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Early menopause is associated with higher disease activity independent of inflammation in postmenopausal-onset rheumatoid arthritis

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Abstract

Objective Early menopause (EM, age ≤ 45 years) is associated with an increased risk of developing rheumatoid arthritis (RA). We aimed to investigate its impact on disease characteristics in RA patients.

Methods This cross-sectional study included natural post-menopausal RA patients from an observational RA cohort recruited between January 2015 and October 2023. Demographic characteristics and clinical data were collected. Patients were divided into EM and usual menopause (UM, menopause age > 45 years) groups. Patients-reported outcomes (PROs, included patient global assessment of disease activity [PtGA], pain visual analogue scale [VAS] and Stanford health assessment questionnaire disability index [HAQ-DI]), and PROs-associated indicators (included 28-joint tender joint count [TJC28] and provider global assessment of disease activity [PrGA]) were assessed.

Results Among 1427 female RA patients, 557 natural post-menopausal RA patients were enrolled. The peak menopause age was between 46 and 50 years, with RA incidence peaking 5 years post-menopause. Compared with UM patients, RA patients with natural EM ($n = 98$,17.6%) exhibited more serious disease, including worse PROs and PROs-associated indicators, as well as higher C-reactive protein (CRP, all $P < 0.05$). Among 344 (61.8%) patients with RA onset after menopause, EM patients ($n = 62$, 18.0%) were characterized with worse PROs and PROs-associated indicators than those with UM patients (all $P < 0.05$), but no difference in inflammatory makers. Multivariate linear regression showed that menopause age was independently and negatively associated with PROs, including PtGA (β = -0.872, *95% CI* -1.619, -0.125), HAQ-DI (β = -0.646, *95% CI* -1.059, -0.233) in RA patients especially in those onset after menopause (PtGA [β = -1.028, *95% CI* -2.022, -0.034]; HAQ-DI [β = -0.916, *95% CI* -1.461, -0.370]).

Conclusion Early menopause impacts on PROs independent of inflammation in patients with RA especially in those with postmenopausal-onset RA, which imply the importance of differentiation of non-inflammatory disease activity.

Keywords Rheumatoid arthritis, Early menopause, Postmenopausal, Patient-reported outcomes

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Introduction

Rheumatoid arthritis (RA) is a female-predominant autoimmune disease that is characterized with progressive and irreversible joint damage, disability and increased mortality [1]. The menopausal transition, marked by a reduction in estrogen levels, significantly impacts women's lifelong health [2]. This transition is associated with the development of osteoporosis, cardiovascular diseases, and neurodegenerative diseases [3–5], and precipitates bothersome vasomotor symptoms and mood disruption that reduce the quality of life of women. Previous studies also showed that the influence of estrogen on immune function plays a crucial role in the development and progression of RA [6]. The peak incidence of RA in females often coincides with menopausal years [7]. However, the temporal association between RA onset and menopause (e.g., whether RA tends to occur before, during, or after menopause, and if after, how many years post-menopause) remains unclear.

Several studies looking at early age at menopause and RA suggested that it may play a role in risk for RA as well as disease presentation in established RA [8–12]. Early menopause (EM, menopause age ≤ 45 years) was associated with almost 2.4-fold risk of subsequent development of RA [8, 9]. Symptoms of somatoform autonomic dysfunction often emerge during the menopausal transition, post-menopausal status especially EM might exert a negative impact on disease characteristics especially patient-reported outcomes (PROs). However, published data on this association were controversial [10–12]. Wong LE et al. [11]. reported that the EM group which included 22.6% patients undergone hysterectomy and/or oophorectomy, had higher mean patient global assessment and pain scores compared with the usual menopause (UM) group. Similarly, Park EH et al. [12]. also identified that RA patients with EM which included 46.9% patients with surgery demonstrated higher disease activity indices and worse PROs than those in the UM group. Considering the essence of menopause is a natural decline of ovarian function, patients who undergo hysterectomy alone (without concurrent oophorectomy) generally retain normal estrogen secretion. Additionally, patients receiving hormone replacement therapy (HRT) may experience symptoms improvement that complicates the determination of natural menopause age. These could introduce bias when exploring the associations between EM and RA disease characteristics. In addition, emerging paradigms in RA pathophysiology distinguish between inflammatory disease activity-driven by synovitis and non-inflammatory disease activity, which manifests as pain amplification, fatigue, and functional impairment mediated through central sensitization pathways [13]. Therefore, EM may have different effects on "inflammatory" and "non-inflammatory" disease activity of RA.

This study aimed to elucidate the distribution of temporal association between RA onset and menopause and to investigate the differentially associates between EM with inflammatory and non-inflammatory disease activity in RA patients.

Materials and methods

Study design and participants

RA patients were consecutively recruited into our large, real-world, prospective observational cohort study conducted at the Department of Rheumatology and Immunology, Sun Yat-sen Memorial Hospital, Guangdong, China between January 2015 and October 2023 [14–16]. All RA diagnoses, were confirmed clinically and met the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria [17].

Post-menopausal female RA patients were included in this study. The exclusion criteria were as follows: (1) pre- or peri-menopausal patients; (2) patients with other autoimmune diseases (including systemic lupus erythematosus [SLE], systemic sclerosis [SSc], dermatomyositis/polymyositis, etc.); (3) patients with malignancy; (4) patients with endocrine or reproductive disorders (e.g., polycystic ovary syndrome [PCOS], hysterectomy and/or oophorectomy); (5) patients using medications or therapies known to influence sex hormone levels (e.g., levonorgestrel-releasing intrauterine device [LNG-IUD], hormone replacement therapy [HRT], androgen inhibitors or anti-estrogens); (6) patients who did not provide their age at menopause. Ethical approval for this study was obtained from the Ethics Committee at Sun Yat-sen Memorial Hospital (SYSEC-2009-06, SYSEC-KY-KS-012). All patients consented to participate and signed informed consent.

Clinical assessments and data collection

Clinical assessment and data collection were finished by trained research staff at enrollment, including gender, age, RA onset age, menopause status, menopause age, active smoking, body mass index (BMI, kg/m^2), RA disease duration, clinical interview, physical examination, laboratory tests, and radiographic indicators. Active RA was defined as the clinical disease activity index (CDAI) > 2.8. Laboratory test including erythrocyte sedimentation rate (ESR, mm/h, 0–20 mm/h [female], 0–15 mm/h [male]), C-reactive protein (CRP, mg/L, 0–5 mg/L), rheumatoid factor (RF, immunoturbidimetry, mg/L, 0–20 mg/L), and anti-cyclic citrullinated peptide antibody (ACPA, enzyme-linked immunosorbent assay [ELISA], IU/mL, 0–18 IU/mL) was measured centrally within 24 h of sample collection at enrollment. Conventional radiographic assessments of the bilateral hands and wrists were performed within 4 weeks of enrollment

using the Sharp/van der Heijde modified Sharp score, which includes the modified total Sharp score (mTSS) along with subscores for joint erosion (JE) and joint space narrowing (JSN). These assessments were performed by two experienced observers (LF C and JZ L) who were blinded to the clinical data, as previously described.

PROs (including patient global assessment of disease activity [PtGA], pain visual analogue scale [VAS] and the Stanford health assessment questionnaire disability index [HAQ-DI]), and PROs-associated indicators (included 28-joint tender joint count [TJC28] and provider global assessment of disease activity [PrGA]) were assessed by research staff at enrollment.

Definition of menopausal status

According to the Stages of Reproductive Aging Workshop + 10 standard [18], age at menopause was recorded as the year of woman's self-reported age at permanent amenorrhea. Post-menopause was defined as beginning one year after the onset of permanent amenorrhea [18]. EM was defined as menopause age ≤ 45 years, and UM was defined as menopause age > 45 years [9, 10]. Premature menopause was defined as menopause occurring before age of 40 years [19].

The interval from RA onset to menopause (in years) was calculated by subtracting the age at RA onset from the age at menopause. Patients with first arthritis symptom occurred one year after natural menopause were categorized as having RA onset after menopause, otherwise, they were categorized as patients with RA onset before menopause.

Statistical analysis

Statistical software packages R 4.2.2 were utilized for all analyses. Propensity score matching was performed to address potential concerns of age or disease duration bias. The assumption of normality was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean (standard deviation, SD) or median (25th, 75th percentiles) according to the distribution, the student's *t*-test or the Mann-Whitney *U* test were used to compare the differences between EM and UM groups. Categorical variables are expressed as numbers (percentages), Chi-square test or Fisher's exact test was used to compare the differences between groups.

Univariate and multivariate linear regression analyses were conducted to evaluate the associations between menopause age and RA disease indicators in RA patients. Multivariate analyses were adjusted for age, onset age, BMI, disease duration, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA). In this analysis, RA disease indicators including PtGA, pain VAS, HAQ-DI, TJC28, PrGA, 28-joint swollen joint count (SJC28), CDAI, ESR, CRP, mTSS, JSN and JE was normalized using a ln (x + 1) transformation for fitting these multifactorial models. In addition, sensitivity analyses were conducted through converted RA disease indicators into categorical variables according to the median of these indicators, and analyzed the correlation between RA menopausal age or early menopause and RA disease using logistic regression. $P < 0.05$ is considered statistically significant.

Results

Demographic characteristics of post-menopausal RA patients

Among 1427 female RA patients recruited in our cohort, 629 patients who were in pre-menopause or peri-menopause, 72 patients with a diagnosis of malignancy, 48 patients with concurrent autoimmune diseases, 29 patients with a history of hysterectomy and/or oophorectomy, 17 patients using LNG-IUD or HRT and 75 patients without providing their menopause age were excluded (Fig. 1). Ultimately, there were 557 natural post-menopausal female RA patients eligible for analysis, with a mean age of 60.6 ± 7.9 years, a median disease duration of 79 (27, 132) months. Among them, 383 patients (69.0%) had positive RF, 379 (68.2%) had positive ACPA, and 473 (84.9%) were in active disease. Compared with the 75 excluded patients without providing their menopause age, the included patients showed no differences of RA disease characteristics, except for younger (60.6 ± 7.9 years vs. 62.7 ± 7.1 years, $P = 0.031$, Supplementary Table 1).

The distribution of RA onset age and menopause age in post-menopausal RA patients

Among 557 post-menopausal female RA patients, the mean age of RA onset was 51.9 ± 10.8 years, with a peak RA-onset age of 51–55 years. The mean age of menopause was 49.0 ± 4.2 years, and the peak age of menopause was 46–50 years. Both age of RA onset and menopause showed an unimodal distribution (Fig. 2A).

There were 344 RA patients (61.8%) showing RA onset after menopause, with a mean menopause age of 48.9 ± 4.0 years, and an average interval from menopause to RA onset of 8.9 ± 7.4 years. While 213 patients (38.2%) experienced RA onset before menopause, with mean menopause age of 49.2 ± 4.2 years, the interval time from RA onset to menopause was 6.9 ± 7.3 years. Notably, the peak age of RA onset occurred approximately 5 years after the peak age of menopause (Fig. 2B).

Of the 98 EM patients (17.6%), the mean menopause age was 42.2 ± 3.1 years (range: 30–45 years), and 17.3% (17/98) experienced premature menopause, with an average age of 36.9 ± 2.6 years. There were 62 EM patients (11.1%) with RA onset after menopause, with menopause age of 42.2 ± 3.0 years, in which 19.4% (12/62) were

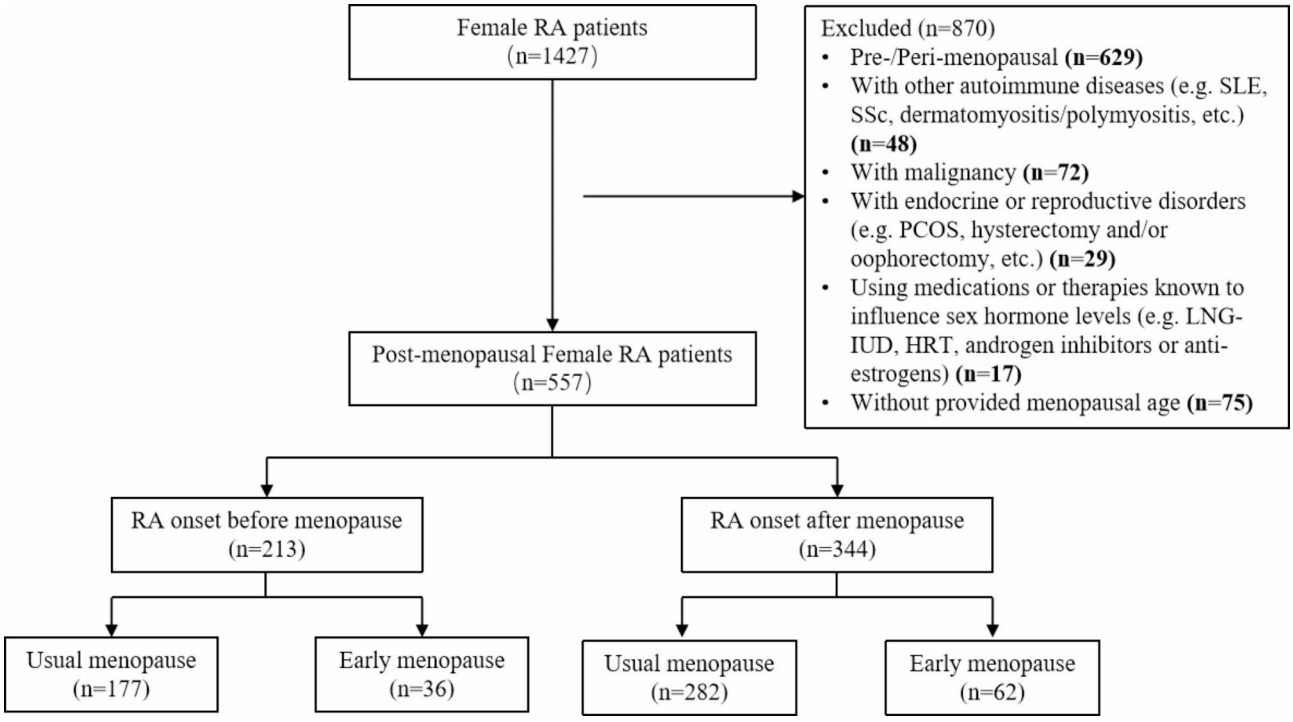

Fig. 1 Flow chart of post-menopausal RA patient's enrollment. RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; PCOS, polycystic ovary syndrome; LNG-IUD, levonorgestrel-releasing intrauterine device; HRT, hormone replacement therapy

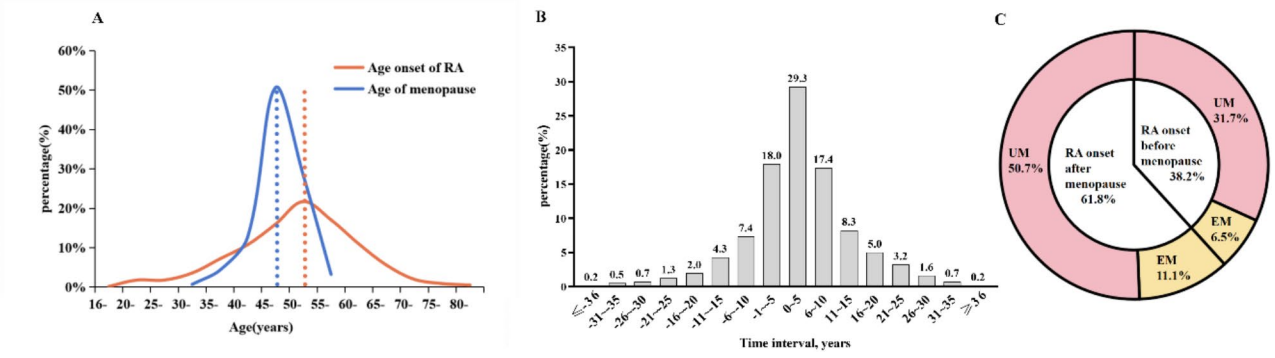

Fig. 2 The distribution of RA onset age and menopause age in post-menopausal RA patients. (**A**) The distribution of RA onset age and menopause age in post-menopausal women with RA; (**B**) The distribution of time interval between the age of RA onset and menopause; (**C**) Percentage of post-menopausal women with RA onset before and after menopause. RA, rheumatoid arthritis; EM, Early menopause; UM, Usual menopause

premature menopause, with mean menopause age of 37.1 ± 2.6 years, while there were 36 EM patients (6.5%) with RA onset before menopause, with menopause age of 42.2 ± 3.0 years, in which 13.9% (5/36) were premature menopause, with mean menopause age of 36.4 ± 2.7 years (Fig. 2C).

Clinical characteristics between patients with RA onset before and after menopause

Among all post-menopausal RA patients, compared with RA onset before menopause, RA onset after menopause had an older age (62.9 ± 7.8 years vs. 57.0 ± 6.7years) and RA onset age (57.8 ± 7.5 years vs. 42.2 ± 8.1 years), higher CRP (median 6.5 mg/L vs. 4.7 mg/L), but shorter disease duration (median 42 months vs. 132 months), lower proportion of positive RF (65.0% vs. 75.5%), and lower level of radiographic assessment indices including mTSS (median 8 vs. 50), JSN (median 2 vs. 19) and JE (median 6 vs. 23, all $P < 0.05$, Table 1).

After matching by age (1:1), compared with RA onset before menopause, patients with RA onset after menopause also demonstrated older onset age, shorter disease duration, lower proportion of positive RF, and lower radiographic assessment indices including mTSS, JSN and JE, as well as younger menopause age (all $P < 0.05$, Table 1).

Table 1 Comparisons of clinical characteristics between patients with RA onset before and after menopause

Characteristics	Before matching			After matching*		
	RA onset before menopause (*n* = 213)	RA onset after menopause (*n* = 344)	*P*	RA onset before menopause (*n* = 195)	RA onset after menopause (*n* = 195)	*P*
Age, years	57.0 ± 6.7	62.9 ± 7.8	< 0.001	58.0 ± 6.1	58.8 ± 5.9	0.184
Onset age, years	42.2 ± 8.1	57.8 ± 7.5	< 0.001	42.7 ± 7.9	55.6 ± 6.3	< 0.001
Menopause age, years	49.2 ± 4.2	48.9 ± 4.0	0.477	49.7 ± 3.8	48.1 ± 4.2	< 0.001
BMI, kg/m^2	22.1 ± 3.4	22.4 ± 3.3	0.267	22.2 ± 3.3	22.5 ± 3.3	0.502
Disease duration, months	132 (95,240)	42 (12,928)	< 0.001	144(96,240)	24 (10,51)	< 0.001
Active smoking, n (%)	7 (3.3)	22 (6.4)	0.108	5 (2.6)	9 (4.6)	0.276
Positive RF, n (%)	160 (75.5)	223 (65.0)	0.010	146 (75.3)	119 (61.3)	0.003
Positive ACPA, n (%)	146 (68.5)	233 (67.9)	0.880	136 (69.7)	135 (69.6)	0.973
CDAI	12 (5,25)	14 (6,25)	0.485	12 (5,25)	14 (6,25)	0.726
PROs						
PtGA	4 (2,6)	4 (2,6)	0.990	4 (2,6)	4 (2,6)	0.592
Pain VAS	2 (2,5)	3 (2,5)	0.361	3 (2,5)	3 (2,5)	0.546
HAQ-DI	0.3 (0,1.0)	0.4 (0,1.0)	0.308	0.4 (0,1.0)	0.3 (0,1)	0.916
PROs-associated indicators						
TJC28	3 (1,9)	4 (1,9)	0.091	3 (1,9)	4 (1,9)	0.122
PrGA	4 (2,6)	4 (2,6)	0.728	4 (2,6)	4 (2,6)	0.899
SJC28	2 (0,5)	2 (0,5)	0.558	2 (0,5)	2 (0,5)	0.524
Inflammatory makers						
ESR, (mm/h)	40 (22,63)	45 (24,77)	0.068	39 (22,63)	42(22,76)	0.257
CRP, (mg/L)	4.7 (3.2,18.0)	6.5 (3.3,27.6)	0.019	4.7 (3.1,17.9)	6.1 (3.3,24.0)	0.144
Radiographic assessment						
mTSS	50 (8,96)	8 (4,19)	< 0.001	52 (9,98)	6 (2,13)	< 0.001
JSN	19 (4,39)	2 (0,6)	< 0.001	19 (3,41)	1 (0,5)	< 0.001
JE	23 (6,49)	6 (2,11)	< 0.001	24 (6,52)	5 (1,9)	< 0.001

* matching age 1:1

RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; PROs, patient-reported outcomes; PtGA, patient global assessment of disease activity; Pain VAS, pain visual analogue scale; HAQ-DI, Health Assessment Questionnaire Disability Index; TJC28, 28-joint tender joint counts; PrGA, provider global assessment of disease activity; SJC28, 28-joint swollen joint counts; CDAI, Clinical Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; mTSS, modified total Sharp score; JSN, joint space narrowing; JE, joint erosion

Higher disease activity in post-menopausal RA patients with EM

Among all post-menopausal RA patients, compared with UM patients, those with EM experienced a younger age at RA onset (47.3 ± 12.4 years vs. 52.9 ± 10.2 years), longer disease duration (median 110 months vs. 71 months), higher disease activity (CDAI, median 16 vs. 14), including worse PROs [PtGA (median 5 vs. 4), pain VAS (median 4 vs. 3) and HAQ-DI (median 0.6 vs. 0.4)] and PROs-associated indicators [TJC28 (median 5 vs. 3) and PrGA (median 4 vs. 3)], as well as higher CRP (median 11.8 mg/L vs. 5.6 mg/L, all $P < 0.05$, Table 2), but no differences in radiographic indicators. Further to match with disease duration (3:1), EM patients still had higher disease activity, including worse PROs, PROs-associated indicator, and CRP than UM patients (all $P < 0.05$, Table 2).

Among 344 patients with RA onset after menopause, compared with UM patients, those with EM also had longer disease duration (median 54 months vs. 37 months), higher disease activity indicated by higher CDAI, including worse PROs (PtGA, HAQ-DI) and PROs-associated indicators (TJC28 and PrGA, all $P < 0.05$, Table 3), but no differences in inflammatory and radiographic indicators. These differences remained significant after additional matching for disease duration (3:1, Table 3). In contrast, among 213 patients with RA onset before menopause, RA patients with EM showed no differences in disease indicators compared with those UM patients (all $P > 0.05$, Supplementary Table 2).

Association between menopause age and RA disease indicators

To explore the impact of early menopause on the disease indicators of RA, univariate and multivariate linear regression analyses were performed (Fig. 3). Univariate analyses showed that menopause age was negatively associated with CDAI (β = -1.431, *95% CI* -2.567, -0.295), including PROs (PtGA [β =-0.872, *95% CI* -1.619, -0.125], HAQ-DI [β =-0.646, *95% CI* -1.059, -0.233]) and PROs-associated indicators (PrGA [β =-0.907, *95% CI* -1.637, -0.177]). After adjustment for potential cofounders,

Table 2 Clinical characteristics of RA patients with early menopause before and after matching

Characteristics	Before matching			After matching*		
	Usual menopause (*n* = 459)	Early menopause (*n* = 98)	*P*	Usual menopause (*n* = 294)	Early menopause (*n* = 98)	*P*
Age, years	61.2 ± 7.3	57.8 ± 9.7	0.001	61.9 ± 7.8	57.8 ± 9.7	< 0.001
Onset age, years	52.9 ± 10.2	47.3 ± 12.4	< 0.001	51.6 ± 10.9	47.3 ± 12.4	0.001
Menopause age, years	50.5 ± 2.5	42.2 ± 3.1	< 0.001	50.4 ± 2.5	42.2 ± 3.1	< 0.001
BMI, kg/m^2	22.3 ± 3.3	22.2 ± 3.7	0.863	22.2 ± 3.2	22.2 ± 3.7	0.913
Disease duration, months	71 (24,132)	110 (41,181)	0.011	108 (42,177)	110 (41,181)	0.978
Active smoking, n (%)	21 (4.6)	7 (7.1)	0.307	13 (4.4)	7 (7.1)	0.486
Positive RF, n (%)	309 (67.6)	74 (75.5)	0.125	208 (71.0)	74 (75.5)	0.388
Positive ACPA, n (%)	311 (67.9)	68 (69.4)	0.775	203 (69.0)	68 (69.4)	0.950
CDAI	13 (6,24)	18 (9,32)	0.006	14 (6,28)	18 (9,32)	0.019
PROs						
PtGA	4 (2,6)	5 (2,7)	0.004	4 (2,6)	5 (2,7)	0.021
Pain VAS	3 (2,5)	4 (2,6)	0.021	3 (2,5)	4 (2,6)	0.037
HAQ-DI	0.3 (0,1.1)	0.8 (0.1,1.5)	0.016	0.5 (0,1.3)	0.8 (0.1,1.5)	0.018
PROs-associated indicators						
TJC28	3 (1,8)	5 (1,13)	0.040	3 (1,9)	5 (1,13)	0.060
PrGA	3 (2,6)	4 (2,6)	0.005	4 (2,6)	4 (2,6)	0.020
SJC28	2 (0,5)	2 (0,7)	0.149	2 (0,5)	2 (0,7)	0.242
Inflammatory makers						
ESR, (mm/h)	41 (23,67)	53 (24,98)	0.061	42 (25,66)	53 (24,98)	0.119
CRP, (mg/L)	5.0 (3.3,20.6)	12.1 (3.3,34.6)	0.021	5.3 (3.3,21.5)	12.1 (3.3,34.6)	0.041
Radiographic assessment						
mTSS	11 (5,51)	17 (7,49.9)	0.370	14 (6,58)	17 (7,49.9)	0.919
JSN	4 (0,19)	5 (1,23)	0.429	6 (1,29)	5 (1,23)	0.724
JE	7 (3,28)	11 (4,28)	0.398	9 (4,33)	11 (4,28)	0.966

* matching disease duration 3:1

RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; PROs, patient-reported outcomes; PtGA, patient global assessment of disease activity; Pain VAS, pain visual analogue scale; HAQ-DI, Health Assessment Questionnaire Disability Index; TJC28, 28-joint tender joint counts; PrGA, provider global assessment of disease activity; SJC28, 28-joint swollen joint counts; CDAI, Clinical Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; mTSS, modified total Sharp score; JSN, joint space narrowing; JE, joint erosion

including age, onset age, BMI, disease duration, RF and ACPA, multivariate linear regression analyses showed that menopause age was still independently and negatively associated with PROs and PROs-associated indicators in RA patients, including PtGA (β = -0.872, *95% CI* -1.619, -0.125) and HAQ-DI (β = -0.646, *95% CI* -1.059, -0.233), as well as PrGA (β = -0.907, *95% CI* -1.637, -0.177, all $P < 0.05$, Fig. 3), but not SJC, inflammatory makers and radiographic indicators. Further subgroup analysis showed that menopause age was independently and negatively associated with PtGA (β = -1.028, *95% CI* -2.022, -0.034) and HAQ-DI (β = -0.916, *95% CI* -1.461, -0.370) in patients with RA onset after menopause (Supplementary Table 3). In sensitivity analyses, logistic analysis showed that menopause age (Supplementary Table 4) or EM (Supplementary Table 5) was still associated with PROs and PROs-associated indicators in RA patients, but not SJC, inflammatory makers and radiographic indicators.

Discussion

This study focused on RA patients with EM and explored the impact of EM on RA disease activity, especially in patients with RA onset after menopause. The result demonstrated EM was associated with poorer PROs independent of inflammation in patients with postmenopausal-onset RA. The results imply the importance of differentiation of non-inflammatory disease activity especially in those postmenopausal-onset RA patients with EM.

RA is more common among women than men at all ages [7]. An inception cohort study of residents of Rochester, Minnesota reported that the incidence of RA in men was extremely low in the 18–34 age group, after which it progressively increased with age until it peaked in the oldest age group (85 years), where it decreased dramatically. In contrast, the incidence of RA in women increased sharply in age 45–54 years, continued to rise until age 55–64 years, after which it steadily declined [7]. Similarly, Bengtsson C et al. reported that compared with women aged 25–44 years, women aged 45 years or older had an increased risk of RA, with the peak hazard ratio

Table 3 Clinical characteristics of patients with RA onset after early menopause before and after matching

Characteristics	Before matching			After matching*		
	Usual menopause (*n* = 282)	Early menopause (*n* = 62)	*P*	Usual menopause (*n* = 186)	Early menopause (*n* = 62)	*P*
Age, years	63.3 ± 7.3	60.8 ± 9.4	0.019	64.7 ± 7.3	60.8 ± 9.4	0.001
Onset age, years	58.7 ± 6.6	54.0 ± 9.8	< 0.001	58.9 ± 6.6	54.0 ± 9.8	< 0.001
Menopause age, years	50.4 ± 2.4	42.2 ± 3.0	< 0.001	50.2 ± 2.4	42.2 ± 3.0	< 0.001
BMI, kg/m^2	22.4 ± 3.2	22.3 ± 3.5	0.739	22.3 ± 3.4	22.3 ± 3.5	0.975
Disease duration, months	37 (12,84)	54 (24,120)	0.018	54 (24,101)	54 (24,120)	0.613
Active smoking, n (%)	16 (5.7)	5 (8.1)	0.556	11 (5.9)	5 (8.1)	0.556
Positive RF, n (%)	180 (64.1)	43 (69.4)	0.429	126 (67.7)	43 (69.4)	0.813
Positive ACPA, n (%)	190 (67.6)	43 (69.4)	0.791	127 (68.3)	43 (69.4)	0.875
CDAI	14 (6,24)	18 (10,35)	0.011	13 (6,23)	18 (10,35)	0.006
PROs						
PtGA	4 (2,6)	5 (3,7)	0.004	4 (2,6)	5 (3,7)	0.005
Pain VAS	3 (2,5)	4 (2,6)	0.052	3 (2,5)	4 (2,6)	0.062
HAQ-DI	0.3 (0,1.0)	1.0 (0.1,1.9)	< 0.001	0.3 (0,1.0)	1.0 (0.1,1.9)	< 0.001
PROs-associated indicators						
TJC28	4 (1,8)	6 (2,15)	0.045	3 (1,7)	6 (2,15)	0.018
PrGA	3 (2,5)	5 (2,7)	0.009	3 (2,5)	5 (2,7)	0.013
SJC28	2 (0,5)	3 (0,7)	0.103	2 (0,4)	3 (0,7)	0.035
Inflammatory makers						
ESR, (mm/h)	43 (24,73)	50 (22,97)	0.240	46 (25,79)	50 (22,97)	0.523
CRP, (mg/L)	6.0 (3.3,26.0)	12.5 (3.3,41.2)	0.067	7.0 (3.3,32.0)	12.5 (3.3,41.2)	0.174
Radiographic assessment						
mTSS	7 (4,16)	13 (4,41)	0.165	9 (5,23)	13 (4,41)	0.576
JSN	2 (0,6)	2 (1,9)	0.276	3 (1,9)	2 (1,9)	0.690
JE	5 (2,9)	10 (3,24)	0.123	5 (2,12)	10 (3,24)	0.275

*matching disease duration 3:1

RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; PROs, patient-reported outcomes; PtGA, patient global assessment of disease activity; Pain VAS, pain visual analogue scale; HAQ-DI, Health Assessment Questionnaire Disability Index; TJC28, 28-joint tender joint counts; PrGA, provider global assessment of disease activity; SJC28, 28-joint swollen joint counts; CDAI, Clinical Disease Activity Index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; mTSS, modified total Sharp score; JSN, joint space narrowing; JE, joint erosion

at 55–59 years in the Nurses' Health Studies of Unites States [8]. A similar age-of-onset trend was observed in our study, with the peak onset age of RA between 46 and 50 years. Moreover, our results showed a distinct incidence peak of RA approximately 5 years after natural menopause. The acute decline in ovarian function may contribute to the development of RA- associated autoimmunity and potentially increase risk of RA in women.

Early or premature menopause is characterized by impaired ovarian reserve, elevated follicle-stimulating hormone, and low serum estrogen levels. The underlying cause remains unidentified, and genetic, autoimmune, metabolic, infectious, or iatrogenic reasons should be sought. Autoimmune disorders have been considered associated with those conditions. Among healthy women, the prevalence of EM was 3.6% in America, 7.6% in Asia, 9.1% in Europe, and 13.0% in China, respectively [20–22]. In contrast, the prevalence of EM in patients with rheumatic diseases appears to be higher, it ranges from 33.3 to 44% in systemic sclerosis [23–25], and an exceptionally high prevalence of premature menopause (18.4%) have been observed in patients with systemic lupus erythematosus [26]. Banas T et al. [27]. demonstrated that natural menopause occurs at a younger age in female RA patients than in healthy controls, and women with premenopausal RA onset experience an earlier menopause than those with post-menopausal onset (mean 48.7 vs. 50.0 years). Our results showed a similar menopause age in patients with RA regardless of whether RA onset occurred before or after menopause. Previous studies have also indicated that EM was relatively common in RA patients, with an occurrence rate of approximately 17–25% [9–11]. Similarly, a high prevalence of EM (17.6%) in all post-menopausal RA patients was also found in our study, including 11.1% and 6.5% in RA onset before and after menopause, respectively. The causal relationship between early age at menopause and RA development requires further investigation.

Previous studies have suggested that EM may negatively impact PROs of RA. However, the findings were controversial. For instance, Pikwer M et al. [10] reported that women with EM had lower mean HAQ scores at all time points across a 10-year follow-up compared to those with normal or late menopause. However, this study was

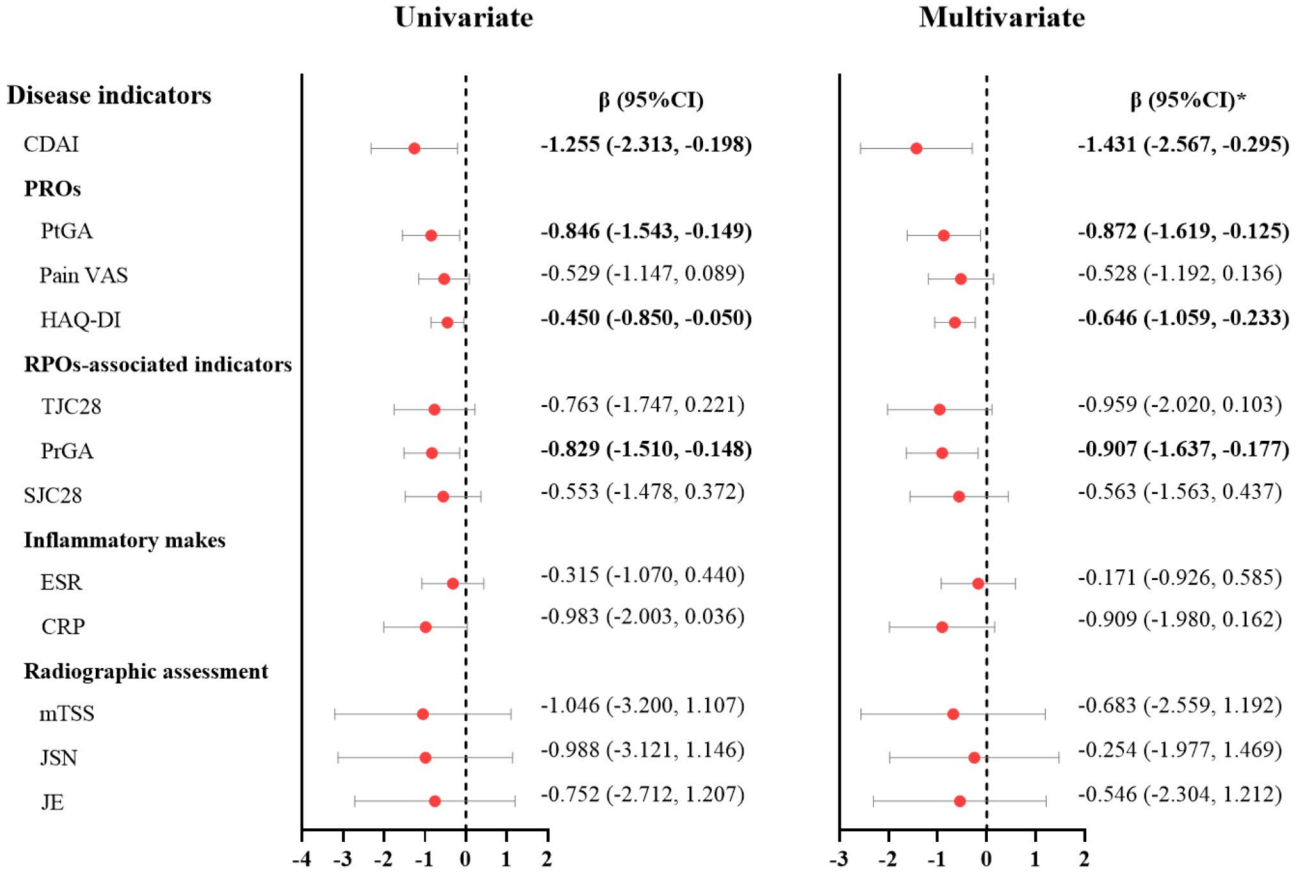

Fig. 3 Linear regression of association between menopause age and RA disease indicators. * Multivariate analysis was adjusted by age, onset age, BMI, disease duration, RF and ACPA. RA, rheumatoid arthritis; PROs, patient-reported outcomes; PtGA, patient global assessment of disease activity; Pain VAS, pain visual analogue scale; HAQ-DI, Health Assessment Questionnaire Disability Index; TJC28, 28-joint tender joint counts; PrGA, provider global assessment of disease activity

a nested case-control study that only included a limited sample size of only 134 RA patients. In contrast, a cross-sectional study by Wong LE et al. [11] conducted among 534 post-menopausal women reported that the EM group had higher PtGA and pain scores than the UM group. Additionally, Park EH et al. [12] firstly identified that RA patients with EM demonstrated higher disease activity and worse PROs over a 5-year follow-up, using a large nationwide prospective observational RA cohort of 2878 post-menopausal women in Korea. However, there were higher prevalence of neoplastic disease in EM group than UM group in Park EH *et al.*' study, which may have adversely affected various PROs. In our study, natural post-menopausal female RA patients were included and those with surgical or medical-induced menopause or with malignancies were excluded. Our results validated that female RA patients with EM exhibit worse PROs compared to those with UM. Additionally, a subgroup analysis based on RA onset before and after menopause indicated that worse PROs, rather than inflammatory or radiographic indicators, were more prominent in EM patients with RA onset after menopause. Linear regression analysis further showed that menopause age was independently and negatively associated with PtGA and HAQ-DI. These results imply the importance of differentiation of inflammatory and non-inflammatory disease activity, which leads to different treatment strategy.

The poor PROs in the EM group can be partly explained by the falling estrogen or progesterone levels. Although the immunomodulatory roles of female hormones are complex and multifaceted, it has been reported that female hormonal changes associated with EM could heighten pain hypersensitivity and central sensitization in patients with chronic pain [28, 29]. Significant overlap with estrogen-regulated brain networks linked to reproductive and higher-order cognitive functions was observed in recent study. This suggests a connection between female endocrine aging with cognitive functions, spanning mood, memory, stress, pain, and fine motor skills [30, 31]. In addition, we found that EM has a more pronounced impact on postmenopausal-onset RA, which may be related to the window effect of estrogen decline. In EM, earlier ovarian failure could prolong this "window" of estrogen deprivation, and then leads to more

severe PROs. Clinically, our research emphasizes age at menopause and EM-related non-inflammatory disease activity should be considered when treating postmenopausal patients with RA. EM-related symptoms may stem from central sensitization or hormone deficiency-driven pain mechanisms rather than pure inflammation. It is hypothesized that the use of low dose estrogen therapy or implement multidisciplinary interventions (e.g., physical therapy, psychological counseling) targeting non-inflammatory symptoms may improve PROs for those postmenopausal RA patients with EM, which are worth further exploring in the future. In addition, for postmenopausal-onset RA patients, particularly those with EM, clinicians should regularly assess functional status (HAQ-DI) and quality of life (e.g., EQ-5D).

Limitations of this study need to be acknowledged. First, recall bias may influenced our study, as the information about menopausal status at disease onset was self-reported. Second, although our study adjusted for key confounders, some potential confounders such as psychosocial factors (e.g., depression, socioeconomic status) were not adequately adjusted for due to the lack of relevant data in this study. Future prospective cohorts should integrate psychosocial assessments to disentangle these relationships. Third, several studies have explored the relationship between EM and RA prognosis. For example, Park EH et al. reported that RA patients with EM had higher disease activity and worse PROs over a 5-year follow-up [12]. Another study found that RA patients who underwent EM were at significantly higher risk for developing CVD compared to those who did not (HR 1.56; 95% CI 1.08–2.26) [32]. These findings suggest that EM can negatively impact the prognosis of RA patients. However, it is important to acknowledge that the direct impact on prognosis is complex and multifaceted. The potential benefits of delaying menopause in improving RA prognosis remains unclear and requires further investigation.

In conclusion, our cross-sectional results demonstrate that early menopause is associated with worse PROs independent of inflammation in postmenopausal-onset RA patients. This EM-related non-inflammatory disease activity implies tailored treatment strategy rather than more aggressive DMARD therapy for inflammation-related disease activity. Further prospective studies on hormonal modulation or neuropathic pain management for RA patients with EM are warranted.

Supplementary Information

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Supplementary Material 1

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Author contributions
Z-M OY and YW Z participated in conceiving and designing the study, reading and analyzing documents, performing statistical analysis, drafting and revising the manuscript. LF C and JZ L carried out the radiographic assessment. Y L, J P, T W, PW J, HW Z, Y S, KM Y, PY L, and JY H participated in data collection. JD M and L D conceived and participated in designing, revising, supervising the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Sun Yat-sen Memorial Hospital (SYSEC-2009-06, SYSEC-KY-KS-012). All patients consented to participate and signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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