**The Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire: predicting clinical arthritis development**

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**Abstract**

**Objective** There is a need to better define symptom characteristics associated with arthritis development in individuals at risk of rheumatoid arthritis (RA). We investigated whether reported symptoms in at-risk individuals could predict arthritis development and whether predictive symptoms differed between seropositive and seronegative at-risk individuals.

**Methods** At-risk individuals from four cohorts (Netherlands, United Kingdom, Sweden, Switzerland) completed the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire. Participants had either 1) anticitrullinated protein antibodies and/or rheumatoid factor, or 2) relevant symptoms with or without RA-antibodies. Follow up was ≥24 months or until clinical arthritis development. Stepwise forward selection created SPARRA prediction models for the combined group and for a seropositive subgroup.

**Results** Of 214 participants, mean age was 50 years, 67% were female, and 27% (n 58) developed clinical arthritis after a median time of 7 months. Four symptoms predicted arthritis development: self-reported joint swelling, joint pain moving from side to side (combined group only), feeling pins and needles in the joints and often feeling fatigued (predicting non-arthritis).

**Conclusion** Specific symptoms can provide useful information to estimate a person’s RA risk. Differences in predictive symptoms between seropositive and seronegative at-risk individuals need to be further investigated. Future research is needed to determine whether changes in symptoms over time improve prediction and to determine the value of SPARRA in optimizing the selection of individuals who need to consult a rheumatologist.

**Keywords** rheumatoid arthritis, at-risk, symptoms, prediction

**INTRODUCTION**

Accurate prediction of rheumatoid arthritis (RA) depends on an understanding of the pathogenetic course of events. The typical evolution of RA is that individuals with genetic risk factors may develop systemic autoimmunity under relevant environmental influences, followed by symptom development and eventually clinical arthritis(1). The phase of symptom development is when at-risk individuals typically present to medical care. Individuals at risk of developing RA exhibit a high prevalence of diverse and often severe symptoms(2, 3); both musculoskeletal and more general symptoms such as fatigue and weakness are reported(4-9). However, musculoskeletal symptoms are common in primary and secondary care, including in patients who are not at risk of developing arthritis(10). Therefore, there is a need to better define symptom characteristics associated with arthritis development. Information on the prevalence, course and predictive ability of specific symptoms and symptom complexes is largely lacking(1, 9, 11); for this reason, the ‘Symptoms in Persons At Risk of Rheumatoid Arthritis’ (SPARRA) questionnaire was developed to quantify symptoms in the at-risk phase. This questionnaire was based on qualitative research exploring symptoms in seropositive arthralgia patients and newly diagnosed RA patients, together with a review of relevant literature, and has previously been validated(12).

Studies predicting arthritis development mostly rely on biomarkers such as genetic markers, autoantibodies and imaging abnormalities, with symptoms being only a minor component(13-16). Symptoms in at-risk individuals have typically been collected by using simple questionnaires developed for RA patients. In the present study, the ability of the extensive SPARRA questionnaire to predict future arthritis development was assessed. Individuals with seropositive or seronegative arthralgia have a different risk of RA and may also differ in their symptoms as related to arthritis development. Clinicians use the symptom history to differentiate those at risk of arthritis from other patients with non-specific joint symptoms(17). However, a drawback of this approach is the required high level of expertise of the assessors. In contrast, a questionnaire provides self-reported answers to standardized questions.

In an international cohort of persons at risk of RA, we addressed the following research questions:

1. Can symptoms reported by the SPARRA questionnaire predict future arthritis development?
2. Do predictive symptoms differ between seropositive and seronegative at-risk individuals?

**METHODS**

**Study participants**

Individuals at risk of developing RA from 4 European centers with prospective cohorts were asked to complete the SPARRA questionnaire: Reade, Amsterdam, the Netherlands(18), Sandwell and West Birmingham and the University Hospitals Birmingham, United Kingdom(12), Karolinska University Hospital, Sweden(12) and the University Hospital of Geneva, Switzerland(19). At-risk individuals were defined as individuals without clinically apparent arthritis with 1) anticitrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF), or 2) the presence of relevant symptoms (i.e. arthralgia suspicious for progression to RA based on clinical expertise) with or without RA-specific antibodies(1). Participants were eligible if they had completed the SPARRA questionnaire at baseline assessment and follow up data on arthritis development were available.Participants were assessed for clinical arthritis development, defined as ≥1 swollen joints as observed by a rheumatologist (all cohorts). Individuals were included between March 2014 and November 2017, details on inclusion criteria per cohort have been reported previously(12). Participants in the current study were largely the same as in the previous SPARRA publication on internal validation and initial results, with the addition of the most recently included individuals(12).

**Study procedures**

At baseline, individuals completed the SPARRA questionnaire and baseline characteristics were collected such as family history, smoking status, visual analogue scales (VAS, ranged 0-100) for pain, patient global assessment and fatigue and tender joint count of 44 joints. Antibody status was determined using local clinical tests. Subsequently, arthritis development was assessed at 6-month intervals (UK), 12-month intervals (the Netherlands, Sweden, Switzerland), and/or at extra visits in case of suspected arthritis. Follow up was ≥24 months, with a maximum of 60 months, or until clinical arthritis development. The study was approved by the Ethics Committee of each participating center, and all individuals gave written informed consent.

**Questionnaire**

The development of the SPARRA questionnaire has been previously described(12). It includes questions related to 13 symptoms: joint pain, joint swelling, joint stiffness, burning sensations in joints, tingling sensations in joints, numbness, changes in skin color over joints, muscle cramps, weakness or loss of strength, fatigue, emotional distress, concentration difficulties and sleep problems. For each symptom, frequency (0; 1 to 5; 6 to 15; 15 to 30 days per month), severity (none; mild; moderate; severe), impact on daily activities (no; small; moderate; large impact), and, if applicable, location (arm(s); hand(s); leg(s); foot or feet), were scored. Additional questions captured location of joint pain (if present: neck, back, shoulders, elbows, wrists, fingers, hips, knees, ankles, toes) and pattern of symptom development (increased rapidly and then remained constant; gradually increased to current level; intermittent, though always with some symptoms; intermittent with periods without symptoms in between). A copy of the questionnaire is shown in **Supplementary file 1**.

**Statistical analysis**

To ensure easy clinical applicability, the response categories of each question were grouped or dichotomized where applicable, and different cut-off points were tested. This resulted in 69 response options that were analyzed (details are shown in **Supplementary file 2**). Univariable Cox regression analysis was used for preselection of possible predictors. All variables with a *p*<0.2 were then included in a stepwise forward selection procedure using Cox regression (*p*<0.05) to create a multivariable prediction model. Two multivariable prediction models were created: one using all participants (combined group model) and one using all seropositive participants (seropositive subgroup model). Next, for both models, prediction scores were calculated. Points were assigned to each symptom included in the model by rounding the regression coefficients to half points and multiplying by 2, after which all points were summed(15). The diagnostic performance of the prediction models was evaluated using the area under the curve (AUC) of receiver operating characteristics (ROC) curves and Harrell’s C statistics. In general, an AUC of 0.5 suggests no discrimination, 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding. Harrell’s C is a performance measure that also takes into account time until arthritis development. Values around 0.5 indicate no predictive discrimination, values close to 1 indicate high predictive discrimination(20). Both performance measures were calculated for arthritis at one and two years follow up. For internal validation, bootstrap analysis was conducted with 1000 replicates. For the seronegative subgroup, a multivariable model could not be created due to the low number of arthritis cases, therefore, significant univariable associations were identified and corrected for multiple testing with the Bonferroni correction. Finally, in the combined group, the additional value of the SPARRA prediction model over autoantibody data was calculated using the likelihood ratio (LR) test for comparison of nested models. In addition to the main analyses, sensitivity analyses were performed in which the small sample of first degree relatives were omitted. Although all relatives reported symptoms, they came to medical care because they were first degree relatives, and not primarily because of their symptoms, and therefore, from a clinical perspective, they can be considered a separate population. All analyses were repeated without including first degree relatives. Statistical analyses were performed using SPSS V24.0 and R software.

**RESULTS**

In total, 214 individuals were included in the present study (Netherlands: n=118, UK: n=76, Sweden: n=13, Switzerland: n=7). They were individuals with 1) arthralgia and RA-specific antibodies (n=143), or 2) relevant symptoms without antibodies (n=64), or 3) were first degree relatives of RA patients and had RA-specific antibodies (n=7). Of the 238 patients who completed the SPARRA questionnaire, 24 were lost to follow-up. The baseline characteristics of patients with and without follow-up are shown in **Supplementary file 3**. Patients without follow-up versus those with follow up were younger (mean 44 (SD 13) and 51 (13) years, respectively) and had a higher tender joint count (median TJC44 4 (1-15) and 1 (IQR 0-4), respectively). **Supplementary file 4** shows the study flowchart. Baseline characteristics per cohort are shown in **Table 1**. Overall, 67 percent were female, mean age was 50 (SD 13), 46% were ACPA positive (with or without RF), 25% were only RF positive and 29% were seronegative. Total median follow up was 24 (IQR 17-36) months, median follow up of non-arthritis subjects was 25 (24-48) months. In total, 58 persons (27%) developed clinical arthritis after a median of 7 (6-18) months (**Figure 1**). In the ACPA positive subset (n=98), 41 persons (42%) developed clinical arthritis after a median of 12 (6-19) months.

**SPARRA prediction model**

*Combined group*

All 214 individuals were included in the combined group analyses.

Univariable Cox regression analyses resulted in 14 selected variables (**Supplementary file 2**) entering the multivariable Cox regression analysis. Four symptoms were included in the model: 1) joint swelling >5 days of the month, 2) joint pain moving from one side of the body to the other 3) feeling pins and needles or tingling sensations in joints and 4) often feeling fatigued (protective variable) (**Table 2**).

Frequency of joint swelling showed the best discriminative ability when the cut-off was set at >5 days per month (0 or 1 to 5; 6 to 15 or 16 to 30 days per month). Responses to the question ‘Does your joint pain move from joint to joint?’ showed no association with arthritis development when all responses were compared (no; from arms to legs; from legs to arms; from side to side) or when responses were groups as follows: (no; from arms to legs or from legs to arms; from side to side). However, when pain moving from side to side was tested against the other responses combined (from side to side; no or from arms to legs or from legs to arms), it was strongly predictive of arthritis development. Therefore, the presence or absence of this symptom itself was included in the model. Frequency of pins and needles or tingling sensations showed the best discriminative ability when the cut-off was set at ≥1 days per month (0; 1 to 5 or 6 to 15 or 16 to 30 days per month). Because of the high prevalence in the general population of feeling fatigued, the experienced frequency of this symptoms was not dichotomized and all categories were retained (0; 1 to 5; 6 to 15; 15 to 30 days per month). The prevalence for each predictor in the combined group is shown in **Supplementary file 5**. For this model, the calculated risk score ranged from 0 to 7 (**Table 3**), and based on the survival curves, prediction scores could be further categorized into 3 risk categories (low: risk score 0, intermediate: risk scores 1-3, high: risk scores 4-7, **Figure 2**). Median time until arthritis per risk score was 17, 6 and 7 months, respectively. Bootstrap analysis did not change the regression coefficients or the p-values markedly (data not shown). The prediction model AUC was 0.75 (95% CI 0.66-0.84) at 1 year FU, and 0.70 (95% CI 0.60-0.79) at 2 years FU. Harrell’s C was 0.72 at 1 year FU and 0.68 at 2 years FU.

*Seropositive subgroup*

One-hundred-and-fifty individuals were seropositive and were therefore included in this subgroup analysis. Univariable Cox regression analyses resulted in 20 selected variables (**Supplementary file 2**) entering the multivariable Cox regression analysis. In total, three symptoms were included in the final prediction model: 1) joint swelling ≥1 day of the month 2) feeling pins and needles or tingling sensations in joints and 3) often feeling fatigued (protective) (**Table 2**). In this subgroup, frequency of joint swelling showed the best discriminative ability when the cut-off was set at ≥1 days per month (0; 1 to 5 or 6 to 15 or 16 to 30 days per month). The other two predictive symptoms were similar to the combined group model. The prevalence for each predictor in the seropositive subgroup is shown in **Supplementary file 5**. The calculated risk score ranged from 0 to 6 (**Table 3**), and based on the survival curves, prediction scores could be further categorized into 2 risk categories (low: risk scores 0-2, high: risk scores 3-6, **Figure 2**). Median time until arthritis per risk score was 15 and 9 months, respectively. Bootstrap analysis did not change the regression coefficients or the p-values markedly (data not shown). The prediction model AUC was 0.71 (95% CI 0.61-0.81) at 1 year FU, and 0.69 (95% CI 0.59-0.79) at 2 years FU. Harrell’s C was 0.68 at 1 year FU and 0.67 at 2 years FU.

*Seronegative subgroup*

Sixty-four individuals were seronegative, of whom 10 developed arthritis. Because of the low number of arthritis cases, a multivariable prediction model could not be created. Univariable Cox regression analysis showed that two SPARRA symptoms were significantly associated with arthritis development in this group: 1) pattern of symptom development that increased rapidly and then remained constant (HR 5.06, 95% CI 1.25 - 20.48, p=0.023), and 2) experiencing an impact of muscle weakness on the ability to carry out daily activities (HR 0.27, 95% CI 0.08 - 0.95, p=0.042). After correcting for multiple testing using the Bonferroni correction, no items were significantly associated with arthritis development.

**Potential** **added value of SPARRA symptoms over autoantibody status**

To test whether the items from the SPARRA prediction model had additional predictive value over autoantibody data, the SPARRA symptoms (combined model) were added to a prediction model consisting of autoantibody items: 1) RF and ACPA negative, 2) RF negative, ACPA < 3x ULN, 3) RF negative, ACPA > 3x ULN, 4) RF and ACPA positive. Next, the LR test for comparison of nested models was used to compare models. The extended model in which the SPARRA prediction model items were included showed added value over the autoantibody prediction model (change from previous model *p*< 0.001; supplementary file 6).

The sensitivity analyses without including first degree relatives showed no major impact on any of the above outcome and did not change the overall results (supplementary file 7).

**DISCUSSION**

In an international cohort of at-risk individuals, four symptoms were predictive for future clinical arthritis development: joint swelling, joint pain moving from one side of the body to the other (combined group only), feeling pins and needles or tingling sensations in the joints, and often feeling fatigued (predicting non-arthritis).

To identify individuals who will develop RA in the future, the European League Against Rheumatism (EULAR) study group for risk factors of RA recommended identification of symptoms in arthralgia patients which can facilitate the development of prediction tools(1). Following this, the Clinically Suspect Arthralgia (CSA) criteria were designed(21): a combination of clinical features assessed by rheumatologists, that performed well in identifying patients who were considered to be at risk of RA(17). However, given the substantial diversity of symptoms in the at-risk phase, studies also need to include symptoms and signs experienced by patients to retrieve new insights(4). The current study indicates that other symptoms may help differentiate between preclinical arthritis patients and non-specific arthralgia patients.

A history of joint swelling and migratory pain are known risk factors for arthritis development, as confirmed in previous studies(3, 6, 9). However, the frequency and pattern of these symptoms could provide extra information. In seronegative individuals, joint swelling ≤5 days per month may not be suspicious for arthritis development, while in seropositive individuals, any joint swelling is likely to be predictive. For all at-risk individuals, joint pain moving from side to side seems indicative for arthritis development, in contrast to pain moving up and down the body (**Supplementary file 2**). Sensations of pins and needles or tingling sensations in joints have been reported by at-risk individuals in qualitative studies(6) but not before in quantitative studies. Since all SPARRA symptoms are self-reported, it is difficult to determine the cause. Interestingly, carpal tunnel syndrome, resulting in sensations of pins and needles, was reported more frequently in RA patients prior to diagnosis(22, 23). Moreover, peripheral neuropathy is a known extra-articular manifestation of RA and paresthesia’s have been reported by RA patients(24). The sensation of pins and needles in at-risk individuals might indicate neuropathies prior to arthritis diagnosis. Future research into prevalence and patterns of peripheral neuropathy in at-risk individuals is needed to test this hypothesis and could possibly add to our understanding of its etiology in the context of RA(25, 26).

In contrast to the first three symptoms, often feeling fatigued predicted non-arthritis development. Fatigue is a core symptom of fibromyalgia, together with widespread musculoskeletal symptoms(27, 28) and the presence of frequent fatigue (>50% of all days) in an arthralgia population may indicate (being at risk of) fibromyalgia rather than an RA-risk. Future studies are needed to test whether SPARRA symptoms can differentiate fibromyalgia patients from preclinical arthritis patients.

In clinical practice, seronegative RA patients are essentially indistinguishable from their seropositive counterparts at baseline presentation(29, 30). The SPARRA prediction models were similar in the combined group and the seropositive subgroup. However, since the seropositive group was larger (70%), it dominated the combined group model, making differences between the two groups more difficult to detect. In addition, univariate analyses in the seronegative group showed two different symptoms that may contribute to RA prediction in this group. Unfortunately, the number of seronegative patients was insufficient for prediction model analysis. Therefore, future research is needed to explore symptoms in the preclinical phase of seronegative RA, with a SPARRA prediction model being developed in a large, seronegative only subgroup.

Our results suggest that the SPARRA symptoms may have added value over the RA-specific antibody status for predicting arthritis. Next, the added value of the SPARRA prediction model over other previously created clinical prediction models(13-15) should be assessed. In addition, the SPARRA model can be applied if the patient’s antibody status is unknown, in contrast to the previously created prediction models, which all include RF and ACPA antibody status. Therefore, the SPARRA questionnaire might specifically be valuable in the primary care setting to help optimize the selection of patients in whom to determine autoantibodies. Primary care patients commonly self-report symptoms that may be suggestive of inflammatory arthritis(10) and the importance of tools to direct management pathways in primary care is on the research agenda(3). Since this is a different population than the one presently studied, a new prediction model will have to be created specifically for this setting which may differ from the current model. Additionally, the discriminative ability of the current SPARRA model indicates that it should be combined with other characteristics for optimal discrimination. We suggest future research to create a SPARRA model optimized for use in primary care.

Finally, it should be considered whether the trajectory of symptoms assessed here could improve arthritis prediction. Retrospective studies examining frequency of primary care consultation showed that the number of visits increase as an RA diagnosis approaches(23). This suggests an increase in frequency, severity or impact of symptoms prior to RA. Additionally, a prospective study of clinically suspect arthralgia patients showed that 33% of at-risk individuals that did not progress to RA, had complete resolution of symptoms after two years(31). Changes in symptoms measured by the SPARRA questionnaire over time might differentiate between imminent arthritis development and non-specific symptoms. Longitudinal studies into symptom changes before arthritis development are needed.

A strength of this study is that we used a large population of at-risk individuals from several European cohorts. Additionally, the prospective design of the study excludes recall bias which is a limitation in most studies on symptoms in the at-risk phase of RA.

A limitation of our study is that some of the participants who completed the baseline SPARRA questionnaire did not complete their follow-up, resulting in missing data on arthritis development and exclusion from the analyses. However, the percentage of missing data was small (<10%) and the baseline characteristics were overall similar. Another limitation is our sample size, which may have been underpowered for the subgroup analysis and was underpowered to assess the added value of the SPARRA prediction models over other previously created clinical prediction models. Additionally, given the low numbers of arthritis cases, the number of seronegative patients was insufficient for prediction model analysis. Finally, all available data had been used to create the prediction models, introducing a risk of overfitting. Given the number of arthritis events, combined with the heterogeneity of self-reported symptoms, all cases needed to be included to ensure optimal discriminative ability. However, bootstrap analysis were performed and showed similar results. Next, the model needs to be externally validated in (a) different at-risk cohort(s).

**CONCLUSION**

In conclusion, specific symptom details such as pattern of joint pain, frequency of joint swelling, presence of tingling sensations and frequency of feeling fatigued can provide useful additional information to estimate a person’s risk of developing clinical arthritis. Differences in predictive symptoms between seropositive and seronegative at-risk individuals need to be further investigated.

**Authors’ contributions** MvBT, MMtW, DvS and KR designed the study. LvB, MvBT, MF, AF, AF and AHH contributed to data collection. MMtW, LvB, MF, KR and DvS contributed to data analyses and interpretation. All authors reviewed the manuscript and approved the final version for submission.

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**Availability of data and materials** The datasets used during the current study are available from the corresponding author on reasonable request.

**Competing interests** None declared.

**Patient consent** Written informed consent was obtained from all study participants.

**Ethics approval** The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the institutional review boards of each center involved and the ethics committee of the Slotervaart Hospital and Reade, Amsterdam, The Netherlands (U/1740/0327).

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**REFERENCES**

1. Gerlag DM, Raza K, van Baarsen LG, Brouwer E, Buckley CD, Burmester GR, et al. EULAR recommendations for terminology and research in individuals at risk of rheumatoid arthritis: report from the Study Group for Risk Factors for Rheumatoid Arthritis. Ann Rheum Dis. 2012;71:638-41.

2. Smolik I, Robinson DB, Bernstein CN, El-Gabalawy HS. First-degree relatives of patients with rheumatoid arthritis exhibit high prevalence of joint symptoms. J Rheumatol. 2013;40:818-24.

3. Stack RJ, Sahni M, Mallen CD, Raza K. Symptom complexes at the earliest phases of rheumatoid arthritis: a synthesis of the qualitative literature. Arthritis Care Res (Hoboken). 2013;65:1916-26.

4. Kung TN, Bykerk VP. Detecting the earliest signs of rheumatoid arthritis: symptoms and examination. Rheum Dis Clin North Am. 2014;40:669-83.

5. Newsum EC, van der Helm-van Mil AH, Kaptein AA. Views on clinically suspect arthralgia: a focus group study. Clin Rheumatol. 2016;35:1347-52.

6. Stack RJ, van Tuyl LH, Sloots M, van de Stadt LA, Hoogland W, Maat B, et al. Symptom complexes in patients with seropositive arthralgia and in patients newly diagnosed with rheumatoid arthritis: a qualitative exploration of symptom development. Rheumatology (Oxford). 2014;53:1646-53.

7. van Tuyl LH, Stack RJ, Sloots M, van de Stadt LA, Hoogland W, Maat B, et al. Impact of Symptoms on Daily Life in People at Risk of Rheumatoid Arthritis. Musculoskeletal Care. 2016;14:169-73.

8. De Cock D, Van der Elst K, Stouten V, Peerboom D, Joly J, Westhovens R, et al. The perspective of patients with early rheumatoid arthritis on the journey from symptom onset until referral to a rheumatologist. Rheumatol Adv Pract. 2019;3:rkz035.

9. Jutley GS, Latif ZP, Raza K. Symptoms in individuals at risk of rheumatoid arthritis. Best Pract Res Clin Rheumatol. 2017;31:59-70.

10. Hider SL, Muller S, Helliwell T, Prior JA, Scott I, Lawton SA, et al. Symptoms associated with inflammatory arthritis are common in the primary care population: results from the joint symptoms survey. Rheumatology (Oxford). 2019.

11. Novella-Navarro M, Plasencia-Rodriguez C, Nuno L, Balsa A. Risk Factors for Developing Rheumatoid Arthritis in Patients With Undifferentiated Arthritis and Inflammatory Arthralgia. Front Med (Lausanne). 2021;8:668898.

12. van Beers-Tas MH, Ter Wee MM, van Tuyl LH, Maat B, Hoogland W, Hensvold AH, et al. Initial validation and results of the Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire: a EULAR project. RMD Open. 2018;4:e000641.

13. de Hair MJ, Landewe RB, van de Sande MG, van Schaardenburg D, van Baarsen LG, Gerlag DM, et al. Smoking and overweight determine the likelihood of developing rheumatoid arthritis. Ann Rheum Dis. 2013;72:1654-8.

14. Rakieh C, Nam JL, Hunt L, Hensor EM, Das S, Bissell LA, et al. Predicting the development of clinical arthritis in anti-CCP positive individuals with non-specific musculoskeletal symptoms: a prospective observational cohort study. Ann Rheum Dis. 2015;74:1659-66.

15. van de Stadt LA, Witte BI, Bos WH, van Schaardenburg D. A prediction rule for the development of arthritis in seropositive arthralgia patients. Ann Rheum Dis. 2013;72:1920-6.

16. van Boheemen L, van Schaardenburg D. Predicting Rheumatoid Arthritis in At-risk Individuals. Clin Ther. 2019;41:1286-98.

17. van Steenbergen HW, van der Helm-van Mil AH. Clinical expertise and its accuracy in differentiating arthralgia patients at risk for rheumatoid arthritis from other patients presenting with joint symptoms. Rheumatology (Oxford). 2016;55:1140-1.

18. Bos WH, Wolbink GJ, Boers M, Tijhuis GJ, de Vries N, van der Horst-Bruinsma IE, et al. Arthritis development in patients with arthralgia is strongly associated with anti-citrullinated protein antibody status: a prospective cohort study. Ann Rheum Dis. 2010;69:490-4.

19. Alpizar-Rodriguez D, Mueller RB, Moller B, Dudler J, Ciurea A, Zufferey P, et al. Female hormonal factors and the development of anti-citrullinated protein antibodies in women at risk of rheumatoid arthritis. Rheumatology (Oxford). 2017;56:1579-85.

20. Harrell FE, Jr., Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA. 1982;247:2543-6.

21. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ, Brouwer E, Codreanu C, Combe B, et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76:491-6.

22. Muller S, Hider S, Machin A, Stack R, Hayward RA, Raza K, et al. Searching for a prodrome for rheumatoid arthritis in the primary care record: A case-control study in the clinical practice research datalink. Semin Arthritis Rheum. 2019;48:815-20.

23. Beers-Tas MV, Nielen MM, Twisk JWR, Korevaar J, van Schaardenburg D. Increased primary care use for musculoskeletal symptoms, infections and comorbidities in the years before the diagnosis of inflammatory arthritis. RMD Open. 2020;6.

24. Agarwal V, Singh R, Wiclaf, Chauhan S, Tahlan A, Ahuja CK, et al. A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. Clin Rheumatol. 2008;27:841-4.

25. Golding DN. Rheumatoid neuropathy. Br Med J. 1971;2:169.

26. Kaeley N, Ahmad S, Pathania M, Kakkar R. Prevalence and patterns of peripheral neuropathy in patients of rheumatoid arthritis. J Family Med Prim Care. 2019;8:22-6.

27. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46:319-29.

28. Leavitt F, Katz RS, Golden HE, Glickman PB, Layfer LF. Comparison of pain properties in fibromyalgia patients and rheumatoid arthritis patients. Arthritis Rheum. 1986;29:775-81.

29. Cader MZ, Filer AD, Buckley CD, Raza K. The relationship between the presence of anti-cyclic citrullinated peptide antibodies and clinical phenotype in very early rheumatoid arthritis. BMC Musculoskelet Disord. 2010;11:187.

30. Pratt AG, Isaacs JD. Seronegative rheumatoid arthritis: pathogenetic and therapeutic aspects. Best Pract Res Clin Rheumatol. 2014;28:651-9.

31. Ten Brinck RM, Boeters DM, van Steenbergen HW, van der Helm-van Mil AHM. Improvement of symptoms in clinically suspect arthralgia and resolution of subclinical joint inflammation: a longitudinal study in patients that did not progress to clinical arthritis. Arthritis Res Ther. 2020;22:11.

**Table 1** Baseline characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Total(n=214) | Netherlands (n=118) | UK(n=76) | Sweden (n=13) | Switzerland (n=7) |
| Age, mean (SD) | 50 (13) | 51 (13) | 48 (14) | 53 (14) | 55 (11) |
| Female | 144 (67) | 76 (64) | 50 (66) | 12 (92) | 6 (86) |
| FDR with RA | 54 (25) | 23 (20) | 22 (29) | 2 (17) | 7 (100) |
| Current smoking | 33 (15) | 21 (18) | 10 (13) | 1 (8) | 1 (14) |
| TJC44, median (IQR) | 1 (0-6) | 0 (0-2) | 7 (2-16) | ND | 0 (0-3) |
| VAS pain, median (IQR) | 35 (9-62) | 25 (1-48) | 54 (25-74) | 38 (18-68) | ND |
| VAS patient global assessment, median (IQR) | 34 (4-56) | 23 (1-50) | 46 (15-68) | 33 (15-63) | ND |
| RF neg, ACPA neg | 64 (30) | 14 (12) | 50 (66) | 0 (0) | 0 (0) |
| RF pos, ACPA neg | 52 (24) | 45 (38) | 8 (11) | 0 (0) | 1 (14) |
| ACPA pos, RF neg | 43 (20) | 23 (20) | 8 (11) | 6 (46) | 6 (86) |
| ACPA pos, RF pos | 55 (26) | 36 (31) | 13 (17) | 7 (54) | 0 (0) |
| Clinical arthritis development | 58 (27) | 23 (20) | 26 (34) | 7 (54) | 2 (29) |
| Months until arthritis, median (IQR) | 7 (6-18) | 11 (3-17) | 6 (6-14) | 15 (5-29) | NA |

Numbers are n (%) unless otherwise stated.

ACPA: anticitrullinated protein antibodies, FDR: first degree relative, RF: rheumatoid factor, TJC44: tender joint count of 44 joints, UK: United Kingdom, VAS: visual analogue scale

**Table 2** SPARRA prediction models

|  |  |  |
| --- | --- | --- |
|  | Combined groupn=214 | Seropositive subgroupn=150 |
|  | HR | 95% CI | *p* | HR | 95% CI | *p* |
| **Over the past month how many days have you had swelling in your joints?** |  |  |  |  |  |  |
| 0-5 days  | REF |  |  |  |  |  |
| 6-30 days | 2.9 | 1.7; 5.1 | <0.001 |  |  |  |
| *0 days*  |  |  |  | REF |  |  |
| *≥ 1 days* |  |  |  | 3.3 | 1.7; 6.3 | <0.001 |
| **Does your joint pain move from one side of the body to the other?** |  |  |  |  |  |  |
| No  | REF |  |  |  |  |  |
| Yes | 2.6 | 1.5; 4.6 | 0.001 |  |  |  |
| **Over the past month how many days have you had pins and needles or tingling sensations?** |  |  |  |  |  |  |
| 0 days  | REF |  |  | REF |  |  |
| ≥ 1 days | 1.9 | 1.1; 3.3 | 0.029 | 2.2 | 1.2; 4.2 | 0.017 |
| **Over the past month how many days have you had fatigue?** |  |  |  |  |  |  |
| 0 days  | REF |  |  | REF |  |  |
| 1 to 5 days | 0.44 | 0.19; 1.0 | 0.047 | 0.44 | 0.16; 1.2 | 0.103 |
| 6 to 15 days | 0.46 | 0.21; 1.0 | 0.048 | 0.51 | 0.20; 1.3 | 0.143 |
| 16 to 30 days | 0.35 | 0.17; 0.7 | 0.003 | 0.39 | 0.17; 0.86 | 0.019 |

**Table 3** SPARRA prediction model risk scores

|  |  |  |
| --- | --- | --- |
| Symptom | Combined group | Seropositive subgroup |
| Over the past month how many days have you had swelling in your joints? | > 5 days | **2 points** | ≥ 1 day | **2 points** |
| Does your joint pain move from one side of the body to the other? | If yes | **2 points** |  |  |
| Over the past month how many days have you had pins and needles or tingling sensations? | ≥ 1 day | **1 point** | ≥ 1 day | **2 points** |
| Over the past month how many days have you had fatigue? | 0 days1 to 5 days6 to 15 days16 to 30 days | **2 points****0 points****0 points****0 points** | 0 days1 to 5 days6 to 15 days16 to 30 days | **2 points****0 points****1 point****0 points** |

**Figure legends**

**Figure 1** Kaplan Meier plot of clinical arthritis development

a. Combined group; b. Stratified for autoantibody positivity

**Figure 2** Kaplan Meier plot of SPARRA prediction model risk categories

a. Combined group model; b. Seropositive subgroup model