Sex-related differences in clinical characteristics and comorbidities and their impact on clinical outcome in Korean patients with rheumatoid arthritis

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Abstract

Backgrounds:

Rheumatoid arthritis (RA) is more prevalent in women and prior studies have reported several epidemiologic differences between sex and low achievement of remission in women RA. However, these sex differences across various populations remain incompletely understood. This study aimed to elucidate sex-related differences in clinical characteristics and their potential impact on clinical outcome in a large Korean cohort of patients with RA.

Methods

In total, 5,376 RA patients from the KORean Observational study Network for Arthritis (KORONA) database were examined at baseline and for 3 consecutive years using the disease activity score 28 (DAS28), health assessment questionnaire (HAQ), and health-related outcomes. Within a subgroup with active disease (DAS28 $\geq$ 3.2) at baseline, sex impacts on clinical outcome during a 3-year period were analyzed using generalized estimating equation (GEE) models. The sex effect on achieving clinical remission was analyzed using Cox-proportional hazard regression.

Results

At baseline, women (n = 4,574) were younger and had more erosive disease and longer disease duration than men (n = 802) with significantly higher scores in DAS28, HAQ, and patient-reported outcomes. The prevalence of interstitial lung disease, cardiovascular disease, and diabetes in men was significantly higher than that of women. In a RA subgroup with active disease at baseline, a GEE analysis demonstrated that sex significantly influenced the rate of change of DAS28 ($p = 0.035$) over time. In that group, men are associated with achieving DAS28 sustained remission as well as point remission (both $p < 0.001$).

Conclusion

Most comorbidities were more prevalent in men than in women among Korean patients with RA. However, for RA-related clinical outcomes, the longitudinal change in disease activity and the rate of achieving clinical remission were found to be worse in women RA. Therefore, sex-related differences should be considered when managing RA patients.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with an autoimmune nature [1]. RA is more common in women, which are two to three times more prone to develop RA than men, and its

incidence in women has been gradually increasing during the last decades [2, 3]. Because of this female predominance, the role of female hormonal factors in the pathogenesis of RA has been proposed; however, it is still being debated [4]. RA symptoms generally manifest in individuals between 30 and 60 years old, including the perimenopausal period in females. Although inconclusive, nulliparity and short-duration breastfeeding have been suggested as risk factors for female RA development [5, 6]. In addition, several studies have shown that a substantial number of pregnant patients with RA experience clinical remission, but disease flares frequently occur during the postpartum period [7, 8]. Thus, experiences during the course of RA may differ between men and women.

Immune responses in various conditions can differ according to sex. For example, the interplay of sex chromosomes, sex hormones, and immune cells leads to sexually dimorphic responses in virologic control as well as immune-clinical outcomes to vaccination [9, 10]. Furthermore, the increased immune reactivity in women might partially explain the greater prevalence of various autoimmune diseases in females than males [11]. However, the relationship between sex, clinical manifestations, and outcomes of RA has not yet been clarified. Generally, men are more likely to have a later disease onset, seropositivity, and mild disease activity. On the other hand, women are known to have a higher disease activity (evaluated by the disease activity score 28 [DAS28] or clinical disease activity index [CDAI]) and physical disabilities (evaluated by health assessment questionnaire-disability index [HAQ-DI]) than men. Despite the overall high disease activity in women, many studies have concluded that radiographic progression is not significantly different according to sex [12]. In terms of comorbidities, fibromyalgia, depression, and osteoporosis are more common in women RA. Cardiovascular (CV) disease risk is known to be higher in men than in women in the general population, but male and female patients with RA have similar risks [13]. Regarding treatment, men had a high clinical response rate including an early achievement rate of sustained remission, but there were also studies that reported no differences between men and women [12]. Thus, it is estimated that there are sex-related differences in the clinical manifestations and disease course of RA.

During recent years, gender medicine has emerged as a rising medical field, in which differences between women and men are recognized, analyzed, and utilized in the diagnosis and treatment in various aspects – anatomical, physiologic, biologic, functional, social, and response to treatment [14]. So far, there have been no systematic comparative studies of clinical manifestations and comorbidities among Korean patients with RA until now. Previous studies were conducted mainly on Western and Latin American patients [15, 16], and there were only few studies on Asian patients [17]. Therefore, in this study, we aimed to elucidate sex-related differences in clinical characteristics and comorbidities and their potential impact on clinical outcome in a large Korean cohort of patients with RA.

Materials And Methods

Study population

From July 2009 to December 2011, patients over the age of 18 who met the 1987 American College of Rheumatology (ACR) classification criteria for RA were enrolled into the KORean Observational study Network for Arthritis (KORONA) database by rheumatologists from 23 centers [18]. The KORONA database was established to gather high-quality real-world data regarding RA disease outcomes such as quality of life, treatment effectiveness, co-morbidities, and disease progression. All of the 5,376 enrolled patients with RA were included in the analysis to compare and analyze all sex-related clinical features. There was 3 consecutive years' worth of follow-up data until December 2012. The KORONA protocol was approved by the institutional review boards (IRBs) of all participating hospitals. Informed consent was obtained from all patients prior to registration. The data was anonymized and transferred to the Korean College of Rheumatology, and we acquired the data and conducted the analysis under the approval of Seoul National University Bundang Hospital IRB (IRB No. B-1810/501 − 103).

Data collection

All patients in the KORONA database completed an initial questionnaire to establish their demographic profile, including age, sex, age of disease onset, age of diagnosis, comorbidities, and prescribed drugs. Previous medical history and disease-specific outcomes were also recorded. Data on comorbidities were obtained from two sources. One was a questionnaire filled out by a practitioner based on the patient's response, and the other was a physical examination. In the questionnaire, comorbidity was defined as when the patient had been diagnosed or treated for any ailment. Comorbidities included CV disease, hypertension, diabetes mellitus (DM), gastrointestinal disease, pulmonary disease, neoplastic disease, thyroid disease, depression, RA-related interstitial lung disease (ILD), etc. For RA-related laboratory tests, results for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-citrullinated protein antibodies (ACPAs) were obtained. Joint examinations were conducted by rheumatologists or well-trained health professionals. RA disease activity, functional disability, and quality of life were assessed using DAS28-ESR, HAQ-DI, and EuroQoL-5D (EQ-5D), respectively. The health-related outcomes including visual analog scale (VAS) scores for the patient's and physician's global health, patient's pain, fatigue, and sleep disturbance were also obtained.

Statistical analyses

Clinical characteristics and comorbidities at baseline were compared according to sex. Continuous variables were compared using Student's *t*-test (or the Mann-Whitney test, if appropriate), and categorical variables were compared using the chi-square test or Fisher's exact test. All data are expressed as mean and standard deviation, median and interquartile range, and proportions and 95% confidence interval (CI) as appropriate. Factors with $p < 0.05$ were considered as statistically significant across all data. All statistical analyses were performed using R version 3.5.0.

To check differences in the change of DAS28 between males and females from baseline up to 4 years, generalized estimating equation (GEE) models for repeated measures were used among patients with a baseline DAS28 $\geq$ 3.2. Follow-up time and sex were included as the main explanatory variables and an

interaction term was also included in the GEE model, adjusting for age, disease duration, baseline DAS28, and biologics prescribed at the baseline.

To assess the sex impact on achieving DAS28 clinical remission, patients with a DAS28 ≥ 3.2 (moderate or high disease activity) at baseline were selected and analyzed. The cut-off value for clinical remission was defined as a DAS28 < 2.6 [19]. Patients were classified as being in sustained remission if they satisfied the DAS28 < 2.6 at any 2 consecutive years of measurement after baseline. Patients were considered to be in point remission if they satisfied the DAS28 clinical remission criteria at any single year of measurement after baseline. A Cox-proportional hazard regression model was chosen for the analysis of sex impact on the prediction of future remission. Disease activity was measured regularly in this study data. A 1-year interval was maintained for the covariate in the Cox-proportional hazard regression analyses. In the case of one isolated missing measurement, the measurement following the missing value was used. If more than one consecutive measurement was missing, subjects were censored. In the analyses, the following potential confounders were considered: age; duration of disease; seropositivity (none versus RF or ACPA positive status); baseline DAS28 score as a continuous variable; VAS score of physician, patient's pain, fatigue, and sleep discomfort; and CRP at baseline. As the patients did or did not meet the DAS28 clinical remission criteria at different years in time, we set the time of first remission as the event time for the regression analysis. For the sensitivity analyses, same procedures using simplified disease activity index (SDAI) and CDAI were conducted [20].

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the RA patients stratified by sex are summarized in Table 1. A total of 5,376 RA patients (802 men and 4,574 women) were included at baseline analysis. The mean age and age at disease onset were both higher in men. The disease duration was significantly longer in women (9.0 ± 8.1% vs. 7.1 ± 6.7%, $p < 0.001$). The proportion of patients who smoke and consume alcohol was higher in men. All VAS score items showing subjective health-related outcomes were higher in women. Likewise, HAQ scores were significantly higher and EQ-5D scores were lower in women, indicating a lower overall health-related quality of life. Disease activity assessed by DAS28-ESR was also higher in women than in men, and the proportion of RA patients with moderate to high disease activity (DAS28 > 3.2) was also higher in women. There was a high incidence of erosive disease in women, but there was no significant sex-related difference in medication type.

Comorbidities

The number of patients with various comorbidities stratified by sex is shown in Table 2. There were significant differences on the frequency distribution of comorbidities between men and women. The prevalence of most illness was significantly higher in men than in women, including ILD (2.1% vs. 0.6%; $p < 0.001$), CV disease (6.6% vs. 2.7%; $p < 0.001$), DM (12.8% vs. 7.3%; $p < 0.001$), pulmonary disease (11.3% vs. 6.7%; $p < 0.001$) and pulmonary tuberculosis (8.4% vs. 4.1%; $p < 0.001$). Conversely, women presented

with thyroid disease (8.1% vs. 1.6%; $p < 0.001$), neoplastic disease (8.4% vs. 4.5%; $p < 0.001$) and nephrologic disease (2.6% vs. 1.0%; $p = 0.009$) more frequently. Depression was more common in women but there was no significant difference (1.9% vs. 0.9%; $p = 0.053$).

Changes in disease and patients' reported outcomes during follow-up

During the 3-year follow-up period, the differences in DAS28 between sexes were maintained over time in the whole study population (Additional file 1: Fig. S1a). Longitudinal changes in the HAQ, EQ-5D, and patients' pain VAS scores also showed similar trends (Additional file 1: Fig. S1b-d). In order to assess the sex-related differences in clinical outcomes among patients who initially showed moderate to high disease activity, we subsequently performed a subgroup analysis on patients with a DAS28 ≥ 3.2 at baseline. Consequently, a total of 3,053 patients who showed a DAS28 ≥ 3.2 at baseline were included in this analysis. In this group, the baseline DAS28-ESR in women was significantly higher than that in men, and the mean improvement was better in men than in women over 3 consecutive years (Fig. 1a). A similar trend was observed in the health-related quality of life, such as the HAQ or EQ-5D (Fig. 1b-c). The VAS scores for pain and sleep were initially high in females, but a similar mean score was seen after three years (Fig. 1d-e). In the GEE model, after adjusting for age, disease duration, baseline DAS28, and baseline biologic disease-modifying anti-rheumatic drugs (DMARDs) use, sex was found to significantly influence the rate of change of DAS28 ($p = 0.035$), but was not independently associated with this outcome ($p = 0.812$, Table 3). Other significant predictors for DAS28 change included disease duration ($p < 0.001$) and baseline DAS28 ($p < 0.001$) over the 3-year follow-up period.

Factors influencing the prediction of achieving clinical remission

Among 3,053 patients who showed a DAS28 ≥ 3.2 at baseline, a total of 8,024 DAS28 measurements were collected during follow-up, and in 918 (11.4%) of the visits, the DAS28 was < 2.6. Moreover, 178 patients achieved sustained remission during follow-up, and 519 of the remaining patients reached point remission at one or more non-consecutive measurement (Table 4). In the Cox regression model with sustained remission as the outcome variable, women were associated with not achieving sustained remission (hazard ratio [HR] 0.41, 95% CI 0.28–0.58, $p < 0.001$), after adjusting for confounders during follow-up. Women were also a significant negative predictor in the model for point remission (HR 0.53, 95% CI 0.42–0.68, $p < 0.001$). Other variables that demonstrated a relatively significant predictive power for achieving clinical remission included seropositivity (HR 0.54, 95% CI 0.38–0.77 in point remission) and baseline DAS28 (HR 0.63, 95% CI 0.52–0.76 in sustained remission, HR 0.69, 95% CI 0.62–0.77 in point remission). In the sensitivity analyses based on CDAI and SDAI, women also remained as a negative predictor to achieve remission (Additional file 2: Table S1 and S2).

Discussion

This study was the first to investigate the clinical features and serial outcomes comprehensively according to sex in a large nationwide cohort of Korean patients with RA (KORONA). In Korean patients with RA, most comorbidities were more prevalent in men than in women, except for neoplasm and thyroid and nephrologic disease. However, RA-related health outcomes, the longitudinal change in the disease activity and the rate of achieving clinical remission over time were found to be worse in women RA.

At the baseline enrollment of our cohort, male patients showed a later disease onset and had a significantly higher incidence of large joint involvement at first RA diagnosis. The proportion of seropositive RA patients was not different between men and women, but RF titer was higher in men. The titer of ACPAs was not included in the analysis because of the various ACPAs immunoassays at each center. These presentation patterns of RA according to sex have been inconsistently reported in previous RA studies from other countries [12]. In terms of disease activity and severity, women showed a high proportion of radiographic erosion on hand joints and higher scores of DAS28 and HAQ in our RA population. These results may or may not be consistent with previous studies. Earlier studies have reported a more severe disease among men than women in an RA cohort with long disease duration [21]. However, a number of studies since the 2000s have demonstrated that men exhibit an overall mild disease activity than women. In a Dutch cohort study including patients with early RA (209 women and 123 men), women showed significantly higher DAS and worse radiographic joint destruction and physical disability (HAQ-DI)[22]. A Japanese large observational cohort study analyzing 4,823 RA patients also showed high DAS and worse HAQ in women, and the progression of disability was almost three times more rapid in women than in men [17]. Similarly, a Swedish cohort study for early RA patients (538 women, 306 men) showed that women had higher DAS28 and HAQ scores overall, but women below 50 years of age had milder disease than those with older age and closer to that of men [15].

Besides the composite disease activity index, patient-reported outcomes (PROs) are also important aspects for the comprehensive assessment of RA patients. In our cohort, all subjective health-related outcomes, including VAS for patients' global health, pain, fatigue and sleep disturbance as well as EQ-5D were worse in women than in men at baseline. In the QUEST-RA study, a large multinational database of RA patients, women have noted worse HAQ, pain, fatigue, and patients' global VAS compared to men [23]. In addition, women generally tend to report more severe symptoms and poorer scores on questionnaires of self-reported health-related items [24], and this trend is also evident and maintained during the follow-up period in our study. Hence, physicians who treat RA patients should take into account these sex-related differences when interpreting PROs.

In our study population, the prevalence and distribution of comorbidities were significantly different between men and women, although the comorbidities were grouped by system rather than by disease. Men with RA were more likely to have CV and pulmonary diseases including ILD, while women with RA were more likely to have thyroid, neoplastic, and nephrologic disease. Male predominance of ILD as an extraarticular manifestation of RA has been consistently reported. On the other hand, although CV risk is higher in men compared to women in the general population [25], a recent meta-analysis on cerebrovascular/CV risks in RA patients showed a similar increased risk between both sexes [13]. The

prevalence of major depression is about two-fold higher in women than in men and is reported as the most frequent RA comorbidity with a world-wide prevalence of 15% [26, 27]. However, the sexual disparity in the prevalence of depression was not observed in our RA population. Discrepancies in the sex distribution of comorbidities between previous reports and our study may be attributed to the differences in ethnic group and studied RA population (e.g., early vs. established).

As shown in Fig. 1 and the additional file 1 (Fig. S1), the baseline disease activity, PROs, and longitudinal progress in women were better than those in men in either a whole RA population or a subgroup with moderate to high disease activity at the time of enrollment. However, trends in ESR levels did not differ according to sex in the latter group. To investigate whether sex certainly influences the change of disease activity over time, we conducted GEE analyses with adjustment for within-patient correlation of data. The rate of change of DAS28 was significantly influenced by sex over time in our RA cohort. Our results are similar with the previous evidence by Jawaheer *et al*. [28], albeit the patient group of the study was DMARDs-näive at study entry. Other than sex, in the GEE analysis, high baseline DAS28 scores and long disease duration were also considered as significant factors – covariates already known to be unfavorable [29, 30]. Interestingly, the prescription of biologic DMARDs was an insignificant factor in GEE analysis, presumably because the percentage of biologic DMARD users was low in our RA population. Owing to the stringent reimbursement criteria for biologic DMARDs by the Korean health insurance system, the use of biologic DMARDs had been relatively restricted prior to 2014.

The disease process in RA patients may be related to various factors including sex. To identify associated factors for achieving remission, we conducted Cox regression analysis on achieving point remission as well as sustained remission in the population confined to patients with active disease at baseline enrollment. Women with RA achieved remission less frequently than men with RA despite a similar treatment of conventional synthetic DMARDs and more frequent use of biologic DMARDs, which are consistent with the results of previous studies. In early RA patients from the CORRONA registry and British early RA study (ERAS) cohort, male sex was found to be associated with sustained remission [31, 32]. Another study from Finland reported that men achieved remission more frequently than women regardless of the definition of remission. These sexual disparities may be the result of the differences in components of disease activity indices between men and women. For instance, DAS28-ESR is a composite index consisting of ESR and patients' global health, and reference ranges for ESR vary according to age and sex [33]. In addition, women were found to report more intense pain compared to men in the general population, leading to worse subjective assessment in women with RA as well [34, 35]. Indeed, the improvement in all PROs over 12 years was better in men with RA than in women with RA in a large-scale longitudinal survey [36]. In the additional sensitivity analyses using CDAI and SDAI, other composite disease activity indices not including ESR, women were less likely to achieve CDAI as well as SDAI remission in our RA population. A recent study of two large RA cohorts by Maynard *et al*. [37] has shown that women had reduced rates of DAS28-ESR remission but similar rates of other disease activity measures such as DAS28-CRP, CDAI, or RAPID3 as well as objective radiologic MRI measures. In actual clinical practice, a DAS28-ESR of < 2.6 has been the most widely used definition of remission in patients with RA. Taken together, more objective indicators such as imaging studies would be more appropriate

for judging remission in women with RA, and the development and investigation of sex-specific tools for assessing disease activity will be warranted in the future. In addition to sex, our study found that seropositivity, high baseline DAS28, high ESR, and long disease duration were unfavorable risk factors for achieving remissions. These factors are well-known poor prognostic factors for the management of RA [29].

The specific causes for sexual dimorphism in the disease pattern, comorbidities, and disease course in RA patients are unclear, but several explanations have been suggested. Differences in chromosome complement according to sex, including Y-chromosome genes in males and the dosage effect of X-chromosome genes, and gonadal hormones such as estrogen or androgen generate differential effects on immune function [28]. A low muscle mass and a different female body composition can contribute to fragile joint mechanics to some extent. The avoidance of potential teratogenic DMARDs in women of childbearing age with RA might also be a factor affecting sex-related differences.

This study has several limitations. Firstly, most of the serial outcome variables are subjective items rather than objective assessments, such as radiographic joint damage on imaging studies. Secondly, a relatively high percentage of RA patients were lost during the follow-up periods. Moreover, a wide assessment interval (1 year) may not be able to capture a brief flare-up of RA disease activity. Lastly, there may be age-specific effects according to sex hormone status in female patients, but this study did not reflect that effect. Nevertheless, our study has some strengths. As we used a large-scale multicenter database for analysis, the external validity is better than those of studies based on single-center or regional data. In addition, our study is meaningful in that for the first time in Korean patients with RA, the sex-related differences were compared comprehensively in terms of clinical features and longitudinal clinical course. The KORONA data is still being updated, and it is expected that more confirmative results will be obtained in the near future as the number of follow-up patients increases.

Conclusions

Disease presentations and comorbidities were different between men and women, and the treatment response over time, as assessed by composite disease activity indices and PROs, appeared to be worse among Korean women with RA. Sexual dimorphisms in RA patients are often ignored by physicians in the clinical practice; the health professionals treating RA patients should be aware of these sex-related differences and take them into consideration in choosing treatment strategies.

Abbreviations

RA: rheumatoid arthritis; DAS28: disease activity score 28; CDAI: clinical disease activity index; HAQ-DI: health assessment questionnaire-disability index; CV: cardiovascular; ACR: American College of Rheumatology; KORONA: KORean Observational study Network for Arthritis; IRB: institutional review boards; DM: diabetes mellitus; ILD: interstitial lung disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies; EQ-5D: EuroQoL-5D;

VAS: visual analog scale; CI: confidence interval; GEE: generalized estimating equation; SDAI: simplified disease activity index; DMARDs: disease-modifying anti-rheumatic drugs; HR: hazard ratio; PRO: patient-reported outcome

Declarations

Ethics approval and consent to participate

The KORONA protocol was approved by the IRBs of all 23 participating hospitals. Informed consent was obtained from all patients prior to registration. The data was anonymized and transferred to the Korean College of Rheumatology, and we acquired the data and conducted the analysis under the approval of Seoul National University Bundang Hospital IRB (IRB No. B-1810/501-103).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from a committee of clinical research, the Korean College of Rheumatology but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Korean College of Rheumatology.

Competing interests

None of the authors gained any commercial or financial benefit from the work reported. None of the authors have any financial interests that could create a potential conflict of interest or the appearance of a conflict of interest.

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Author’s contributions

SHS involved in the manipulation and interpretation of data and prepared the initial draft of the manuscript. EHP, EHK, YJL and YWS participated in the interpretation of data and underwent critical revision of the manuscript for important intellectual content. YJH conceived and designed the study, participated in the analysis and interpretation of data, and revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Baseline characteristics of the study population stratified by sex

	Men (n = 802)	Women (n = 4,574)	*p* value
Age at enrollment	57.3 ± 11.7	53.4 ± 12.1	<0.001
Age at disease onset	49.8 ± 12.8	43.4 ± 12.7	<0.001
Disease duration	7.1 ± 6.7	9.0 ± 8.1	<0.001
Smoking			<0.001
Never smoker	152 (19.0)	4,356 (95.6)	
Ex-smoker	358 (44.8)	63 (1.4)	
Current smoker	289 (36.2)	139 (3.0)	
Alcohol			<0.001
No drinking	222 (27.9)	3,610 (79.1)	
Ever drinking	197 (24.7)	158 (3.5)	
Current drinking	378 (47.4)	794 (17.4)	
BMI, kg/m^2	23.0 ± 2.9	22.6 ± 3.2	<0.001
Patient pain VAS	28.9 ± 26.8	39.2 ± 28.1	<0.001
Patient's global health VAS	33.2 ± 25.5	41.7 ± 26.2	<0.001
Physician's VAS	24.8 ± 18.9	27.0 ± 19.2	0.002
Fatigue VAS	35.6 ± 28.3	46.2 ± 29.0	<0.001
Sleep disturbance VAS	19.8 ± 25.0	28.2 ± 29.6	<0.001
HAQ	0.4 ± 0.5	0.7 ± 0.7	<0.001
EQ-5D	0.8 ± 0.2	0.7 ± 0.3	<0.001
Laboratory findings			
Seropositivity	718 (93.2)	4,180 (95.3)	0.023
RF-positive	682 (87.5)	3,820 (85.6)	0.173
RF titer	207.2 ± 400.7	105.3 ± 211.2	<0.001
ACPAs-positive	519 (82.6)	2,929 (83.7)	0.555
ESR	24.2 ± 23.3	29.7 ± 23.8	<0.001
CRP	1.2 ± 2.5	0.8 ± 1.8	<0.001
DAS28-ESR	3.1 ± 1.4	3.8 ± 1.3	<0.001
28 tender joint count	3.0 ± 13.1	4.1 ± 8.9	0.031
28 swollen joint count	2.7 ± 17.9	2.5 ± 11.5	0.757
Moderate to high disease activity*	317 (44.3)	2,736 (66.1)	<0.001
First involved joints			
Large joint	475 (59.2)	2,331 (51.0)	<0.001
Small joint	530 (66.1)	3,294 (72.0)	0.001
Presence of erosion on hand X-ray	400 (49.9)	2,551 (55.8)	0.002

Medication			
Methotrexate	644 (80.3)	3,759 (82.2)	0.220
Other csDMARDs	594 (78.5)	3,308 (76.3)	0.201
Glucocorticoids	593 (73.9)	3,402 (74.4)	0.828
NSAIDs	664 (82.8)	3,737 (81.7)	0.490
Biologic DMARDs	33 (4.1)	281 (6.1)	0.029

Values are expressed as numbers (%) or mean ± standard deviation.

* DAS28-ESR > 3.2

BMI: body mass index; VAS: visual analog scale; DAS28: disease activity score using 28 joint counts; HAQ: health assessment questionnaire; EQ-5D: EuroQol-5D; RF: rheumatoid factor; ACPAs: anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table 2 Differences in comorbidities according to sex

	Men (n = 802)	Women (n = 4,574)	*p* value
Rheumatoid nodule	41 (5.1)	172 (3.8)	0.088
RA-ILD	17 (2.1)	28 (0.6)	<0.001
Cardiovascular disease	53 (6.6)	125 (2.7)	<0.001
Hypertension	191 (23.8)	1,143 (25.0)	0.506
Gastrointestinal disease	159 (19.8)	1,031 (22.5)	0.096
Diabetes mellitus	103 (12.8)	334 (7.3)	<0.001
Thyroid disease	13 (1.6)	371 (8.1)	<0.001
Pulmonary disease	91 (11.3)	305(6.7)	<0.001
Neurologic disease	5 (0.6)	37 (0.8)	0.739
Neoplastic disease	36 (4.5)	385 (8.4)	<0.001
Depression	7 (0.9)	88 (1.9)	0.053
Previous fracture	169 (21.1)	747 (16.3)	0.001
Pulmonary tuberculosis	67 (8.4)	189 (4.1)	<0.001
Skin disease	15 (1.9)	121 (2.6)	0.243
Ophthalmologic disease	30 (3.7)	225 (4.9)	0.174
Nephrologic disease	8 (1.0)	118 (2.6)	0.009

Values are expressed as n (%)

RA: rheumatoid arthritis; ILD: interstitial lung disease.

Table 3 Longitudinal analysis of predictors of DAS28 over time using a generalized estimating equation (GEE) model.

Outcome Variable	Independent Variables	Regression Coefficient (β) (95% CI)	*P* value
DAS28-ESR	Age	0.002 (0.000 ~ 0.004)	0.198
	RA duration	0.013 (0.010 ~ 0.016)	< 0.001
	Baseline DAS28	0.668 (0.636 ~ 0.699)	< 0.001
	Biologics prescription	-0.050 (-0.161 ~ 0.061)	0.376
	Sex (men)	0.016 (-0.117 ~ 0.149)	0.812
	Follow-up time	-0.419 (-0.450 ~ -0.387)	< 0.001
	Sex * Follow-up time (interaction)	-0.114 (-0.220 ~ 0.008)	0.035

All covariates adjusted for in the model are listed as independent variables. The reference group for sex was men.

RA: rheumatoid arthritis; DAS28: disease activity scores using 28-joint count.

Table 4 Cox-proportional hazard regression analysis with time to each sustained and point clinical remission after adjusting for confounders (n = 3,053)

	DAS28 sustained remission			DAS28 point remission		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	0.98	0.97-1.00	0.006	0.99	0.98-1.00	0.001
Sex*	0.39	0.27-0.56	<0.001	0.51	0.42-0.63	<0.001
RA duration	0.94	0.92-0.97	<0.001	0.96	0.95-0.97	<0.001
Seropositivity*	0.78	0.38-1.58	0.484	0.57	0.41-0.78	0.01
Baseline DAS28	0.64	0.52-0.77	<0.001	0.66	0.60-0.72	<0.001
CRP	0.99	0.90-1.09	0.810	0.97	0.93-1.02	0.303
Pain VAS	1.00	0.99-1.00	0.104	1.00	0.99-1.00	0.001
Tired VAS	0.99	0.99-1.00	0.005	0.99	0.99-1.00	<0.001
Sleep VAS	0.99	0.99-1.00	0.014	1.00	0.99-1.00	0.001
Physician VAS	1.00	0.99-1.00	0.246	1.00	0.99-1.00	0.048
Biologic DMARDs use	0.98	0.57-1.69	0.948	0.96	0.73-1.27	0.774

All variables represent baseline values.

* The reference group for these variables were as follows: Sex-women; Seropositivity-Seropositive (positive for RF or ACPAs)

RA: rheumatoid arthritis; DAS28: disease activity scores using 28-joint count; CRP: C-reactive protein; VAS: visual analog scale; DMARDs: disease-modifying anti-rheumatic drugs.

Figures

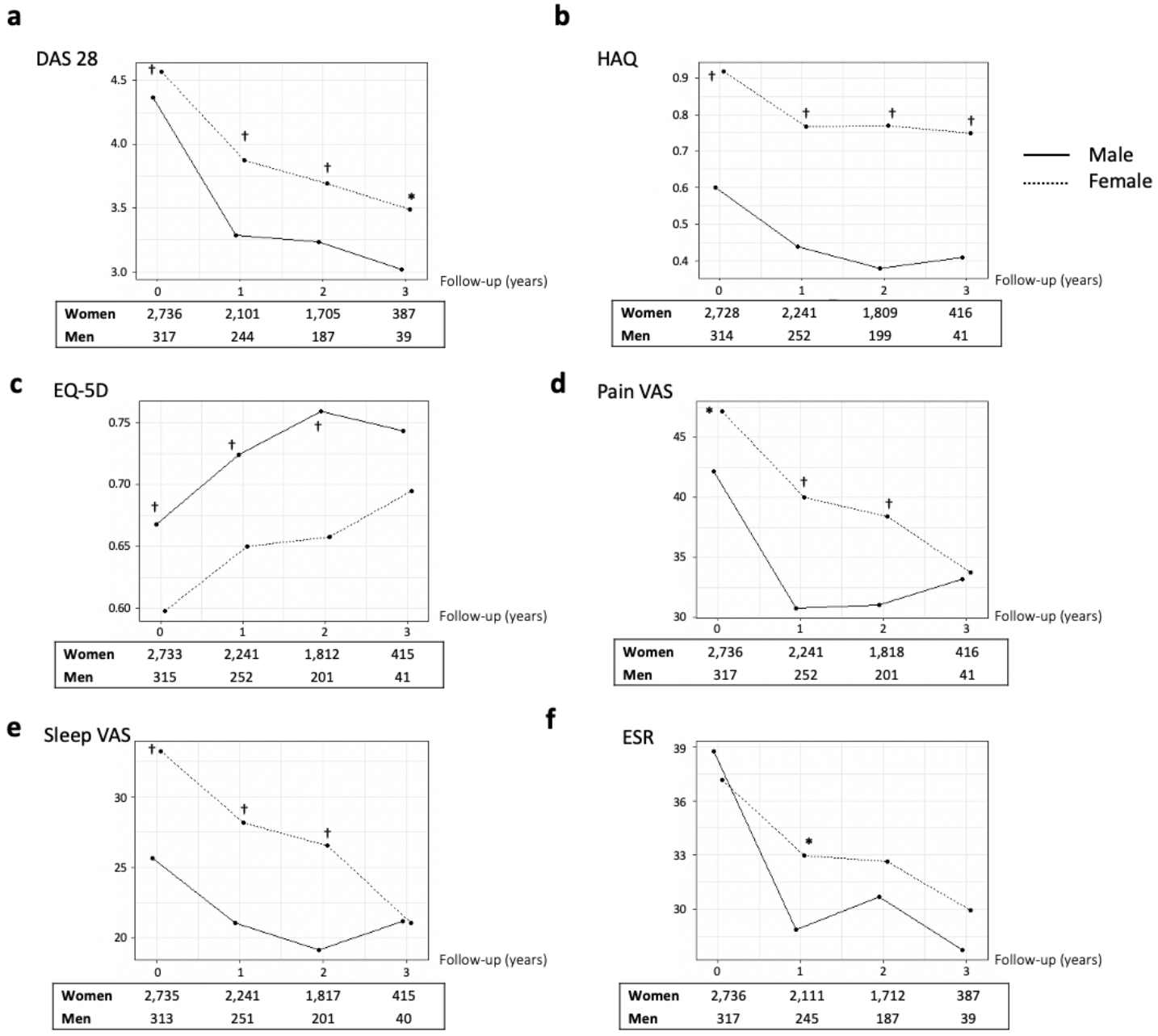

Figure 1

Observed mean values for different outcomes including disease activity score 28 (DAS28), HAQ, EQ-5D, visual analog scale (VAS) for patients' pain and sleep, and ESR between men and women over the 3-year follow-up among RA patients with a baseline DAS28 ≧ 3.2. Numbers of men and women patients with

available data at each time point are shown at the bottom table. *p < 0.05, †p <0.001 compared men and women patients at each time point.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile2TableS12.docx
- AdditionalFile1FigS1.docx