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Background: Clinically suspect arthralgia (CSA) can precede development of clinically evident inflammatory arthritis (IA). Autoantibody, C-reactive protein (CRP), and subclinical inflammation are known predictors, but risk estimation remains insufficiently accurate. Especially CRP has a small effect size and is inadequately reflective of inflammation that can be measured systemically. RNA expression in whole blood of patients with rheumatoid arthritis (RA) have shown differences compared to healthy individuals. Therefore, we hypothesized that differences in RNA expression can be found between CSA patients that do and do not progress to IA.

Objectives: This study assessed whole blood RNA expression levels of inflammatory and immune genes as potential biomarkers for prediction of IA-development in patients with arthralgia.

Methods: Between April 2012-March 2015, 234 patients were consecutively included in the Leiden CSA-cohort. Follow-up ended when patients developed clinically apparent IA (determined at physical examination), or else after 2-years. RNA expression in whole blood, at the moment of inclusion, was determined for 135 genes of the innate and adaptive immune system by dual color Reverse-Transcription Multiplex Ligation-dependent Probe Amplification (dcRT-MLPA) profiling. Cox proportional hazard models were used to associate time-to-event with gene expression level at inclusion, while adjusting for age, gender, and assay plate (model 1). The false discovery rate was used to correct for multiple testing. Genes with significantly different expression were subsequently studied for reproducibility by qPCR, and mutual independence in their association with IA-development. For the latter, we employed a forward selection strategy, starting with the most significantly associated gene and iteratively adding more genes. Resulting mutually independent genes were further investigated for their added predictive value over known risk factors, CRP, ACPA, and subclinical joint inflammation.

Results: 21% of CSA-patients developed IA after mean 3.6 months (IQR:1.6-10.7) follow-up. After correction for multiple testing, six genes were significantly associated with IA-development (model 1), namely IFN- γ , PHEX, IGF-1, IL7R, CD19, or CCR7 (ordered by significance). For all six genes, a lower expression at inclusion was associated with an increased risk of IA-development. IFN- γ was only weakly expressed in peripheral blood, hampering the technical reproducibility between MLPA and qPCR results, and was excluded for further analyses. PHEX and IGF-1 were highly correlated (R^2 0.97) and only IGF-1, but not PHEX, was included in further analyses. Of the remaining significant genes (IGF-1, IL7R, CD19, CCR7), an independent association with IA-development was observed for IGF-1 and IL7R, but not for CD19 or CCR7. qPCR data of IL7R correlated with MLPA results ($p < 0.001$), confirming the robustness of the transcriptomic outcome. Lastly, when analysing IGF-1 and IL7R with known clinical predictors, both IGF-1 and IL7R remained independently associated with progression to IA.

Conclusion: Six genes were differentially expressed between CSA-patients that did or did not progress to IA. Expression of IGF-1 and IL7R showed added value to regularly used predictors. Validation is warranted.

References: None.

Figure 1. Association between RNA expression divided in tertiles of IGF-1 (A) and IL7R (B), and development of inflammatory arthritis

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OP0114

PREDICTING RHEUMATOID ARTHRITIS USING THE SYMPTOMS IN PERSONS AT RISK OF RHEUMATOID ARTHRITIS (SPARRA) QUESTIONNAIRE

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Background: Accurate prediction of rheumatoid arthritis (RA) development in persons at risk of RA can help to select individuals for early intervention trials. Currently, RA prediction mostly relies on biomarkers such as genetic factors, autoantibodies and imaging abnormalities, with symptoms being only a minor component ¹⁻³. However, at-risk individuals exhibit a high prevalence of diverse and often severe symptoms ^{4,5} and information on the predictive ability of individual symptoms or symptom complexes is still largely lacking.

Objectives: We investigated the prevalence and predictive ability of symptoms in persons at-risk of RA, using the validated 'Symptoms in Persons At Risk of Rheumatoid Arthritis' (SPARRA) questionnaire.

Methods: Individuals at-risk of RA from four different cohorts from the Netherlands (n=122), United Kingdom (N=90), Sweden (N=13) and Switzerland (N=20), were asked to fill out the SPARRA questionnaire, consisting of 69 questions (previously described ⁶). Individuals were either defined as persons with anticitrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF; n=193), having relevant symptoms (i.e. clinically suspect arthralgia with or without RA-specific antibodies, n=70) or being first degree relatives (FDR, n=20) of RA patients. All were followed for a minimum of 24 months or until clinical arthritis development. Univariable analyses were performed for possible predictor selection ($p < 0.2$), followed by stepwise forward selection (by Cox regression, $p < 0.1$) to create a multivariable prediction model.

Results: The mean age of all participants was 49 years and 69% was female. In total, 56 persons (23%) developed clinical arthritis (n=22, 25, 7, 2 respectively in the 4 groups) after a median of 11.9 months (IQR 5.3 - 17.8). In total, 23 SPARRA questions were selected from the univariable analyses and entered in the stepwise forward selection procedure. Time to development of RA was predicted by the following questions: pain moving from joint to joint, having moderate or severe swelling in joints, feeling ≥ 1 days fatigue per month and feeling stiffness in joints of one and both feet (table 1).

Table 1. Multivariable prediction model of SPARRA questions to predict clinical arthritis

	HR (95% CI), p
Does your joint pain move from joint to joint?	
No; from arms to legs; from legs to arms (ref)	1
From one side to the other	2.96 (1.57; 5.57), p = 0.001
Over the past month how much joint swelling have you had?	
None or mild (ref)	1
Moderate or severe	3.04 (1.48; 6.25), p = 0.003
Over the past month how many days of the month have you had fatigue?	
0 (ref)	1
≥ 1	0.32 (0.15; 0.67), p = 0.003
Where did you feel joint stiffness?	
Neither feet (ref)	
One foot	0.93 (0.42; 2.08), p = 0.865
Both feet	0.40 (0.17; 0.93), p = 0.032

Conclusion: Asking persons at-risk of RA about joint pain, swelling and stiffness is common clinical practice. However, specific details such as pain moving from one side to the other or degree of joint swelling may provide useful additional information to estimate a person's RA risk. The protective effect noted for fatigue and stiff feet may reflect an underlying pain syndrome rather than RA risk. We are currently performing analyses of the potential added value of SPARRA questions over the clinical prediction model by van der Stadt et al ³ which will help determine the final format of the SPARRA questionnaire.

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