Chinese registry of rheumatoid arthritis (CREDIT) V: sex impacts rheumatoid arthritis in Chinese patients

Nan Jiang[1], Qin Li[2], Hongbin Li[3], Yongfei Fang[4], Lijun Wu[5], Xinwang Duan[6], Jian Xu[7], Cheng Zhao[8], Zhenyu Jiang[9], Yanhong Wang[10], Qian Wang[1], Xiaomei Leng[1], Mengtao Li[1], Xinping Tian[1], Xiaofeng Zeng[1], CREDIT Co-Authors

[1]Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences and Peking Union Medical College; National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Ministry of Science and Technology; State Key Laboratory of Complex Severe and Rare Diseases; Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing 100730, China;
[2]Department of Rheumatology, the First People's Hospital of Yunnan Province, Kunming, Yunnan 650032, China;
[3]Department of Rheumatology, the Affiliated Hospital of Inner Mongolia Medical College, Hohhot, Inner Mongolia 010050, China;
[4]Department of Rheumatology, Southwest Hospital, Third Military Medical University, Chongqing 400038, China;
[5]Department of Rheumatology and Immunology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, Xinjiang 830001, China;
[6]Department of Rheumatology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China;
[7]Department of Rheumatology and Immunology, First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan 650032, China;
[8]Department of Rheumatology, The First Affiliated Hospital of Guangxi Medical University, Manning, Guangxi 530021, China;
[9]Department of Rheumatology, The First Hospital of Jilin University, Changchun, Jilin 130021, China;
[10]Department of Epidemiology and Bio-Statistics, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, Beijing 100005, China.

Abstract

Background: The impact of sex on the clinical manifestations of rheumatoid arthritis (RA) were diversely reported in the literature. The Chinese Registry of rhEumatoiD arthrITis provides a platform for the investigation of this issue in Chinese patients.

Methods: Demographic and clinical parameters were collected from all enrolled patients with RA and from patients with early RA (disease duration ≤6 months). The differences in data regarding disease activity, comorbidities, and medications for RA were compared between men and women. The proportions of patients who achieved remission and low disease activity were compared at enrollment and during 3-, 6-, and 12-month follow-up visits.

Results: A total of 11,564 patients were enrolled, 83.6% of whom were female. In all the enrolled patients and patients with early RA, C-reactive protein (CRP, 12.0 *vs*. 6.7 mg/L), pain visual analogue scale (4.8 *vs*. 4.5), patient's and physician's global assessment (4.9 *vs*. 4.5 and 4.9 *vs*. 4.5), 28-joint disease activity score using DAS28-CRP (4.3 *vs*. 4.0) simplified disease activity index (21.9 *vs*. 19.9), and clinical disease activity index (19.3 *vs*. 18.0) were significantly higher in men than in women. Additionally, the swollen joint count/tender joint count and DAS28 using erythrocyte sedimentation rate were higher in male patients than in female patients with early RA. More female patients with early RA reached the treatment target at baseline than male patients (23.4% *vs*. 18.2%, assessed by CDAI). At 3 months, 6 months, and 12 months, the proportion of remission and treatment target achievement was similar in both sexes. Coronary artery disease (CAD) and stroke were more frequent in men than in women.

Conclusions: In Chinese patients with RA, men were found to have more active disease, as well as more cases of CAD and stroke. Therefore, sex should be carefully considered during the personalization of RA treatment.

Keywords: Rheumatoid arthritis; Sex; Disease activity; Treatment target; Comorbidities

Introduction

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases, and is characterized by chronic destructive synovitis and multisystem involvement.[1] Most epidemiological studies have shown a prevalence of RA ranging from 0.5% to 1.0%.[2] RA can occur at any age, although the peak incidence is in the 6th decade.[3] The overall female to male ratio is about 2:1 to 3:1.[4] The impact of sex on the clinical manifestations, disease activities, treatment responses, comorbidities, and

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002110

Nan Jiang, Qin Li, and Hongbin Li contributed equally to this study.

Correspondence to: Dr. Xinping Tian, Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, No. 1, Shuaifuyuan, Wangfujing Ave, Dongcheng District, Beijing 100730, China
E-Mail: tianxp6@126.com

Chinese Medical Journal 2022;135(18)
Received: 18-10-2021; **Online:** 08-09-2022 **Edited by:** Lishao Guo

outcomes of RA have been reported in several studies.[5-10] However, studies with a large sample size were insufficient, and the results were variable among the investigators.

The Chinese Registry of rhEumatoiD arthrITis (CREDIT), which was established in November 2016, is the first nationwide online multi-center registry for RA in China. Based on data from the CREDIT cohort, the prevalence of remission, the predictors of achieving treatment target, the correlation of disease activity indices, and the major comorbidities of Chinese patients with RA have been described.[11-14] CREDIT provides a platform for investigating the influence of sex on the characteristics of RA.

Methods

Ethical approval

Ethics approval (No. S-478) for the registry was obtained from the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH), which was accepted by all participating centers as the central IRB. Informed consent was obtained from all the patients during enrollment.

Patient recruitment

Based on the CREDIT online registry, the study was conducted at 274 rheumatology centers in 31 provinces across China. As the leading center, the PUMCH is responsible for the training, communication, and funding of the registry. Chinese RA patients who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria[15,16] were recruited in the registry. We enrolled 11,564 patients who had baseline and at least 3 months of follow-up data. Data were collected between November 2016 and June 2021.

Data collection

All CREDIT centers used the same protocol-directed methods to provide uniform evaluations and record patient data. Investigators received training on diagnosis confirmation, disease activity evaluation, data input, and data quality control. In this study, demographic and clinical indices were collected at enrollment and follow-up visits, including sex, age, disease duration, initial fulfillment of RA classification criteria, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), titer of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies, pain visual analogue scale (VAS), tender joint count (TJC, 28 joint count), swollen joint count (SJC, 28 joint count), patient's and physician's global assessment (PtGA and PhGA), 28-joint disease activity score (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), and medications for RA, as well as medical history ofinterstitial lung disease (ILD), coronary artery disease (CAD), stroke, malignancy, and fragility fracture. The proportions of patients who achieved treatment target for RA was calculated. The treatment target was defined as remission or low disease activity (LDA), according to the 2014 treat-to-target recommendation.[17]

Statistical analysis

The demographic and clinical characteristics of patients of different sexes were compared in all patients with RA and in patients with early RA (defined as disease duration $\leq$6 months), with Chi-squared test for categorical variables, and Student's t test or Wilcoxon's test for continuous variables according to the distribution. Categorical variables are presented as counts. Continuous variables are presented as means $\pm$ standard deviations or medians and quartiles according to the distribution. Statistical significance was set at $P < 0.05$. All analyses were conducted using the SPSS 22.0 statistical package (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Among the 11,564 patients, 83.6% were female. The median age was 52.0 years, the median disease duration was 3.0 years, and the median CDAI was 18.3. At baseline, 26.8% of the patients received conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) monotherapy, 32.2% received double or triple csDMARD combination, and 6.8% received biologic DMARDs/targeted synthetic DMARDs plus one csDMARD. The percentage of patients who were prescribed glucocorticoids (GCs) and non-steroidal antiinflammatory drugs (NSAIDs) at baseline were 41.4% and 23.0%, respectively. The patients' baseline characteristics are shown in Table 1.

Comparison of patients of different sexes

As shown in Table 2, RF, CRP, pain VAS, PtGA, PhGA, disease activity score using CRP (DAS28-CRP), SDAI, and CDAI were all significantly higher in male patients than in female patients. As for comorbidities, the ratios of ILD, CAD, and stroke were higher in male patients, while malignancies were more commonly observed in female patients. A higher proportion of male patients received GCs and NSAIDs, while more female patients received csDMARD monotherapy.

The proportions of patients who achieved LDA or remission are shown in Table 3. At baseline, a higher proportion of female patients reached the treatment target according to DAS28-CRP, while more male patients were in remission according to DAS28 using erythrocyte sedimentation rate (DAS28-ESR). However, no such differences were observed when disease activity was assessed using other indices. At 3 months, 6 months, or 12 months, most of the disease activity indices showed no significant difference between males and females.

Comparison of patients with early RA

The characteristics of patients with early RA were analyzed separately. As shown in Table 4, age, SJC, TJC, ESR, CRP, pain VAS, PtGA, PhGA, DAS28-ESR, DAS28-CRP, SDAI, and CDAI were all significantly higher in men than in women. CAD and stroke were more commonly observed in male patients than in female

Table 1: Baseline characteristics of 11,564 patients with RA based on the CREDIT online registry between November 2016 and June 2021.

Parameters	Values
Female	9666 (83.6)
Age (years)	52.0 (43.0, 60.0)
Disease duration (years)	3.0 (1.0, 8.0)
Score of ACR/EULAR criteria	8.0 (7.0, 9.0)
RF positive	7015/8391 (83.6)
RF titer (U/mL)	57.5 (24.2, 112.0)
Anti-CCP positive	6200/8260 (75.1)
Anti-CCP titer (U/mL)	119.0 (20.0, 400.0)
SJC	3 (0, 10)
TJC	4 (1, 11)
ESR (mm/h)	30.0 (15.0, 54.0)
CRP (mg/L)	7.4 (2.5, 22.0)
Pain VAS	4.6 (2.5, 6.4)
PtGA	4.6 (2.6, 6.3)
PhGA	4.4 (2.5, 6.1)
DAS28-ESR	4.7 (3.4, 6.0)
DAS28-CRP	4.1 (2.9, 5.3)
SDAI	20.1 (10.8, 34.5)
CDAI	18.3 (9.8, 31.8)
ILD	246 (2.1)
CAD	187 (1.6)
Stroke	78 (0.7)
Malignancy	106 (0.9)
Fragility fracture	147 (1.3)
Medications	
csDMARDs monotherapy	3096 (26.8)
csDMARDs combination	3727 (32.2)
Mono-csDMARD + bDMARDs/ tsDMARDs	790 (6.8)
GC usage	4783 (41.4)
NSAIDs usage	2656 (23.0)

Data are presented as medians (Q1, Q3) or *n* (%). ACR: American College of Rheumatology; anti-CCP: Anti-cyclic citrullinated peptide; bDMARDs: Biologic disease-modifying anti-rheumatic drugs; CAD: Coronary artery disease; CDAI: Clinical disease activity index; CREDIT: Chinese Registry of Rheumatoid Arthritis; CRP: C-reactive protein; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP: 28-joint disease activity score using C-reactive protein; DAS28-ESR: DAS28 using erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GC: Glucocorticoid; ILD: Interstitial lung disease; NSAIDs: Non-steroidal anti-inflammatory drugs; PhGA: Physician's global assessment; PtGA: Patient's global assessment; RF: Rheumatoid factor; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count; tsDMARDs: Targeted synthetic disease-modifying anti-rheumatic drugs; VAS: Visual analogue scale.

patients. The ratios of ILD, malignancy, and fragility fractures were similar in the 2 sexes. More male patients with early RA received GC treatment, while more female patients received csDMARD monotherapy.

Treatment target achievement and remission achievement in patients with early RA are shown in Table 5. At baseline, the proportions of treatment target achievement were higher in female patients than in male patients, and the differences were significant according to DAS28-CRP, CDAI, and SDAI. The proportions of remission were similar between men and women at baseline; only, a higher proportion of female patients was observed in DAS28-CRP. At 3 months, 6 months, and 12 months, the proportions of treatment target achievement and remission were still higher in female patients according to most of the indices, but most of the differences were not statistically significant.

Discussion

In the current study, we compared the clinical characteristics at baseline and proportion of patients who achieved LDA or remission at follow-up between male and female patients with RA. The results showed that male patients had higher disease activity at baseline, while more female patients with early RA were in remission or in a LDA state at baseline. At 3 months, 6 months, and 12 months, the proportions of remission and treatment target achievement were similar between the 2 sexes.

As previously reported, RA is a disease that frequently occurs in women.[18] Our data showed an approximately 4-fold increase in the frequency of RA in women *vs*. men, which was consistent with the results reported by other investigators,[6,10,19] especially in a large Japanese cohort, which was constituted by the same ethnic group as our cohort.[20]

The RF was reported to be equally prevalent among sexes in Quantitative Standard Monitoring of Patients with RA registry,[21] which was conducted in 6004 RA patients in 25 countries. In our study, we found that RF titer was significantly higher in male patients. The results were consistent with data from familial RA patients in the North American Rheumatoid Arthritis Consortium cohort.[22] In our patients with early RA, the RF titer was also higher in men, although the difference was not significant ($P = 0.069$). As RF is a well-accepted unfavorable prognostic factor, the results might indicate a worse prognosis in male patients with RA.

Sex impacts on RA presentation and progression were diversely reported in previous studies [Table 6]. In 1998, Weyand et *al*[23] reported a more aggressive disease appearance in men than in women, among 165 patients. Subsequently, the influence of sex on disease activity, radiographic progression, and patient-report outcome in patients with RA has been reported in numerous studies. Some studies have shown that men were unlikely to achieve point remission,[19] or had worse bone erosion.[6] More studies indicated that women had higher disease activity, worse patient-report outcome, or more rapid disease progression.[6,20,21,24] However, there were conflicting results among these reports, or even in the same report, when different disease parameters were studied. In addition, some investigators reported finding no significant difference between sexes in clinical, laboratory, or radiological findings.[5,25,26] According to the existing literature, there is no conclusion regarding the influence of sex on disease activity of RA. The diversity of results among the investigators was possibly due to multiple reasons, including different ethnic groups, different disease stages of patients, and different disease indices

Table 2: Comparison of baseline characteristics of patients of different sexes.

Parameters	Male ($n = 1898$)	Female ($n = 9666$)	*P* values
Age (years)	56.0 (47.0, 65.0)	51.0 (42.0, 59.0)	<0.001*
Disease duration (years)	2.1 (0.6, 5.8)	3.1 (1.0, 8.7)	<0.001*
Score of ACR/EULAR criteria	8 (7, 9)	8 (7, 9)	0.411
RF positive	1160/1376 (84.3)	5855/7015 (83.5)	0.450
RF titer (U/mL)	64.4 (25.8, 123.0)	56.0 (24.0, 110.0)	<0.001*
Anti-CCP positive	1015/1347 (75.4)	5185/6913 (75.0)	0.810
Anti-CCP titer (U/mL)	127.5 (20.0, 488.4)	115.5 (19.9, 399.5)	0.092
SJC	4 (0, 11)	3 (0, 10)	0.236
TJC	4 (1, 12)	4 (1, 11)	0.083
ESR (mm/h)	30.0 (14.0, 60.0)	30.0 (15.0, 53.0)	0.752
CRP (mg/L)	12.0 (3.4, 33.4)	6.7 (2.3, 20.0)	<0.001
Pain VAS	4.8 (2.9, 6.4)	4.5 (2.5, 6.3)	0.008
PtGA	4.9 (2.8, 6.3)	4.5 (2.6, 6.3)	0.044
PhGA	4.6 (2.7, 6.3)	4.3 (2.5, 6.1)	0.003
DAS28-ESR	4.8 (3.3, 6.1)	4.7 (3.4, 5.9)	0.287
DAS28-CRP	4.3 (2.0, 5.6)	4.0 (2.9, 5.3)	<0.001
SDAI	21.9 (11.5, 37.2)	19.9 (10.7, 33.9)	<0.001
CDAI	19.3 (10.0, 33.0)	18.0 (9.8, 31.4)	0.022
ILD	57 (3.0)	189 (1.6)	0.004
CAD	60 (3.2)	127 (1.3)	<0.001
Stroke	32 (1.7)	46 (0.5)	<0.001
Malignancy	9 (0.5)	97 (1.0)	0.034
Fragility fracture	19 (1.0)	128 (1.3)	0.265
Medications			
csDMARDs monotherapy	449 (23.7)	2647 (27.4)	0.001
csDMARDs combination	601 (31.7)	3126 (32.3)	0.573
Mono-csDMARD+ bDMARDs/tsDMARDs	131 (6.9)	659 (6.8)	0.921
GC usage	841 (44.3)	3942 (40.8)	0.005*
NSAIDs usage	470 (24.8)	2186 (22.6)	0.042*

* $P < 0.05$. Data are presented as medians (Q1, Q3) or *n* (%). ACR: American College of Rheumatology; anti-CCP: Anti-cyclic citrullinated peptide; bDMARDs: Biologic disease-modifying anti-rheumatic drugs; CAD: Coronary artery disease; CDAI: Clinical disease activity index; CRP: C-reactive protein; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP: 28-joint disease activity score using C-reactive protein; DAS28-ESR: DAS28 using erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GC: Glucocorticoid; ILD: Interstitial lung disease; NSAIDs: Non-steroidal anti-inflammatory drugs; PhGA: Physician's global assessment; PtGA: Patient's global assessment; RF: Rheumatoid factor; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count; tsDMARDs: Targeted synthetic disease-modifying anti-rheumatic drugs; VAS: Visual analogue scale.

used. Moreover, menopause status was reported to be an important factor influencing disease activity. Post-menopausal women were revealed to have more active disease than men and pre-menopausal women.[23,25]

In our large-scale registry of Chinese patients, the acute phase reactants, the PtGA/PhGAs, and the disease activity assessed by the composite indices were all higher in men than in women at baseline, both in patients with early RA and established RA. Fewer male patients were in remission or in a LDA state compared to females. The higher percentage of GC usage in men at baseline also demonstrated more active disease in male patients, as GC is the most frequently used medication for inflammation control and symptom relief. In our study, csDMARD monotherapy was more commonly used in male patients. We infer that this result was also because male patients had more active disease given that physicians tend to prescribe csDMARD monotherapies for patients with less severe disease. Taken together, these results indicated that male patients had higher disease activity. Furthermore, since patients with early RA were less affected by treatment or other factors and had comparable disease duration, the higher disease activity observed in male patients can reflect the original state of the disease to a large extent.

At follow-up visits in our cohort, the differences in disease activity between men and women were diminished. Although there were still some differences in the proportions of remission and LDA, statistical significance was only observed in a minority of the indices. These alterations can be interpreted as the impact of the treatment. After effective treatment for RA, the disease activity was lowered in men, so that the disparity of their baseline disease activity with women was diminished to some extent. There were some conflicting results between data of all patients and patients with early RA, especially in remission or LDA achievement defined by DAS28. We considered that the early RA data, which was much less influenced by treatment and other factors, were more reliable for this issue. Moreover, in clinical practice, CDAI is considered to be a more suitable and reliable disease activity index than DAS28; therefore, we believe that

Table 3: LDA and remission achievement in patients of different sexes.

Parameters	LDA or remission achievement			Remission achievement		
	Male	Female	*P* values	Male	Female	*P* values
Baseline ($n = 11,564$)	$n = 1898$	$n = 9666$		$n = 1898$	$n = 9666$	
DAS28-ESR	437 (23.0)	2129 (22.0)	0.349	302 (15.9)	1276 (13.2)	0.002*
DAS28-CRP	536 (28.2)	3066 (31.7)	0.003*	364 (19.2)	1918 (19.8)	0.508
CDAI	486 (25.6)	2570 (26.6)	0.378	131 (6.9)	659 (6.8)	0.921
SDAI	457 (24.1)	2498 (25.8)	0.107	130 (6.8)	684 (7.1)	0.732
3 months ($n = 8032$)	$n = 1355$	$n = 6677$		$n = 1355$	$n = 6677$	
DAS28-ESR	608 (44.9)	2730 (40.9)	0.007*	395 (29.2)	1787 (26.8)	0.076
DAS28-CRP	697 (51.4)	3541 (53.0)	0.296	496 (36.6)	2473 (37.0)	0.781
CDAI	680 (50.2)	3158 (47.3)	0.053	203 (15.0)	928 (13.9)	0.304
SDAI	649 (47.9)	3172 (47.5)	0.811	201 (14.8)	960 (14.4)	0.672
6 months ($n = 4821$)	$n = 742$	$n = 4079$		$n = 742$	$n = 4079$	
DAS28- ESR	364 (49.1)	1852 (45.4)	0.072	262 (35.3)	1259 (30.9)	0.018*
DAS28-CRP	402 (54.2)	2352 (57.7)	0.083	293 (39.5)	1736 (42.6)	0.125
CDAI	394 (53.1)	2146 (52.6)	0.811	136 (18.3)	729 (17.9)	0.795
SDAI	385 (51.9)	2143 (52.5)	0.749	135 (18.2)	702 (17.2)	0.527
1 year ($n = 2848$)	$n = 423$	$n = 2425$		$n = 423$	$n = 2425$	
DAS28-ESR	205 (48.5)	1152 (47.5)	0.752	143 (33.8)	798 (32.9)	0.737
DAS28-CRP	239 (56.5)	1469 (60.6)	0.119	174 (41.1)	1084 (44.7)	0.185
CDAI	239 (56.5)	1623 (45.7)	0.095	78 (18.4)	468 (19.3)	0.689
SDAI	230 (54.4)	1385 (57.1)	0.832	70 (16.5)	486 (20.0)	0.097

* $P < 0.05$. Data are presented as medians (Q1, Q3) or n (%). CDAI: Clinical disease activity index; CRP: C-reactive protein; DAS28-CRP: 28-joint disease activity score using C-reactive protein; DSA28-ESR: DAS28 using erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; LDA: Low disease activity; SDAI: Simplified disease activity index.

Table 4: Comparison of baseline characteristics of patients with early RA.

Parameters	Male ($n = 402$)	Female ($n = 1368$)	*P* values
Age (years)	56.0 (47.0, 64.0)	49.0 (39.0, 57.0)	<0.001*
Disease duration (years)	0.24 (0.14, 0.36)	0.24 (0.13, 0.37)	0.523
Score of ACR/EULAR criteria	7 (7, 9)	7 (7, 9)	0.159
RF positive	264/303 (87.1)	860/1026 (83.8)	0.175
RF titer (U/mL)	63.5 (26.6, 129.0)	58 (24.9, 113.7)	0.069
Anti-CCP positive	231/302 (76.5)	813/1011 (80.4)	0.144
Anti-CCP titer (U/mL)	170.5 (20.6, 543.4)	179.0 (30.0, 458.0)	0.947
SJC	4 (1, 13)	4 (1, 10)	0.044*
TJC	6 (2, 14)	5 (1, 11)	0.014*
ESR (mm/h)	36.0 (17.0, 62.0)	30.0 (16.0, 54.0)	0.013*
CRP (mg/L)	17.0 (5.1, 45.0)	6.5 (2.4, 21.9)	<0.001*
Pain VAS	5.1 (3.2, 6.6)	4.7 (2.8, 6.2)	0.001*
PtGA	5.1 (3.1, 6.5)	4.7 (2.9, 6.2)	0.004*
PhGA	5.1 (3.3, 6.4)	4.4 (2.7, 6.0)	<0.001*
DAS28-ESR	5.1 (3.8, 6.4)	4.8 (3.5, 6.0)	0.002*
DAS28-CRP	4.6 (3.5, 5.9)	4.1 (3.0, 5.3)	<0.001*
SDAI	26.1 (14.3, 41.5)	20.8 (12.0, 34.6)	<0.001*
CDAI	22.4 (12.7, 37.7)	19.0 (11.0, 32.0)	0.002*
ILD	6 (1.5)	30 (2.2)	0.431
CAD	12 (3.0)	16 (1.2)	0.014*
Stroke	7 (1.7)	3 (0.2)	0.002*
Malignancy	4 (1.0)	11 (0.8)	0.757
Fragility fracture	4 (1.0)	15 (1.1)	1.000
Medications			
csDMARDs monotherapy	101 (25.1)	443 (32.4)	0.006
csDMARDs combination	118 (29.4)	416 (30.4)	0.711
Mono-csDMARDs + bDMARDs/tsDMARDs	31 (7.7)	88 (6.4)	0.428
GC usage	165 (41.0)	479 (35.0)	0.029
NSAIDs usage	123 (30.6)	391 (28.6)	0.453

* $P < 0.05$. Data are presented as medians (Q1, Q3) or *n* (%). ACR: American College of Rheumatology; anti-CCP: Anti-cyclic citrullinated peptide; bDMARDs: Biologic disease-modifying anti-rheumatic drugs; CAD: Coronary artery disease; CDAI: Clinical disease activity index; CRP: C-reactive protein; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-CRP: 28-joint disease activity score using C-reactive protein; DAS28-ESR: DAS28 using erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GC: Glucocorticoid; ILD: Interstitial lung disease; NSAIDs: Non-steroidal anti-inflammatory drugs; PhGA: Physician's global assessment; PtGA: Patient's global assessment; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SDAI: Simplified disease activity index; SJC: Swollen joint count; TJC: Tender joint count; tsDMARDs: Targeted synthetic disease-modifying anti-rheumatic drugs; VAS: Visual analogue scale.

Table 5: LDA and remission achievement in patients with early RA.

Parameters	LDA or remission achievement			Remission achievement		
	Male	Female	*P* values	Male	Female	*P* values
Baseline ($n = 1770$)	$n = 402$	$n = 1368$		$n = 402$	$n = 1368$	
DAS28-ESR	72 (17.9)	274 (20.0)	0.354	38 (9.5)	144 (10.5)	0.576
DAS28-CRP	83 (20.6)	393 (28.7)	0.001*	52 (12.9)	238 (17.4)	0.038*
CDAI	73 (18.2)	320 (23.4)	0.029*	24 (6.0)	80 (5.8)	1.000
SDAI	66 (16.4)	312 (22.8)	0.007*	21 (5.2)	83 (6.1)	0.550
3 months ($n = 1323$)	$n = 309$	$n = 1014$		$n = 309$	$n = 1014$	
DAS28-ESR	142 (46.0)	469 (46.3)	0.948	87 (28.2)	312 (30.8)	0.396
DAS28-CRP	163 (52.8)	583 (57.5)	0.150	114 (36.9)	430 (42.4)	0.086
CDAI	160 (51.8)	520 (51.3)	0.897	40 (12.9)	186 (18.3)	0.031*
SDAI	155 (50.2)	523 (51.6)	0.697	41 (13.3)	190 (18.7)	0.032*
6 months ($n = 754$)	$n = 154$	$n = 600$		$n = 154$	$n = 600$	
DAS28-ESR	76 (49.4)	298 (49.7)	1.000	55 (35.7)	219 (36.5)	0.925
DAS28-CRP	70 (45.5)	383 (63.8)	<0.001*	57 (37.0)	280 (46.7)	0.037*
CDAI	77 (50.0)	330 (55.0)	0.278	30 (19.5)	134 (22.3)	0.511
SDAI	74 (48.1)	335 (55.8)	0.086	28 (18.2)	133 (22.2)	0.322
1 year ($n = 398$)	$n = 77$	$n = 321$		$n = 77$	$n = 321$	
DAS28-ESR	37 (48.1)	173 (53.9)	0.376	25 (32.5)	121 (37.7)	0.431
DAS28-CRP	38 (49.4)	207 (64.5)	0.019*	30 (39.0)	166 (51.7)	0.057
CDAI	42 (54.5)	197 (61.4)	0.301	15 (19.5)	62 (19.3)	1.000
SDAI	39 (50.6)	199 (62.0)	0.072	14 (18.2)	65 (20.2)	0.752

* $P < 0.05$. Data are presented as *n* (%). CDAI: Clinical disease activity index; CRP: C-reactive protein; DAS28-CRP: 28-joint disease activity score using C-reactive protein; DAS28-ESR: DAS28 using erythrocyte sedimentation rate; ESR: Erythrocyte sedimentation rate; LDA: Low disease activity; RA: Rheumatoid arthritis; SDAI: Simplified disease activity index.

Table 6: Previous reports of sex impacts on RA.

Author	Country	Number of patients (female%)	Conclusions
Weyand *et al*[23]	USA	165 (66.7)	Men were correlated with a higher risk of bony erosions and an accelerated course of RA
Voulgari *et al*[5]	Greece	38 (71.2)	There was no significant difference between sexes in clinical, laboratory, and radiological findings
Gossec *et al*[25]	France	266 (50.0)	No difference in clinical or radiological indicators was observed
Jawaheer *et al*[6]	USA	292 (77.1)	Men and women had similar disease activity and joint damage at baseline. Men had significantly worse erosion. Responses to treatment over time were better in male patients
Rintelen *et al*[10]	Australia	557 (77.6)	Female patients had significantly higher SDAI and CDAI level than males
Kuiper *et al*[26]	Holland	332 (63.0)	DAS was equivalent between sexes at study entry, but was significantly higher in females at follow-ups
Tengstrand *et al*[24]	Sweden	8 (63.7)	Women had higher DAS28 and HAQ scores at study entry and at 2-year follow-up. Men had a higher frequency of remission
Iikuni *et al*[20]	Japan	823 (83.5)	Women overall have higher RA disease activity and are prone to greater and faster progression of disability
Jawaheer *et al*[19]	USA	10,299 (76.6)	Women had more severe disease at baseline. Men were more likely to achieve sustained remission in early RA, but were unlikely to achieve point remission in established RA
Sokka *et al*[21]	25 countries	600 (79.2)	Women had higher pain VAS, PtGA, DAS28, and HAQ scores

CDAI: Clinical disease activity index; DAS28:28-joint disease activity score; HAQ: Health Assessment Questionnaire; PtGA: Patient's global assessment; RA: Rheumatoid arthritis; SDAI: Simple disease activity index; VAS: Visual analogue scale.

remission or LDA achievement defined by CDAI was more important in our real-world cohort. More long-term follow-up data are needed to demonstrate the differences in prognosis between men and women.

ILD is an important complication of RA and usually occurs in patients with long disease duration and inadequately controlled RA.[27] In our study, the prevalence of ILD was higher in male patients, which was consistent with the results of other investigators.[28,29] In early RA, given that the disease duration was too short to develop ILD, the ratios of ILD were low and showed no significant difference between sexes. It is widely accepted that the risks of cardiovascular disease and cerebrovascular disease are increased in patients with RA. In the general population, men are known to be at a higher risk of cardiovascular and cerebrovascular diseases than women. In patients with RA, the relative risk of cardiovascular disease was found to be equally increased for men and women in a meta-analysis including 13 studies.[30] Therefore, the higher percentages of CAD and stroke in males observed in our registry were quite reasonable.

The present study has some limitations. First, the CREDIT cohort has only been established for 5 years, and a number of patients were recently recruited. Thus, the long-term follow-up data regarding the outcomes of RA were insufficient. Second, radiological information and health assessment questionnaire were not collected in this study, so the differences in joint damage and patient-report outcomes between men and women could not be well assessed. Third, fibromyalgia and osteoporosis, 2 important comorbidities of RA, were not recorded. The above unresolved questions remain to be answered in future studies with the development of the CREDIT cohort.

In conclusion, we conducted a large-scale study on the influence of sex on clinical characteristics of Chinese patients with RA. At baseline, male patients were found to have more active RA and a lower proportion of treatment target achievement than female patients. During the 1 year of follow-up, the differences in the percentages of LDA and remission between men and women were diminished to some extent. Male patients had more CAD and stroke than female patients. The results of our study suggest that the more active RA in men should call our attention and be intensively managed, and physicians should pay attention to the prevention and management of cardiovascular diseases in male patients with RA.

Acknowledgments

We acknowledge the contributions from all CREDIT centers all over China and HealthCloud Co., Ltd. as the system provider.

Funding

The work was supported by grants from the Chinese National Key Technology R&D Program, Ministry of Science and Technology (Nos. 2017YFC0907601, 2017YFC0907602, and 2017YFC0907603); the Beijing Municipal Science and Technology Commission (Nos. Z201100005520022, 23, and 25–27); and the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-1-005).

Conflicts of interest

None.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016;388:2023–2038. doi: 10.1016/S0140-6736(16)30173-8.
2. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, *et al*. Rheumatoid arthritis. Nat Rev Dis Primers 2018;4:18001. doi: 10.1038/nrdp.2018.1.
3. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum 2010;62:1576–1582. doi: 10.1002/art.27425.
4. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360–1372. doi: 10.1001/jama.2018.13103.
5. Voulgari PV, Papadopoulos IA, Alamanos Y, Katsaraki A, Drosos AA. Early rheumatoid arthritis: does gender influence disease expression? Clin Exp Rheumatol 2004;22:165–170.
6. Jawaheer D, Maranian P, Park G, Lahiff M, Amjadi SS, Paulus HE. Disease progression and treatment responses ina prospective DMARD-naive seropositive early rheumatoid arthritis cohort: does gender matter? J Rheumatol 2010;37:2475–2485. doi: 10.3899/jrheum.091432.
7. Twigg S, Hensor EMA, Freeston J, Tan AL, Emery P, Tennant A, *et al*. Effect of fatigue, older age, higher body mass index, and female sex on disability in early rheumatoid arthritis in the treatment-to-target era. Arthritis Care Res (Hoboken) 2018;70:361–368. doi: 10.1002/acr.23281.
8. Aurrecoechea E, Llorca Diaz J, Diez Lizuain ML, McGwin G Jr, Calvo-Alen J. Gender-associated comorbidities in rheumatoid arthritis and their impact on outcome: data from GENIRA. Rheumatol Int 2017;37:479–485. doi: 10.1007/s00296-016-3628-7.
9. Radovits BJ, Fransen J, van Riel PL, Laan RF. Influence of age and gender on the 28-joint Disease Activity Score (DAS28) in rheumatoid arthritis. Ann Rheum Dis 2008;67:1127–1131. doi: 10.1136/ard.2007.079913.
10. Rintelen B, Haindl PM, Maktari A, Nothnagl T, Hartl E, Leeb BF. SDAI/CDAI levels in rheumatoid arthritis patients are highly dependent on patient's pain perception and gender. Scand J Rheumatol 2008;37:410–413. doi: 10.1080/03009740802241717.
11. Yu C, Li M, Duan X, Fang Y, Li Q, Wu R, *et al*. Chinese registry of rheumatoid arthritis (CREDIT): I. Introduction and prevalence of remission in Chinese patients with rheumatoid arthritis. Clin Exp Rheumatol 2018;36:836–840.
12. Jin S, Li M, Fang Y, Li Q, Liu J, Duan X, *et al*. Chinese registry of rheumatoid arthritis (CREDIT): II. Prevalence and risk factors of major comorbidities in Chinese patients with rheumatoid arthritis. Arthritis Res Ther 2017;19:251. doi: 10.1186/s13075-017-1457-z.
13. Xiang Y, Wang Q, Li H, Duan X, Fang Y, Yang P, *et al*. Chinese registry of rheumatoid arthritis (CREDIT): III. The transition of disease activity during follow-ups and predictors of achieving treatment target. Int J Rheum Dis 2020;23:1719–1727. doi: 10.1111/1756-185X.13996.
14. Song X, Wang YH, Li MT, Duan XW, Li HB, Zeng XF, *et al*. Chinese registry of rheumatoid arthritis: IV. Correlation and consistency of rheumatoid arthritis disease activity indices in China. Chin Med J 2021;134:1465–1470. doi: 10.1097/CM9.0000000000001517.
15. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–1588. doi: 10.1136/ard.2010.138461.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–2581. doi: 10.1002/art.27584.

17. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, *et al*. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15. doi: 10.1136/annrheumdis-2015-207524.
18. Favalli EG, Biggioggero M, Crotti C, Becciolini A, Raimondo MG, Meroni PL. Sex and management of rheumatoid arthritis. Clin Rev Allergy Immunol 2019;56:333–345. doi: 10.1007/s12016-018-8672-5.
19. Jawaheer D, Messing S, Reed G, Ranganath VK, Kremer JM, Louie JS, *et al*. Significance of sex in achieving sustained remission in the consortium of rheumatology researchers of North America cohort of rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2012;64:1811–1818. doi: 10.1002/acr.21762.
20. Iikuni N, Sato E, Hoshi M, Inoue E, Taniguchi A, Hara M, *et al*. The influence of sex on patients with rheumatoid arthritis in a large observational cohort. J Rheumatol 2009;36:508–511. doi: 10.3899/jrheum.080724.
21. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, *et al*. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther 2009;11:R7. doi: 10.1186/ar2591.
22. Jawaheer D, Lum RF, Gregersen PK, Criswell LA. Influence of male sex on disease phenotype in familial rheumatoid arthritis. Arthritis Rheum 2006;54:3087–3094. doi: 10.1002/art.22120.
23. Weyand CM, Schmidt D, Wagner U, Goronzy JJ. The influence of sex on the phenotype of rheumatoid arthritis. Arthritis Rheum 1998;41:817–822. doi: 10.1002/1529-0131(199805)41:5<817::AID-ART7>3.0.CO;2-S.
24. Tengstrand B, Ahlmen M, Hafstrom I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. J Rheumatol 2004;31:214–222.
25. Gossec L, Baro-Riba J, Bozonnat MC, Daures JP, Sany J, Eliaou JF, *et al*. Influence of sex on disease severity in patients with rheumatoid |arthritis. J Rheumatol 2005;32:1448–1451.
26. Kuiper S, van Gestel AM, Swinkels HL, de Boo TM, da Silva JA, van Riel PL. Influence of sex, age, and menopausal state on the course of early rheumatoid arthritis. J Rheumatol 2001;28:1809–1816.
27. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest 2009;136:1397–1405. doi: 10.1378/chest.09-0444.
28. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, *et al*. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583–1591. doi: 10.1002/art.27405.
29. Kronzer VL, Huang W, Dellaripa PF, Huang S, Feathers V, Lu B, *et al*. Lifestyle and clinical risk factors for incident rheumatoid arthritis-associated interstitial lung disease. J Rheumatol 2021;48:656–663. doi: 10.3899/jrheum.200863.
30. Fransen J, Kazemi-Bajestani SM, Bredie SJ, Popa CD. Rheumatoid arthritis disadvantages younger patients for cardiovascular diseases: a meta-analysis. PLoS One 2016;11:e0157360. doi: 10.1371/journal. pone.0157360.

How to cite this article: Jiang N, Li Q, Li H, Fang Y, Wu L, Duan X, Xu J, Zhao C, Jiang Z, Wang Y, Wang Q, Leng X, Li M, Tian X, Zeng X. Chinese registry of rheumatoid arthritis (CREDIT) V: sex impacts rheumatoid arthritis in Chinese patients. Chin Med J 2022;135:2210–2217. doi: 10.1097/CM9.0000000000002110