

Research Letter

Delayed Referral of Female Patients With Rheumatoid Arthritis: Where Are We Now? A Study Spanning 3 Decades

To the Editor:

In patients with rheumatoid arthritis (RA), timely initiation of treatment with disease-modifying antirheumatic drugs is associated with better outcomes.^{1,2} In many countries, the swiftness of treatment initiation depends highly on timely referral to the rheumatologist by the general practitioner (GP).³ An abundance of evidence supports that patients with RA should be seen by a rheumatologist ≤ 12 weeks after symptom onset.^{2,4} Seemingly small differences in delay may have important implications: referral within 0 to 6 weeks associates with better outcomes than referral within 6 to 12 weeks.⁵

Twenty years ago, it was observed at our outpatient rheumatology clinic (Leiden University Medical Centre [LUMC], the Netherlands) that the time between the first appointment with the GP and referral to the rheumatologist (referral delay) was approximately 5 weeks longer in female than in male patients with RA.⁶ Similar findings were reported in Norway.⁷ Notably, the time between symptom onset and the first appointment with the GP (patient delay) was similar between the sexes.

Much has changed in 20 years. Rapid referral of patients with RA, regardless of their sex, has been increasingly advocated and incorporated in the European Alliance of Associations for Rheumatology (EULAR) guidelines. This has also influenced national guidelines such as Dutch guidelines for GPs.⁸ Also locally, in the Dutch Leiden region, activities to diminish referral delay were undertaken.⁹ Since recent sex-specific data on referral delay are lacking, we assessed how excessive referral delay in female patients with RA developed over the past 3 decades. We took advantage of a unique regionwide inception cohort of patients with early arthritis that had 27 years of data.

All patients provided written informed consent. The study protocol of the Leiden Early Arthritis Clinic (EAC) cohort (B19.008) was approved by the medical ethical committee of LUMC.

The Leiden EAC has enrolled patients with clinically apparent arthritis of recent onset (symptom duration < 2 yrs) since 1993; this was described extensively elsewhere.² For the current study, all consecutive patients with RA with available referral delay data were studied. Apart from the years prior to the original publication by Lard et al (1993-2000),⁶ 2 additional time periods were studied: 2001-2010 and 2011-2020 (up to March 2020). Between 2001 and 2010, GPs in the region received education (written and oral) on the importance of early referral. During 2011 to 2020, in addition to the education of GPs, an easy-access screening clinic was operating in the intermediate setting between primary and secondary care. GPs in the region were instructed to quickly refer any patient in whom they doubted

the presence of arthritis.⁹ All education and instructions for GPs were not sex-specific. For each time period, we studied referral delay, patient delay, and the percentage of patients with RA with total delay (between symptom onset and first visit with the rheumatologist) ≤ 12 weeks as generally recommended by guidelines.

RA was defined as a clinical diagnosis plus fulfillment of the 1987 American College of Rheumatology (ACR)/EULAR criteria within 1 year of presentation at the EAC.¹⁰ In additional analyses, patients with RA fulfilling the 2010 ACR/EULAR criteria were included also since the latter criteria were designed for higher sensitivity in early disease but were not yet developed when Lard et al reported their findings.^{6,10} Referral delay was available in 962 of 1524 (63.12%) patients with RA. Reassuringly, patients with and without referral delay data had similar characteristics, arguing against major selection bias (Supplementary Table S1, available with the online version of this article).

Nine hundred sixty-two consecutive patients with RA were studied: 630 women (65.5%) and 332 men (34.5%). Detailed patient characteristics are presented in Supplementary Table S2 and Data S1 (available with the online version of this article). Median referral and patient delay over time are depicted in Figure 1A-C. During 1993-2000, median referral delay was 4.4 weeks longer in female than male patients with RA (median [IQR] of 14.3 [6.1-26.0] vs 9.9 [4.6-17.4] weeks; $P = 0.03$). Thereafter, excessive median referral delay in female patients with RA decreased to a statistically insignificant difference of 1.7 weeks in 2001-2010. Finally, in 2011-2020, median (IQR) referral delay was similar in women and men (4.7 [1.9-12.9] and 5.4 [2.0-9.7]; $P = 0.99$). Contrasting with referral delay, patient delay was stable and similar in both sexes during all time periods. Studying the percentage of patients with RA with total delay ≤ 12 weeks (Figure 1D) showed a similar time pattern as referral delay. Similar improvement over time was seen when also patients with RA who fulfilled the 2010 ACR/EULAR criteria were studied (Supplementary Figure S1).

In summary, the inequity of longer referral delay in female compared to male patients with RA has been eliminated. To the best of our knowledge, our study is the first to demonstrate this development. After the aforementioned report from 2005,⁷ this is the first study to address sex-specific referral delay in the field of rheumatology. Limitations include incompleteness of referral delay data and unknown generalizability outside the local health-care system. Therefore, we encourage other rheumatology clinics to evaluate the referral delay in their region. It remains to be determined which factors drove the improvement. The approach of GPs (eg, clinical interpretation of symptoms, referral strategy) may have improved. Additionally, patients themselves may have contributed. For example, the presentation of symptoms and the demand for medical aid by female and male patients with RA may have grown more alike. In the era of implementation of guidelines on early referral, our study is an example of the improvement of a historical gender inequity regarding access to rheumatological care.

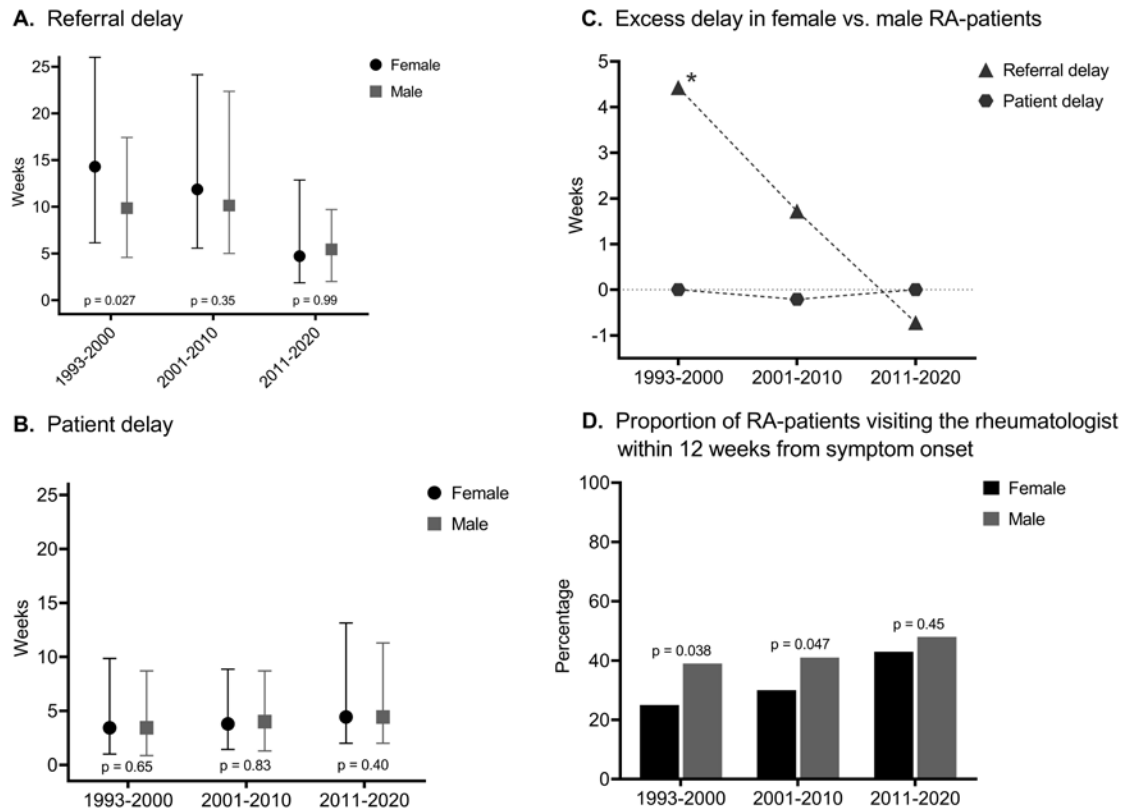



Figure 1. Comparisons between female and male patients with RA over the years. (A) Referral delay; (B) patient delay; (C) excess delay in female compared to male patients with RA; and (D) the proportion of patients with total delay ≤ 12 weeks. (A,B) Dots and squares represent the median. Error bars represent the IQR. (C) Excess delay was calculated per time period by subtracting the median delay in male patients with RA from the median delay in female patients with RA. * In 1993-2000, median referral delay was significantly longer in female vs male patients with RA ($P = 0.03$).

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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