



# The impact of gender on time to rheumatoid arthritis classification: a retrospective analysis of a population-based cohort

Caitrin M. Coffey<sup>1</sup> · John M. Davis III<sup>1</sup> · Cynthia S. Crowson<sup>1</sup>

Received: 13 May 2019 / Accepted: 28 June 2019 / Published online: 23 July 2019  
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

## Abstract

The objective is to compare the time to fulfillment of 1987 and 2010 ACR/EULAR classification criteria between female and male patients with rheumatoid arthritis (RA) and to assess the potential impact of gender on the time to DMARD therapy. Time from first provider-documented joint swelling to fulfillment of 1987 and 2010 ACR/EULAR criteria was measured in a population-based cohort of adults with incident RA, who were stratified by male or female gender. Disease characteristics, time to start of DMARD therapy, and choice of initial DMARD were compared between groups. The study included 214 patients with RA (148 females and 66 males). Median times from first joint swelling to fulfillment of 1987 (6.5 vs 2.5 days,  $p=0.48$ ) and 2010 (1 vs 0 days,  $p=0.34$ ) classification criteria were not different between female and male patients overall. There was no difference in time to first DMARD therapy in female vs male patients (15.5 vs 16 days,  $p=0.90$ ), and methotrexate was used most frequently as first DMARD in both genders (61% female vs 64% male,  $p=0.76$ ). Among the 49 female and 20 male RF/ACPA-negative patients, females experienced a higher median time from first joint swelling to fulfillment of the 1987 (65 vs 11 days,  $p=0.063$ ) and 2010 (65 vs 0 days,  $p=0.035$ ) classification criteria. Overall, there was no significant delay in meeting 1987 and 2010 ACR/EULAR classification criteria between female and male RA patients, though time to meeting both 1987 and 2010 criteria was slightly longer in males compared with females. Among seronegative patients, females experienced a significant delay to meeting 2010 criteria from first clinically detected synovitis.

**Keywords** Rheumatoid arthritis · Gender bias · Sex factors · Early diagnosis · Early arthritis

## Introduction

Rheumatoid arthritis (RA) is characterized by inflammation and destruction of synovial joints that accumulates over time, leading to disability and mortality [1]. RA occurs more commonly in women than men, and disease characteristics differ between genders with regard to comorbidities, extra-articular manifestations, core measures of disease activity, and treatment response [2–7].

Early diagnosis and initiation of therapy has been correlated with better outcomes, higher rates of remission, and reduced joint damage and disability for all RA patients [1, 8–10]. Early treatment with disease-modifying anti-rheumatic drugs (DMARD) most effectively prevents joint damage and is associated with higher likelihood of achieving remission [10]. Prior studies have attributed delays in therapy initiation to delays in presentation to primary and subspecialty care. Delays in diagnosis have also been associated with anti-citrullinated protein antibody (ACPA) positivity and lower income in a Canadian early RA cohort, while severity of disease activity, higher inflammatory markers, and worse patient global scores were identified as factors associated with shorter time to diagnosis [11]. Gender has not previously been found to be predictive of time to diagnosis, and there is no known association between gender and time to meeting American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA. However, it has been suggested that female patients may experience a delay from primary care

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00296-019-04360-2>) contains supplementary material, which is available to authorized users.

✉ Cynthia S. Crowson  
crowson@mayo.edu

<sup>1</sup> Division of Rheumatology (JMD, CSC), Internal Medicine (CMC) and Department of Health Sciences Research (CSC), College of Medicine and Science, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA

visit to rheumatologist referral compared with males [12, 13]. In addition, delays to diagnosis have been demonstrated for female patients with other rheumatologic conditions, such as ankylosing spondylitis [14].

To date, the time from first symptoms to time of classification by ACR/EULAR classification criteria has not been compared between male and female patients with early RA. The impact of RA classification on initiation and choice of DMARD therapy between male and female RA patients has also not been described. We aimed to compare the time from first provider-documented joint swelling to fulfillment of 1987 and 2010 ACR/EULAR classification criteria between female and male patients who fulfill criteria for RA, and to assess the potential impact of gender on the time to DMARD therapy [1, 15].

## Materials and methods

### Study population

The Mayo Clinic and Olmsted Medical Center Institutional Review Boards (IRB) approved this retrospective cohort study (IRB# 17-002593 approved April 5, 2017 and 017-OMC-17 approved May 2, 2017), and a waiver of informed consent was granted. The project was conducted in accordance with the ethical principles outlined in the 1964 Declaration of Helsinki and subsequent amendments.

Subjects were identified using the resources of the Rochester Epidemiology project, a geographically based collaboration of healthcare facilities allowing access to complete medical records from all providers in Olmsted County, MN [16]. Subjects were adult residents of Olmsted County, MN who developed incident RA between 2009 and 2014. Eligibility required age  $\geq 18$  and fulfillment of either the 1987 or 2010 ACR/EULAR classification criteria (Supplemental Table) for RA. All subjects were followed longitudinally until their death, migration from Olmsted County or until December 31, 2017.

### Data collection and study variables

Retrospective review of medical records and diagnoses was performed by a trained nurse abstractor. Additional record review was performed by study personnel (CMC, CSC).

Subjects were divided into groups based on male or female gender recorded in their electronic medical record at the time of RA diagnosis. First joint swelling was defined as the first clinically recognized synovitis as documented by a provider, including rheumatology, general, or other specialist providers. Times from first joint swelling to meeting 1987 and 2010 ACR/EULAR classification criteria, receiving a clinical diagnosis of “rheumatoid arthritis” and/

or “inflammatory arthritis” as in clinical documentation, and to day of first prescribed DMARD therapy were calculated in days. All available visits in the medical record were reviewed to determine fulfillment of classification criteria. Baseline disease characteristics and initial DMARD therapy were compared between groups. Subjects were further stratified by seropositive [rheumatoid factor (RF)- and/or anti-citrullinated peptide antibody (ACPA)-positive] and seronegative (RF- and ACPA-negative) status for additional analysis.

### Statistical methods

Descriptive statistics (percentages, medians, 25th and 75th percentiles, means and standard deviations) were used to summarize the data. Normality was assessed by visual inspection of histograms; medians and 25th/75th percentiles were reported where appropriate. Comparisons between groups were made using Chi-square and rank sum tests as appropriate. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, U.S.) and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

214 patients with RA were included; of these, 148 were female and 66 male. No patients were excluded due to lack of complete information in the medical records. The baseline characteristics of patients by gender are shown in Table 1. The mean age was 53.6 (SD  $\pm$  15.2) years for females and 59.1 (SD  $\pm$  12.5) years for males at the time of fulfilling 2010 criteria ( $p=0.007$ ). RF and ACPA status, obesity, joint involvement, and presence of erosive disease did not differ between groups at baseline. Male patients were more likely to be current (23% vs 16%) or former (39% vs 24%,  $p=0.007$ ) smokers at the time of meeting 2010 classification criteria, and more male than female patients had abnormal ESR and/or CRP (83% vs 66%,  $p=0.010$ ). Patients were followed for a median (range) of 4.1 (1.0–7.4) years, during which disease activity measures were available for a median (range) of 8 (2–19) visits per patient.

Median times from first joint swelling to fulfillment of the 1987 (6.5 vs 2.5 days,  $p=0.48$ ) and 2010 (1 vs 0 days,  $p=0.34$ ) classification criteria were not significantly different in female vs male patients (Table 2). There was no significant difference in days from fulfillment of 2010–1987 criteria between genders. Overall 48% of females and 52% of males met 2010 criteria at baseline. Those who met criteria after baseline did so by developing additional joint involvement or erosions. Median times from first joint swelling to receiving a clinical diagnosis of “rheumatoid arthritis” or

**Table 1** Baseline characteristics of 214 patients at time of meeting 2010 American college of rheumatology/European league against rheumatism classification criteria for rheumatoid arthritis

Baseline characteristic	Female, N=148	Male, N=66	p value
Age, mean (±SD), years	53.6 (±15.2)	59.1 (±12.5)	0.007
RF/ACPA positive	97 (67%)	46 (70%)	0.68
Smoking status			0.010
Current smoker	23 (16%)	15 (23%)	
Former smoker	36 (24%)	26 (39%)	
Never smoker	89 (60%)	25 (38%)	
Education level			0.20
≤High school graduate	28 (20%)	19 (29%)	
Some college or 2 years degree	59 (41%)	20 (30%)	
≥4 years college degree	55 (39%)	27 (41%)	
Obese (BMI ≥30 kg/m <sup>2</sup> )	60 (41%)	25 (38%)	0.71
≥10 joints involved	104 (70%)	46 (70%)	0.95
ESR and/or CRP elevated <sup>a</sup>	98 (66%)	55 (83%)	0.010
Presence of erosions	28 (19%)	19 (29%)	0.11

RF rheumatoid factor, ACPA anti-citrullinated peptide antibody, BMI body mass index, ESR erythrocyte sedimentation rate, CRP C-reactive protein

<sup>a</sup>Elevated ESR and/or CRP were defined as higher than the upper limit of normal as defined by local laboratory standards

“inflammatory arthritis” (0 vs 9.5 days,  $p=0.09$ ) were not different between female and male patients (Table 2).

The median time in days from first joint swelling to first DMARD (15.5 vs 16 days,  $p=0.90$ ) and first glucocorticoid therapy (5 vs 9.5 days,  $p=0.70$ ) did not differ between female and male patients (Table 2). Methotrexate was used as first DMARD in 91 of 148 female patients (61%) and 42 of 66 male patients (64%,  $p=0.76$ ). There was no significant difference between groups in the choice of first DMARD started, use of methotrexate as first line DMARD, or starting dose of methotrexate (data not shown).

When the analyses were stratified by RF/ACPA status, gender comparisons between the 99 female and 46 male RF/ACPA-positive patients were similar to the overall results (Table 2). However, among the 49 female and 20 male RF/ACPA-negative patients, females experienced a higher median time from first joint swelling to fulfillment of the 1987 (65 vs 11 days,  $p=0.063$ ) and 2010 (65 vs 0 days,  $p=0.035$ ) classification criteria. The proportions of seropositive patients who met 2010 criteria at baseline were similar (59% female and 50% male), but among seronegative patients, females were significantly less likely to meet 2010 criteria at baseline than males (24% vs 56%,  $p=0.018$ ). Among the seronegative patients, there was no difference in

**Table 2** Comparison of time in days from first joint swelling to fulfillment of the 1987 or 2010 American college of rheumatology/

European league against rheumatism criteria and to first treatments between male and female patients with incident rheumatoid arthritis between 2009 and 2014

Group	Outcomes	Female N=148	Male N=66	p value
Overall	1987 ACR/EULAR criteria	6.5 (0, 122)	2.5 (0, 57)	0.48
	2010 ACR/EULAR criteria	1 (0, 94)	0 (0, 29)	0.34
	Diagnosis of RA or inflammatory arthritis <sup>a</sup>	0 (0, 71)	9.5 (0, 76)	0.44
	First DMARD	15.5 (0, 100)	16 (4, 83)	0.90
	First glucocorticoid	5 (0, 97)	9.5 (0, 81)	0.70
		Female N=99	Male N=46	
RF/ACPA-positive	1987 ACR/EULAR criteria	0 (0, 49)	25 (0, 44)	0.59
	2010 ACR/EULAR criteria	0 (0, 23)	0.5 (0, 32)	0.47
	Diagnosis of RA or inflammatory arthritis <sup>a</sup>	0 (0, 31)	9.5 (0, 76)	0.09
	First DMARD	11 (0, 73)	16 (4, 83)	0.36
	First glucocorticoid	7 (0, 97)	20 (0, 90)	0.32
		Female N=49	Male N=20	
RF/ACPA-negative	1987 ACR/EULAR criteria	65 (0, 398)	11 (0, 153)	0.063
	2010 ACR/EULAR criteria	165 (0, 254)	0 (0, 13)	0.035
	Diagnosis of RA or inflammatory arthritis <sup>a</sup>	13 (0, 125)	6 (0, 84)	0.37
	First DMARD	60 (5, 210)	15 (1, 155)	0.25
	First glucocorticoid	4 (0, 102)	0 (0, 12)	0.035

Values in table are time in days from first documented joint swelling to each outcome, reported as median (25th percentile, 75th percentile)

<sup>a</sup>Diagnosis of RA or inflammatory arthritis was made in all but 5 patients (all female). All patients met both 1987 and 2010 criteria for RA

age (mean 55.5 vs 56.7 years;  $p=0.72$ ) between females and males. The delay in time from first joint swelling to initiation of first DMARD (median 60 vs 15 days;  $p=0.25$ ) was not significantly different, but the delay in glucocorticoid initiation (median 4 vs 0;  $p=0.035$ ) was significantly longer in females than in males. Similar proportions of females and males had > 10 joints involved at the time they met 2010 criteria (82% vs 85%,  $p=0.74$ ), but the time from first joint swelling to > 10 joints involved was significantly longer for females than males (median 65 vs 0,  $p=0.038$ ). Seronegative females were also more likely to be anti-nuclear antibody (ANA) positive than their male counterparts (30% vs 11%), but this difference did not reach statistical significance ( $p=0.11$ ).

## Discussion

Early diagnosis and treatment initiation are established and modifiable contributors to better patient outcomes in RA. To our knowledge, this is the first study to compare the time to meeting ACR/EULAR classification criteria between male and female patients diagnosed with RA. In our population, there was no difference in time to meeting 1987 or 2010 ACR/EULAR criteria between male and female patients overall. However, among seronegative patients, there was a delay in meeting 2010 criteria for females compared with males. No difference was observed in time to or choice of first DMARD therapy between male and female patients. A longer time to initiating corticosteroid therapy was seen for female compared with male patients in the seronegative group.

RA is more prevalent in females than males, a phenomenon that is thought to result from effects of differing sex hormones, epigenetics, and immune system function [2]. In addition to biological sex differences in RA, including reported differences in comorbidities and extra-articular disease manifestations [17, 18], female gender has been associated with lower quality of life [19], worse disease activity and functional scores [4, 5, 20], and lower response to therapy and achievement of remission [3, 5, 6]. Somatic symptom reporting differs between genders [21], which may confound the comparison in core measures of disease activity between the two groups. Notably, these gender differences have also been reported in other rheumatologic disease processes, such as ankylosing spondylitis [22]. However, mortality has historically been reported as higher in men than women with RA, as in the general population [23].

Prior work has shown evidence for a window of opportunity, a time period including the first 12–20 weeks of symptoms during which initiation of treatment is most beneficial for long-term outcomes [9, 10]. A delay in referral to subspecialty care, as has been observed in female compared

with male patients [12, 13], could impact the time to initiating DMARD therapy; therefore, putting women with RA at risk for delayed treatment and thus, potentially worse outcomes. However, subsequent work has demonstrated no known delay in clinical diagnosis for females with RA [11]. The results of the current study, showing that there was no delay in meeting RA classification criteria for either gender in the overall RA population and in seropositive individuals, are in agreement with existing research. In the CATCH early arthritis cohort, factors that contribute to delay in diagnosis by a rheumatologist from first self-reported symptom were analyzed, and sex was not associated with diagnosis occurring within the first 6 months of disease, though time in days and time to meeting classification criteria were not compared between groups [11].

When patients were stratified by seropositive and seronegative status, gender was not associated with a delay in meeting ACR/EULAR classification criteria in seropositive individuals. However, in the seronegative group, there was a significant delay into meeting 2010 criteria and in initiating corticosteroids for female patients. Possible explanations include differing disease assessment between genders, or later presentation of male patients to a healthcare provider. In patients with early seronegative disease, symptoms in female patients could be more often attributed to fibromyalgia, other non-inflammatory conditions, or other rheumatologic diseases; a hypothesis that is supported by a trend toward more female than male seronegative patients having a positive ANA. Prior studies have suggested a subspecialty referral delay in female RA patients [12, 13], which could also impact time to classification particularly in the seronegative group for whom clinical suspicion for RA by the general practitioner may be lower than for seropositive individuals.

The current findings are also consistent with existing literature regarding treatment initiation between genders. In the multinational QUEST-RA study, time to initiation of DMARD therapy and choice of therapy were similar between female and male patients [5]. Jamal et al. have also reported that gender did not impact likelihood of treatment initiation within the first 3 months of symptoms in RA in an urban, Canadian population [24]. However, these studies also reported longer mean delays from time of first reported symptoms to first DMARD therapy, with delay of 10 months observed in the former [5] and of over 13 months in the latter [24] populations. These differences again may be due to underlying differences in patient populations and regional access to healthcare. Our study's use of first provider-detected synovitis as the baseline timepoint, rather than self-reported symptoms, as in the QUEST-RA and CATCH cohorts, may result in shorter reported delays particularly in cases, where symptoms emerge long before medical care is sought.

Strengths of this study include a median of over 4 years of follow-up and a geographically based population with ready access to both primary and specialty care, making long delays to provider assessment unusual. The retrospective nature of this work allowed for analysis of time to assessment and treatment within routine clinical care rather than a specialty care model for early RA. Use of the Rochester Epidemiology Project made access to records across all healthcare facilities in the geographic area possible, minimizing loss of data from follow-up encounters. This study also has several limitations, including a small sample size and retrospective design. The documentation of first synovitis as noted by a provider may underestimate duration of symptoms in those patients for whom there was a long delay in seeking medical care. Treatment and disease-monitoring outcomes, which have been reported to differ between male and female RA patients, were outside the scope of this study. The study also included a primarily Caucasian, US population, which may limit generalizability to more ethnically diverse groups in the United States and to international populations.

The results of this study may be subject to bias, due to its retrospective study design. Subjects were included based upon fulfillment of ACR/EULAR classification criteria for RA, and the possibility of selection bias arises as those who have RA, but have not fulfilled criteria, such as those who experience a substantial delay in time to diagnosis, would not be included as they may not fulfill criteria until after the study interval has ended. The chance of this contributing in the present study was minimized by a length follow-up interval of median 4.1 (range 1.0–7.4) years. The retrospective design necessarily means that only information documented in medical records was considered and that only those symptoms and criteria that came to medical attention were available for analysis. The comprehensive nature of the medical records from all healthcare providers in the area is likely to minimize information bias, though a difference in healthcare seeking behavior between male and female patients would contribute to bias.

More information is needed regarding factors that impact early RA classification, diagnosis and treatment, as well as about gender differences in the presentation, diagnosis, and longitudinal course of disease. Here, we demonstrate that there was no delay in meeting ACR/EULAR 1987 and 2010 RA classification criteria between male and female patients in seropositive RA and that time to treatment initiation with DMARDs was not different between genders in a geographically based population with readily available access to both primary and specialty rheumatologic care. However, a delay to 2010 ACR/EULAR classification criteria was noted for female patients with seronegative RA, a novel finding warranting additional investigation. The ACR/EULAR classification criteria have previously demonstrated

better performance in early RA for seropositive vs seronegative patients [25], and our results suggest that gender did not appear to impact early classification in the seropositive group, but may in individuals with seronegative RA. The results of this study also suggest that previously described differences in the RA disease course between male and female patients are likely due to factors other than treatment delay, and further study is needed to improve gender-specific outcomes in RA.

**Funding** This work was supported by a grant from the National Institutes of Health (NIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (Award Number R01AR46849), and was made possible using the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the NIH under Award Number R01AG034676. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

### Compliance with ethical standards

**Conflict of interests** The authors have no conflicts of interest to disclose.

### References

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO et al (2010) 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. *Arthritis Rheum* 62:2569–2581
2. Krasselt M, Baerwald C (2017) Sex, symptom severity, and quality of life in rheumatology. *Clin Rev Allergy Immunol*. <https://doi.org/10.1007/s12016-017-863:1-16>
3. Forslind K, Hafström I, Ahlmén M, Svensson B, BARFOT Study Group (2007) Sex: a major predictor of remission in early rheumatoid arthritis? *Ann Rheum Dis* 66:46–52
4. Bergstra SA, Allaart CF, Ramiro S, Chopra A, Govind N, Silva C, Murphy EA, Landewe RBM (2018) Sex-associated treatment differences and their outcomes in rheumatoid arthritis: results from the METEOR Register. *J Rheum* 45:1361–1366
5. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, Skacic V et al (2009) Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther* 11:R7
6. Jawaheer D, Maranian P, Park G, Lahiff M, Amjadi SS, Paulus HE (2010) Disease progression and treatment responses in a prospective DMARD-naïve seropositive early rheumatoid arthritis cohort: does gender matter? *J Rheum* 37:2475–2485
7. Hallert E, Thyberg I, Hass U, Skargren E, Skogh T (2003) Comparison between women and men with recent onset rheumatoid arthritis of disease activity and functional ability over 2 years (the TIRA project). *Ann Rheum Dis* 62:667–670
8. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symons DP et al (2003) Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. *Arthritis Rheum* 48:46–53

9. Van Nies JAB, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AHM (2015) Evaluating relationships between symptoms duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden Early Arthritis Clinic and ESPOIR cohorts. *Ann Rheum Dis* 74:806–812
10. van Nies JA, Krabben A, Schoones JW, Huizinga TWJ, Kloppenburg M, van der Helm-van Mil AHM (2014) What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis* 73:861–870
11. Barnabe C, Xiong J, Pope JE, Boire G, Hitchon C, Haraoui B et al (2014) Factors associated with time to diagnosis in early rheumatoid arthritis. *Rheumatol Int* 34:85–92
12. Palm O, Purinszky E (2005) Women with early rheumatoid arthritis are referred later than men. *Ann Rheum Dis* 64:1227–1228
13. Lard LR, Huizinga TW, Hazes JM, Vlieland TP (2001) Delayed referral of female patients with rheumatoid arthritis. *J Rheum* 28:2190–2192
14. Jovani V, Blasco-Blasco M, Ruiz-Cantero MT, Pascual E (2017) Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and meta-analysis. *J Rheum* 44:174–183
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS et al (1988) The American Rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 31(3):315–324
16. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA (2011) Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *Am J Epidemiol* 173(9):1059–1068 **PMID: 21430193**
17. Weyand CM, Schmidt D, Wagner U, Goronzy JJ (1998) The influence of sex on the phenotype of rheumatoid arthritis. *Arthritis Rheum* 41:817–822
18. Aurrecochea E, Llorca Diaz J, Diez Lizuain M, McGwin G Jr, Calvo-alen J (2017) Gender-associated comorbidities in rheumatoid arthritis and their impact on outcome: data from GENIRA. *Rheumatol Int* 37:479–485
19. Aurrecochea E, Llorcadias J, Diezlizuain M, McGwin G Jr, Calvo-alen J (2015) Impact of gender on quality of life of patients with rheumatoid arthritis. *J Arthritis* 4:160
20. Ahlmen M, Svensson B, Albertsson K, Forslind K, Hafstrom I, BARFOT Study Group (2010) Influence of gender on assessments of disease activity and function in early rheumatoid arthritis in relation to radiographic joint damage. *Ann Rheum Dis* 69:230–233
21. Barsky AJ, Peekna HM, Borus JF (2001) Somatic symptom reporting in women and men. *J Gen Intern Med* 16:266–275
22. Rusman R, van Vollenhoven RF, van der Horst-Bruinsma IE (2018) Gender difference in axial spondyloarthritis: women are not so lucky. *Curr Rheum Rep* 20:35
23. Isomaki HA (1994) Mortality in patients with rheumatoid arthritis. In: Wolfe F, Pincus T (eds) *Rheumatoid arthritis: pathogenesis, assessment, outcome, and treatment*. Marcel Dekker Inc, New York, pp 235–246
24. Jamal S, Alibhai MH, Badley EM, Bombardier C (2011) Time to treatment for new patients with rheumatoid arthritis in a major metropolitan city. *J Rheumatol* 38:1282–1288
25. Boeters DM, Gajoux-Viala C, Constantin A, van der Helm-van Mil AHM (2017) The 2010 ACR/EULAR criteria are not sufficiently accurate in the early identification of autoantibody-negative rheumatoid arthritis: results from the Leiden-EAC and ESPOIR cohorts. *Semin Arthritis Rheum* 47:170–174

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.