) for his kind inspiration of PSM.

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