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Research Article

Development and validation of a clinical rule for recognition of early inflammatory arthritis

Short title: A clinical rule that supports identification of patients suspected of having IA

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ABSTRACT

Objectives: National and international guidelines recommend prompt referral of patients presenting with inflammatory arthritis (IA), but general practitioners (GPs) feel uncertain in their proficiency to detect synovitis through joint examination, the method of choice to identify IA. Our objective was to develop and validate a rule composed of clinical characteristics to assist GPs and other physicians in identifying IA.

Design: Split-sample derivation and validation study.

Setting: The Leiden Early Arthritis *Recognition* Clinic (EA*R*C); a screening clinic for patients in whom GPs suspected the presence of IA.

Participants: 1,288 consecutive patients visiting the EA*R*C .

Primary and secondary outcome measures: Associations of clinical characteristics with the presence of IA were determined using logistic regression in 644 patients, while validating the results in the other 644 patients (split-sample validation). To facilitate application in clinical practice, a simplified rule (with scores ranging from 0 to 7.5) was derived and validated.

Results: IA was identified by a rheumatologist in 41% of patients. In univariable analysis, male gender, age ≥60 years, symptom duration of <6 weeks, morning stiffness >60 minutes, a low number of painful joints (1-3 joints), presence of patient-reported joint swelling, and difficulty with making a fist were associated with IA in the derivation dataset. Using multivariable analysis, a simplified rule consisting of these seven items was derived and validated which yielded an Area Under the Receiver Operator Characteristic curve (AUC) of 0.74 (95%CI 0.70–0.78) in the derivation dataset. Validation yielded an AUC of 0.71 (95%CI 0.67–0.75). Finally, the model was repeated to study predicted probabilities with a lower prevalence of inflammatory arthritis to simulate performance in primary care settings.

Conclusions: Our rule, composed of clinical parameters, had reasonable discriminative ability for IA and could assist physicians in decision-making in patients with suspected IA increasing the appropriateness of health care utilization.

KEYWORDS:

Inflammatory Arthritis, General Practitioners, Early Recognition, Clinical Decision Rule, Rheumatoid Arthritis

Strengths and limitations of this study

- A clinical rule could help to select patients to refer for additional investigations (laboratory or imaging) or to secondary care. This could promote early identification of inflammatory arthritis and increase appropriateness of health care utilization.
- Data were collected prospectively in a population of patients in which general practitioners had doubt on the presence of inflammatory arthritis.
- The main limitation is that data were not collected in primary care itself, but in a setting intermediary between primary and secondary care. Further external validation in GP settings is therefore required.

BACKGROUND

Early initiation of disease modifying anti-rheumatic drugs is strongly associated with improved outcomes of rheumatoid arthritis (RA).[1] National and international guidelines attempt to facilitate this by emphasizing prompt referral of patients presenting with inflammatory arthritis (IA) to a rheumatologist. The European League Against Rheumatism (EULAR) taskforce for the management of early IA recommends referral within 6 weeks of onset of symptoms[2], while in the United Kingdom (UK) the National Institute for Health and Care Excellence (NICE) guidelines advises referral to a rheumatologist in patients with new, persistent (>3–4 weeks) synovitis within three working days.[3] However, it was demonstrated that this referral timeline is achieved in only 17% of patients.[4] On average, RA patients are seen four (and sometimes more than eight) times by general practitioners (GPs) before they refer to secondary care[5-8], which may reflect the difficulty of differentiating patients with early IA from patients with other types of common musculoskeletal symptoms. A recent qualitative study revealed that GPs acknowledge the importance of early detection and referral, but feel uncertain in their proficiency to detect synovitis through joint examination, the method of choice to identify IA.[2,9] As a consequence, the referral to a rheumatologist may be delayed, which contributes to overall treatment delay in early RA, as observed in Europe.[10,11]

This is further complicated by the high incidence of consultations for various common musculoskeletal symptoms and the low incidence of early IA in primary care.[12] The consultation prevalence of any musculoskeletal symptom in primary care in the UK approximates 2405 per 10,000 per year [13], making it the most common organ system consulted for at GP practices.[12-14] Although musculoskeletal symptoms are common, GPs

suspect IA (based on pattern recognition) in only a very small minority of patients.[5] In these patients, GPs often lack confidence in joint assessment for synovitis.

To support early detection, several initiatives have been developed, including triage systems. The best studied triage system (the Early Inflammatory Arthritis Questionnaire) was developed and validated for patients attending secondary and tertiary care.[15-17] Furthermore, several referral guidelines for GPs[6,18-22], and public awareness campaigns have been developed, for instance one attempting to simplify pattern recognition to the "S-Factor": Stiffness, Swelling, Squeezing. However, none of these initiatives were designed using primary care data, and all assume that GPs can differentiate between the presence and absence of joint swelling[6,18-20], which continues to be a barrier to the early detection of IA.

Altogether there is a contradiction with the need to refer as quickly as possible while evidence who must be referred or, in line with this, in whom additional investigations are appropriate is lacking. To solve the issue, we have developed and validated a rule composed of clinical characteristics, by taking advantage of data from a setting intermediate between primary and secondary care. This intermediate setting of an the Early Arthritis *Recognition* Clinic was a local solution to promote early referrals and is not easy implementable in other regions. The clinical rule derived from these data however, is easy to apply and may assist in the decision-making process in patients with musculoskeletal symptoms with suspected IA at other places, in order to promote early identification of IA.

METHODS

Study population

To promote early recognition of early IA, the Early Arthritis *Recognition* Clinic (EA*R*C) was initiated in September 2010 in Leiden, the Netherlands. The outpatient clinic of the department of Rheumatology of the Leiden University Medical Center (LUMC) is the only referral center in a healthcare region of ~400,000 people. GPs were instructed to refer patients to the EA*R*C in whom they were unsure about the presence of IA (instead of a 'wait-and-see' approach or performing additional tests). The EA*R*C system has reduced referral delay from 8 to 2 weeks, and improved early identification of IA.[11,23] To emphasize the importance of early identification of IA and aiming to inform on the purpose of the EA*R*C, a region-wide educational campaign was conducted among regional GPs.

In addition to (and distinct from) the EA*R*C, the LUMC also has an Early Arthritis Clinic (EAC). The EAC was established in 1993 to include and follow patients with early arthritis and to offer the possibility of rapid access to rheumatology care, usually within a week of referral. To differentiate between the clinics, GPs were instructed to refer to the EAC if there was a clear synovitis or very high suspicion of IA (i.e. to continue as they had before, since there was no benefit for such patients to go the EA*R*C first) and to refer to the EA*R*C when in doubt about the presence of IA (i.e. to not 'wait-and-see' or order additional tests).

The EA*R*C screening clinic was held twice a week between 2010–2014 and once a week from 2014 onwards. After GP referral, patients can visit the EA*R*C without an appointment. All patients that visited the EA*R*C between 2010 and September 2015 were studied.

Data collection

At the EA*R*C, patients completed a short questionnaire about their joint symptoms, after which they were seen by an experienced rheumatologist (AvdHvM or other senior rheumatologists) who performed a full 66-joint examination. If synovitis was determined by physical examination, patients were fast-tracked to visit the EAC within 1 week for further evaluation and treatment. Patients without IA were discharged to primary care. The questionnaire completed by patients, provided in S1 Appendix, contained questions on age, gender, date of symptom onset, date of first visit to GP, presence of a (sub)acute symptom onset (versus a gradual symptom-onset), morning stiffness (duration in minutes), which part of the day symptoms were worst, and whether they had difficulty with making a fist. Patients were asked to indicate on a 52-joint mannequin which joints were painful and which joints they considered to be swollen. IA, defined as synovitis confirmed by the rheumatologist at physical examination, was used as outcome.

Collected data was anonymized and entered in a research database at chronological order of visiting the EA*R*C. The local medical ethical committee approved this study.

Derivation and validation of the model

We used half of the dataset for derivation and the other half for validation of results (split-sample validation). To prevent bias by (unknown) effects of inclusion period, patients with odd ID-numbers (1,3,etc) were included in the derivation dataset and those with even ID-numbers (2,4,etc) were used for validation.

To prevent exclusion of patients with one or more missing variables, we imputed missing values using chained equations[24]; frequencies of missing variables are presented in S2 Appendix. The variables ‘difficulty with making a fist’ and ‘self-reported joint swelling’

were most frequently missing as these were added to the questionnaire after April 1st 2012, thus absence of these data was considered to occur completely at random.

We conducted logistic regression analysis modelling with presence of IA (defined as rheumatologist-confirmed synovitis on physical examination) as dependent variable. Continuous variables were categorized using clinically relevant cut-offs: age: <40 / 40–59.9 / ≥60 years; duration of symptoms: <6 / 6–11 / 12–51.9 / ≥52 weeks; duration of morning stiffness: ≤60 / >60 minutes; number of painful joints: 0 / 1–3 / 4–10 / ≥11; number of swollen joints: 0 / 1–3 / 4–10 / ≥11. We performed univariable logistic regression to evaluate associations between dependent variables and presence of IA. Variables with p-values <0.05 in univariable analyses were entered in multivariable regression analyses (enter model) to obtain a model with a small number of variables. If several categories within a variable had similar regression coefficients in multivariable modelling, we pooled these categories and repeated the analysis. In sub-analysis, we also performed a multivariable logistic regression model with the pooled categories using backward selection.

To obtain a simplified rule applicable in daily care, we rounded the regression coefficients of the final multivariable logistic regression model to the nearest 0.5 (irrespective of p-value). This resulted in an easily calculable risk score. For each value of the risk score, we determined test characteristics (i.e. sensitivity and specificity) and predicted probabilities of the presence of inflammatory arthritis.

We evaluated the overall discriminative ability of the models using the Area Under the Receiver Operating Characteristic curve (AUC). The model's calibration was assessed by generating a calibration plot to measure goodness of fit, where the data was partitioned in 10

equally sized groups based on the predicted probabilities using the final fitted multivariable model. In each group, the average predicted probability on current IA was compared with the observed prevalence, both in the derivation and validation dataset. Additionally, the Hosmer-Lemeshow statistic was calculated.

Patients included in this study represent the difficult group in whom GPs were uncertain of the presence of suspected IA; patients with a very high degree of suspicion were referred directly to the EAC, whereas patients with a very low degree of suspicion for inflammatory arthritis may not have been sent to the EA*R*C. This means that pre-test and post-test probabilities of IA are likely to be different when the simplified rule is used in primary care itself. Accurate data on this probability in GP practices is lacking, but a study among sixteen GP practices revealed that 27% of 188 patients assigned with the International Classification of Primary Care-1 code for suspected inflammatory arthritis in their medical record had confirmed RA (n=38), polyarthritis (n=5), or oligoarthritis (n=8) following rheumatologist's assessment. Another study among GPs found that 18% of patients with suspected inflammatory arthritis was referred; though data on rheumatologists' diagnoses was not provided.[25] Guided by these very scarce data obtained in GP practices, post-test probabilities on the presence of inflammatory arthritis were simulated with an estimated pre-test probability of 20%.[5] We adjusted the intercept of the regression model as described in [26,27] and plotted average estimated predicted probabilities against the regression and simplified risk score.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 23.0). P-values <0.05 were considered significant.

Patient involvement

Patient research partners agreed with the pathway of care at the EA*R*C. They also provided feedback on the questionnaire, which was expanded in 2012 with two questions.

RESULTS

Patients

1,288 patients in whom GPs were unsure about the presence of IA visited the EA*R*C between 2010 and 2015; of these, 41% had synovitis at joint examination. The frequency of inflammatory arthritis was stable throughout the study years (S3 Appendix). Baseline characteristics of patients in both derivation and validation dataset are presented in Table 1.

Model derivation

In univariable analyses, male gender, age ≥60 years, symptom duration of <6 weeks, an acute onset of symptoms, morning stiffness >60 minutes, a low number of painful joints (1–3 joints), presence of patient-reported joint swelling (1–3 joints), and difficulty with making a fist were associated with the presence of IA in the derivation dataset (Table 2). 'Symptoms worst in the early morning' was not associated with IA and therefore not included in multivariable analysis. Two multivariable models were created with categorized variables; first a model with categories similar to the univariable analysis (Table 3, model 1), and secondly a model pooling categories per variable with similar regression coefficients (Table 3, model 2). Performing this second model in the derivation dataset revealed that male gender, age ≥60 years, symptom duration of <6 weeks, a low number of painful joints (1–3 joints), and presence of patient-reported joint swelling were independently associated with the presence of IA (Table 3). The AUC of model 2 was 0.75 (95%CI 0.70–0.79) in the

derivation dataset. In sub-analysis, model 2 was repeated with a backward selection procedure, showing similar regression coefficients (S4 Appendix).

Generation of a simplified rule

In order to facilitate usage in routine clinical practice, a simplified model was generated (S5 Appendix). The obtained regression coefficient of acute onset of symptoms in multivariable modelling was -0.015, yielding 0 points. Also after exclusion of this variable, the regression coefficients of the other seven variables in the model did not change yielding similar points. This resulted in a simplified rule consisting of seven scored items and a total score ranging from 0 to 7.5 with corresponding predicted risks (Figure 1). Risks of IA predicted by the model as a function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates) are presented in Figure 2A; as shown, simplification did not majorly affect the predicted risks. The calibration plot shows that predicted probabilities correlated well with the observed proportions of patients with IA (S6 Appendix). The Hosmer-Lemeshow test for the derivation dataset yielded a P-value of 0.36. If cut-offs are required and a highly sensitive approach is preferred (>90% sensitivity), this is obtained by a cut-off score of ≥4. When a highly specific approach is preferred (>90% specificity), this is obtained by a cut-off score of ≥6. Test characteristics for all cut-off points are presented in S7 Appendix. The AUC of the simplified score, measuring discrimination, was 0.74 (95%CI 0.70–0.78; S8 Appendix).

Validation

The final multivariable model (model 2) was applied in the validation dataset, revealing similar results (Table 3). The AUC was 0.72 (95%CI 0.68–0.77). Figure 2A shows the predicted probabilities of the simplified rule are almost similar to those obtained in the

derivation data. The AUC of the simplified rule was 0.71 (95%CI 0.67–0.75) in the validation dataset. The calibration plot is shown in S6 Appendix, the Hosmer-Lemeshow test for the validation dataset yielded a P-value of 0.43.

Simulation of accuracy in a setting with a lower prevalence of IA

In contrast to test characteristics, predicted probabilities depend on the prior risk (i.e. prevalence) of IA. The frequency of IA among primary care patients with GP-determined clinical suspicion of IA may be different than that observed in the EA*R*C. Based on observations in GP practices[5,25], a simulation was run for the regression and simplified score with a prevalence of inflammatory arthritis set at 20%. Estimated predicted probabilities for different scores of the multivariable model and simplified rule (in derivation and validation datasets) are presented in Figure 2B.

Our simplified rule was implemented in a web application that provides predictions on the presence of current IA for individual patients; a screenshot is presented in Figure 3. The web application is accessible online at http://caretool.eu/

DISCUSSION

GPs play a crucial role in the early identification of RA and often lack confidence in detecting joint synovitis.[9] In an attempt to solve the contradiction between the need to refer very early and absence of evidence who must be referred, we provided an evidence-based and simple method to identify the presence of IA in patients in whom IA is suspected. This clinical rule helps to select patients to refer for additional investigations (laboratory or

imaging) or to secondary care. Hence, the Clinical Arthritis RulE could increase appropriateness of health care utilization.

This study is different from studies that derived tools to facilitate triage of patients that have been referred to secondary or tertiary care[15-17] as our study did not aim to prioritize patients that are already referred. In addition, we aimed to facilitate recognition of IA (as this would necessitate referral to a rheumatologist) and did not perform a longitudinal study to predict development of specific diagnoses (e.g. RA) later-on. This explains why several factors were found to be associated with presence of IA that are not generally considered typical for RA (male gender, a low number of painful joints, a short symptom duration). GPs generally do well in identifying those at high risk for development of RA (i.e. women at younger ages with subacute smouldering polyarticular, symmetric complaints), and therefore we aimed this tool to assist GPs in decision-making for more atypical or non-classical presentations of IA (e.g. due to overlap of symptoms with other diagnoses) leading to doubt. Indeed, many of the patients that did not have synovitis at the EA*R*C had symptoms due to diagnoses that are characterized by longstanding or extensive joint pain (e.g. osteoarthritis, fibromyalgia), explaining higher scores for a short symptom duration or a low number of symptomatic joints.

Adding other clinical variables might increase the discriminative ability of the model. Potential examples include the squeeze test of the metacarpophalangeal joints (although the diagnostic accuracy was shown to be only moderate[28]), information on family history, or functional impairments. These items were not routinely collected before December 2015. Adding data on laboratory investigations to our rule could potentially also increase its

discriminative ability. However, our data do not permit us to evaluate this, as additional investigations were done afterwards and only in patients with synovitis at joint examination.

A strength of our EA*R*C for the purpose of this study is that GPs in our region are familiar with early referral, that regional healthcare logistics make rheumatology care rapidly available for patients with arthritis, with the EA*R*C as ultimate service for patients in whom GPs suspect (but are unsure about) IA. With the availability of the EA*R*C every week and lack of any waiting list for the EA*R*C, we assume a low number of patients not showing up at the EA*R*C despite being encouraged by their GP to visit the EA*R*C. As the EA*R*C serves as a unique bridge between primary and secondary care, its patients closely resemble the population GPs have contact with and have doubts about. Although the EA*R*C is successful[11,23], this approach may be more difficult to implement in other centres or regions due to a shortage of rheumatologists, or long traveling distances to rheumatology outpatient clinics, and as such a different system is needed to aid GPs in identifying IA. This prompted us to derive a validated rule composed of clinical characteristics that could assist GPs in decision-making for more atypical or non-classical (but nevertheless suspect) presentations of IA, as classical presentations usually don't cause GPs concern.

GPs were discouraged (both by our local communication with GPs and according to national guidelines for GPs) to perform autoantibody testing.[29] Autoantibody testing in primary care in this region was infrequent[5], unlike in other parts of the world. Autoantibody testing may falsely reassure doctors and patients, especially when results are negative, and as such we believe a model based on clinical presentation is more appropriate to facilitate rapid referral. Another strength is that we studied patients in whom the GPs have indicated a lack of confidence to identify the presence of synovitis. Patients with clinically obvious IA had early

access to rheumatologic care already. This may enhance the generalizability of the present data to the setting of doubt in primary care.

A disadvantage of our setting is that the data were not collected in primary care itself, but in a setting intermediary between primary and secondary care. Although musculoskeletal symptoms are a very common reason for consulting primary care, suspected IA is relatively unusual, and the average full-time GP diagnoses only one new patient with RA each year.[30] Additionally, although the EA*R*C is easily accessible on a weekly basis, the number of patients that were referred but did not visit the EA*R*C is unknown. The prevalence of IA in patients in whom GPs are unsure about the presence of inflammatory arthritis may be lower than 41%. A study performed in primary care suggested a prevalence of 27%.[5] Based on these scarce data, we demonstrated the predictive accuracy of the model using a simulated prevalence of 20%. Because of the limitation that no other data are available on the prevalence of IA when GPs suspect IA, this estimated prevalence could be an overestimation. However, the observed data could also be an underestimation as in our setting GPs were instructed to refer patients with high suspicion/definite arthritis to the regular outpatient clinic. Further external validation in GP settings is therefore required.

GPs in our region are well informed about the importance of the early detection of IA, but we have no reason to presume that the detection skills of GPs in our region are different from that of GPs elsewhere. We expect that our rule (Clinical Arthritis RulE - CARE) might support GPs and other health care professionals in the decision-making process in patients with musculoskeletal symptoms in whom they suspect IA, regardless of the region. Of course, the consequences of an increased score will likely depend on the setting and relation with secondary care: it can either influence the decision to directly refer a patient or to first

ask for additional laboratory tests (e.g. acute phase reactants or autoantibodies; Figure 4). A clinical decision aid may be of value to this end as well, as for most laboratory investigations the diagnostic accuracy depends on the prior risk. Using a simple clinical decision aid first may be more cost-effective than performing additional investigations in all patients in whom there is doubt about IA. Depending on the setting and consequences of a high score, either a sensitive method or a specific method may be preferred; for this reason cut-offs for both situations are provided. The web application facilitates implementation of the Clinical Arthritis RulE by GPs, physicians, and other health care professionals such as physiotherapists in their daily work.

CONCLUSION

In conclusion, this study developed a clinical rule that supports the identification of patients suspected of having IA by physicians that feel insufficiently experienced in assessment of synovitis by joint examination. We hope the current data are a prelude to a data-driven method that supports GPs, physicians, and other health care professionals in decision-making in patients with suspected early IA.

LIST OF ABBREVATIONS

AUC = Area Ander the Curve

CARE = Clinical Arthritis Rule

EAC = Early Arthritis Clinic

EA*R*C = Early Arthritis Recognition Clinic

GPs = General Practitioners

IA = Inflammatory Arthritis

LUMC = Leiden University Medical Center

MCP = Metacarpophalangeal

NICE = National Institute for Health and Care Excellence

RA = Rheumatoid Arthritis

UK = United Kingdom

DECLARATIONS

Ethics approval and consent to participate

The medical ethical committee of the Leiden University Medical Centre ("Commissie Medische Ethiek") approved the study.

Consent for publication

Not applicable.

Availability of data and material

The calculator presented in this paper is available online at http://caretool.eu. Statistical code and dataset are available from R.M. ten Brinck (e-mail; r.m.ten_brinck@lumc.nl) at reasonable request.

Competing interests

The authors declare that they have no competing interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work. The disclosure forms are available at request.

Patient consent

Obtained.

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Authors' contributions

RtB, BvD, and AvdHvM designed the study. RtB, BvD, and SlC conducted the statistical analysis. RtB, BvD and AvdHvM conducted the literature search and wrote the article. All authors contributed intellectually to the writing or revising of the manuscript, and approved the final version.

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Table 1. Characteristics of patients visiting the Early Arthritis *Recognition* Clinic

	Derivation (N=644)	Validation (N=644)
Male, n (%)	190 (30)	198 (31)
Age in years, mean ± SD	52 ± 16	51 ± 17
Symptom duration in weeks, median (IQR)	10 (3–45)	12 (4–45)
Acute onset of symptoms *, n (%)	252 (39)	238 (37)
Symptoms worst in the early morning, n (%)	372 (58)	351 (55)
Morning stiffness in minutes, median (IQR)	10 (0–30)	10 (0–30)
Number of painful joints, median (IQR)	7 (2–15)	6 (3–15)
Number patient-reported swollen joints, median (IQR)	2 (1–5)	2 (1–5)
Difficulty with making a fist, n (%)	329 (51)	301 (47)
Arthritis present at joint examination by experienced rheumatologist, n (%)	271 (42)	252 (39)

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Abbreviations: IQR = interquartile range; SD = standard deviation.

Table 2. Univariable logistic regression in the derivation dataset with presence of synovitis upon joint examination as outcome.

		Arthritis (N=271)	No arthritis (N=373)	OR (95% CI)
Male, n (%)		104 (38)	86 (23)	2.1 (1.5–2.9)
Age, n (%)	<40	49 (18)	104 (28)	*(ref)*
	40–59.9	109 (40)	172 (46)	1.3 (0.89–2.0)
	≥60	113 (42)	97 (26)	2.5 (1.6–3.8)
Symptom duration in weeks, n (%)	<6	124 (46)	103 (28)	3.8 (2.4–5.9)
	6–11	38 (14)	62 (17)	1.9 (1.1–3.9)
	12–51.9	66 (24)	75 (20)	2.7 (1.7–4.5)
	≥52	43 (16)	132 (36)	*(ref)*
Acute onset of symptoms *, n (%)		122 (45)	131 (35)	1.5 (1.1–2.1)
Symptoms worst in early morning, n (%)		158 (58)	214 (57)	1.1 (0.69–1.6)
Morning stiffness >60 min, n (%)		45 (17)	40 (11)	1.7 (1.03–2.7)
Number of painful joints, n (%)	0	1 (0)	10 (3)	*(ref)*
	1–3	110 (41)	82 (22)	13.2 (1.7–105.5)
	4–10	76 (28)	123 (33)	6.1 (0.77–49.0)
	≥11	84 (31)	158 (42)	5.2 (0.65–41.3)
Number of patient-reported swollen joints, n (%)	0	18 (7)	71 (19)	*(ref)*
	1–3	115 (42)	119 (32)	3.7 (2.0–6.9)
	4–10	87 (32)	115 (31)	2.9 (1.5–5.5)
	≥11	51 (19)	68 (18)	2.9 (1.4–5.9)
Difficulty with making a fist, n (%)		156 (58)	172 (46)	1.6 (1.1–2.4)

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Abbreviations: CI = confidence interval; OR = odds ratio.

Table 3. Multivariable logistic regression analyses with synovitis upon joint examination as outcome. Model 1 includes categories of clinically applicable cut-offs; if within variables several categories had similar regression coefficients, categories were pooled (Model 2).

		Model 1		Model 2		
		Derivation		**Derivation**		**Validation**
		OR (95% CI)		**OR (95% CI)**	**B**	**OR (95% CI)**
Male		1.7 (1.1–2.5)		1.7 (1.1–2.5)	0.517	1.7 (1.1–2.4)
Age (years)	<40	*(ref)*	0–59.9	*(ref)*	(*ref*)	*(ref)*
	40–59.9	1.5 (0.96–2.5)	≥60	2.1 (1.4–3.1)	0.750	2.1 (1.5–3.0)
	≥60	2.9 (1.7–4.8)				
Symptom duration (weeks)	<6	3.8 (2.3–6.4)	<6	3.6 (2.2–6.0)	1.279	3.4 (2.0–5.7)
	6–11	1.7 (0.92–3.1)	6–51.9	2.2 (1.4–3.6)	0.797	1.9 (1.2–3.0)
	12–51.9	2.9 (1.7–5.0)	≥52	*(ref)*	(*ref*)	*(ref)*
	≥52	*(ref)*				
Acute onset of symptoms*		1.0 (0.67–1.5)		0.99 (0.66–1.5)	-0.015	1.0 (0.70–1.5)
Morning stiffness (minutes)	>60	1.6 (0.88–2.9)	>60	1.6 (0.91–2.9)	0.485	1.2 (0.62–2.3)
Number of painful joints	0	*(ref)*	0	*(ref)*	(*ref*)	*(ref)*
	1–3	9.3 (1.1–78.2)	1–3	10.0 (1.2–83.4)	2.300	7.9 (0.91–68.6)
	4–10	4.5 (0.53–37.6)	≥4	4.5 (0.54–37.1)	1.497	5.2 (0.61–45.1)
	≥11	3.3 (0.39–28.4)				
Number of patient-reported swollen joints	0	*(ref)*	0	*(ref)*	(*ref*)	*(ref)*
	1–3	3.2 (1.6–6.4)	≥1	3.5 (1.9–6.6)	1.253	3.7 (1.9–7.0)
	4–10	3.4 (1.7–7.0)				
	≥11	4.3 (1.9–10.0)				
Difficulty with making a fist		1.6 (0.97–2.5)		1.6 (0.99–2.6)	0.467	1.4 (0.91–2.2)
Intercept		-4.8			-4.6	-4.6
AUC		0.76 (0.71–0.80)		0.75 (0.70–7.79)		0.72 (0.68–0.77)

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Variables with p-values <0.05 in univariable analysis in the derivation set were entered in multivariable regression analyses. Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

Figure 1. The Clinical Arthritis RulE (CARE) and corresponding predicted risks of the presence of inflammatory arthritis per score.

Legend:

Observed risks of current inflammatory arthritis were obtained by calculating the proportion of patients with a positive outcome (rheumatologist-confirmed synovitis) for each value of the risk score in the derivation dataset.

Figure 2. The Clinical Arthritis RulE (CARE) and presentation of the predicted probabilities of the presence of current inflammatory arthritis based on the regression model, and the simplified score as observed in the derivation and validation datasets (A), and estimated predicted probabilities in a simulation with a pre-test probability (i.e. prevalence) of inflammatory arthritis of 20% (B).

Legend:

Predicted probabilities of the final multivariable logistic regression model, fitted in the derivation set as function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates (green line)). Furthermore, for each value of the simplified score the mean predicted probability is plotted in the derivation and validation dataset (blue and orange dots).

FIGURE 3. A stylized representation of the Clinical Arthritis RulE, to be used in patients in whom GPs doubt about the presence of inflammatory arthritis.

Legend:

The web application that provides predictions on the predicted risk of inflammatory arthritis for individual patients as can be accessed at http://caretool.eu/

FIGURE 4. Flowchart of decision-making in patients with suspected early IA based on clinical characteristics and the role of the Clinical Arthritis RulE

OVERVIEW OF SUPPORTING INFORMATION

S1 Appendix. The questionnaire (in Dutch) completed by patients at the Early Arthritis *Recognition* Clinic (EA*R*C).

S2 Appendix. Frequencies of missing variables.

S3 Appendix. Frequency of synovitis at joint examination per number of visits per year.

S4 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable using backward stepwise logistic regression.

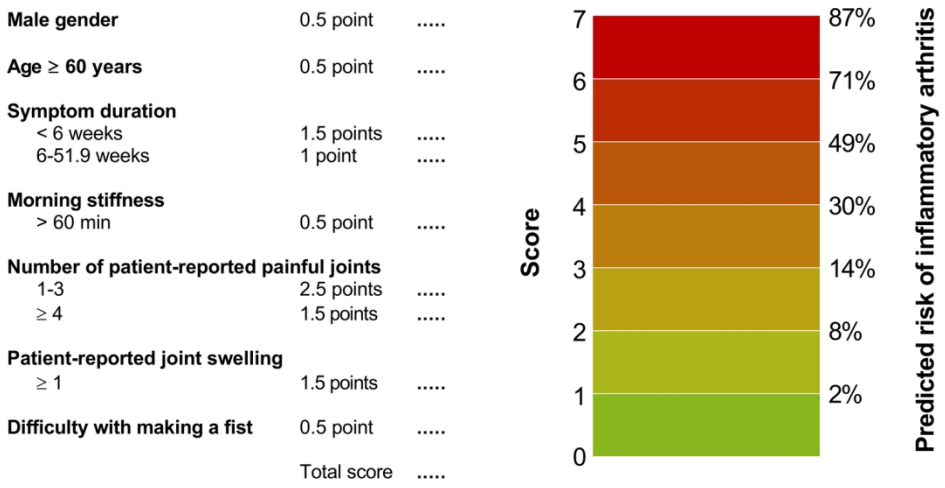
S5 Appendix. Simplified model based on the derivation dataset, with synovitis upon joint examination as dependent variable.

S6 Appendix. Calibration plot showing the observed probabilities on current inflammatory arthritis in the derivation (A) and validation dataset (B) versus the predicted probabilities according to the model.

S7 Appendix. Test characteristics of the simplified model in both the derivation and validation dataset with presence of synovitis upon joint examination as outcome.

S8 Appendix. Receiver operator characteristics curves for the logistic regression models with presence of synovitis upon joint examination as outcome, showing sensitivity and

specificity of both regression score and simplified tool score in the derivation and validation dataset.



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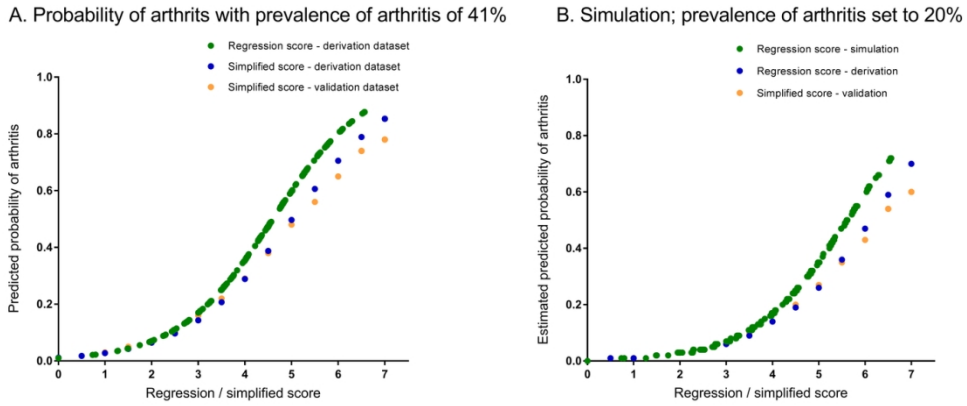
Legend:
Observed risks of current inflammatory arthritis were obtained by calculating the proportion of patients with a positive outcome (rheumatologist-confirmed synovitis) for each value of the risk score in the derivation dataset.

143x78mm (300 x 300 DPI)



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Predicted probabilities of the final multivariable logistic regression model, fitted in the derivation set as function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates (green line)). Furthermore, for each value of the simplified score the mean predicted probability is plotted in the derivation and validation dataset (blue and orange dots).

122x53mm (300 x 300 DPI)

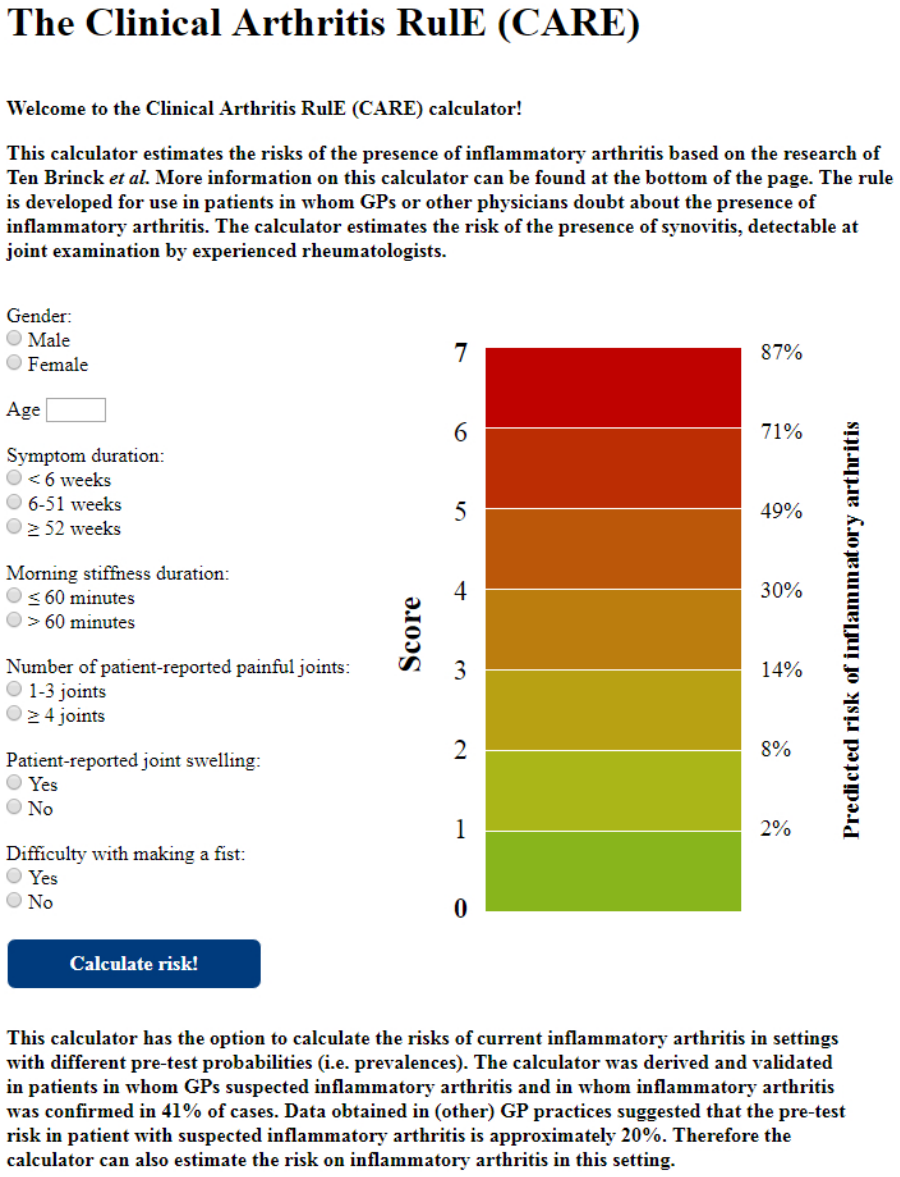


FIGURE 3. A stylized representation of the Clinical Arthritis RulE, to be used in patients in whom GPs doubt about the presence of inflammatory arthritis.

Legend:
The web application that provides predictions on the predicted risk of inflammatory arthritis for individual patients as can be accessed at http://caretool.eu/

271x330mm (72 x 72 DPI)

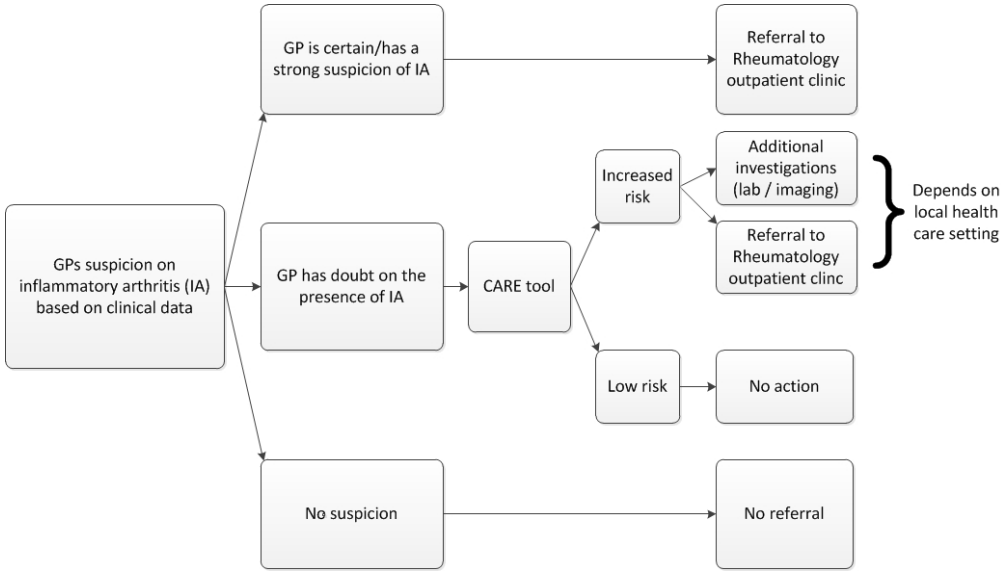


FIGURE 4. Flowchart of decision-making in patients with suspected early IA based on clinical characteristics and the role of the Clinical Arthritis RulE

274x155mm (96 x 96 DPI)

S1 Appendix. The questionnaire (in Dutch) completed by patients at the Early Arthritis Recognition Clinic (EARC).

EARC vragenlijst

U komt bij de reumatoloog aan de beurt als u deze vragenlijst heeft ingevuld.

Heeft u een **LUMC** nummer? Zo ja: wat is uw LUMC nr:

Wat is uw geboortedatum:

Wat is uw geslacht: ☐ vrouw ☐ man

Wat is de datum van uw eerste klacht?

Wat is de datum van uw eerste bezoek aan de huisarts in verband met uw gewrichtsklachten?

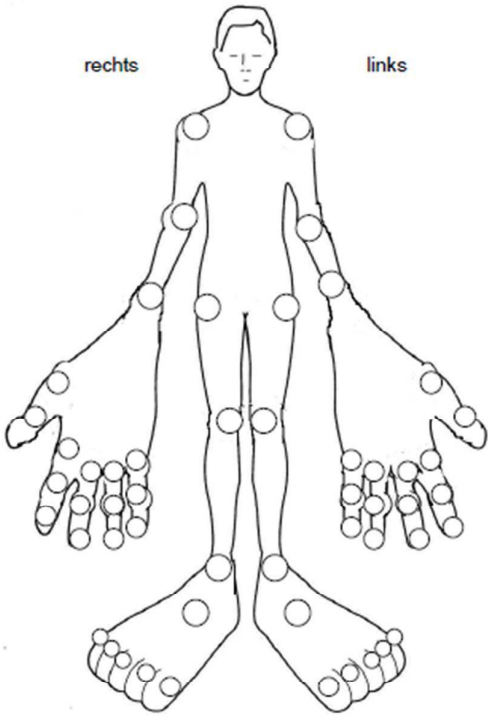
Ontstonden uw klachten plotseling of geleidelijk? (kies één van de twee) ☐ plotseling ☐ geleidelijk

Heeft u last van stijfheid als u 's morgens opstaat? ☐ nee ☐ ja; hoeveel minuten?

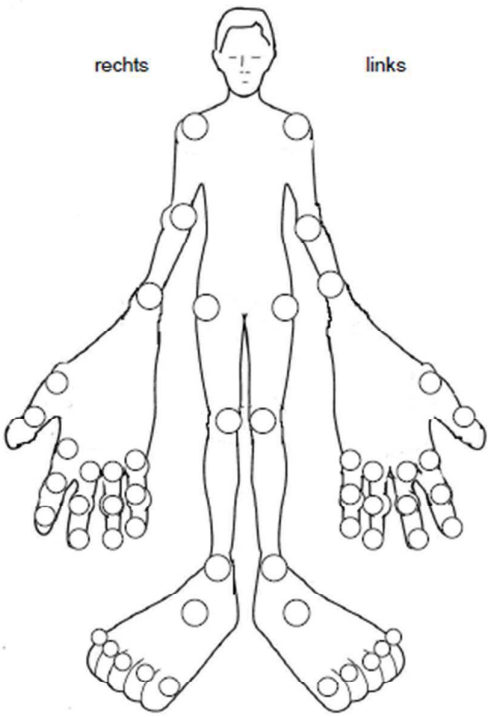
Kost het u moeite om een vuist te maken? ☐ nee ☐ ja

Wanneer heeft u de meeste last van uw gewrichtsklachten? (kies één van de twee) ☐ vroege ochtend ☐ einde van de dag

Wilt u in de pop (in de rondjes) aankruisen in welke gewrichten u **pijn** heeft?



Wilt u in de pop (in de rondjes) aankruisen welke gewrichten u **gezwollen** vindt?



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Legend:

Patients filled this questionnaire at the Early Arthritis *Recognition* Clinic, before they were seen for joint examination by a rheumatologist. This version was used from April 2012 onwards. The question on 'difficulty with making a fist' and the mannequin for 'self-reported joint swelling' were added to the questionnaire at April 1st 2012 and were not included before this date. All other questions were similar before and after April 2012.

S2 Appendix. Frequencies of missing variables.

	Derivation (N=644)	Validation (N=644)
Gender	0 (0)	0 (0)
Age	0 (0)	0 (0)
Symptom duration	48 (8)	32 (5)
Acute onset of symptoms	12 (2)	17 (3)
Morning stiffness in minutes	95 (15)	79 (12)
Number of painful joints	5 (1)	7 (1)
Number of swollen joints	234 (36)	238 (37)
Difficulty with making a fist	249 (39)	254 (39)
Arthritis present	0 (0)	0 (0)

Legend:

Variables are indicated as number of patients with missing data (percentage) unless otherwise indicated. Patient reported swollen-joint count and difficulty with making a fist were added to the questionnaire after April 1st 2012; therefore these missing data was completely at random.

S3 Appendix. Frequency of synovitis per number of visits per year.

	Nr. of visits	Arthritis present (% of visits per year)
2010 (starting from 31 August)	136	61 (45)
2011	264	103 (39)
2012	296	132 (45)
2013	252	105 (42)
2014	203	72 (36)
2015 (up to and including 24 September)	137	50 (37)
Total	**1288**	**523 (41)**

S4 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable using backward stepwise logistic regression.

Step 2.	Derivation (N=644)	
	OR (95%CI)	**B**
Male	1.7 (1.1–2.4)	0.503
Age, years		
0 – 59.9	*(ref)*	(*ref*)
≥ 60	2.1 (1.5–3.2)	0.762
Symptom duration, weeks		
< 6	3.5 (2.1–5.6)	1.246
6–51.9	2.2 (1.4–3.5)	0.783
≥ 52	*(ref)*	(*ref*)
Acute onset of complaints	*Excluded at step 1*	*N/A*
Morning stiffness >60 min	1.7 (1.0–2.7)	0.523
Number of painful joints		
0	*(ref)*	(*ref*)
1–3	10.6 (1.3–87.8)	2.361
≥ 4	4.6 (0.56–37.7)	1.527
Number of swollen joints		
0	*(ref)*	(*ref*)
≥ 1	3.1 (1.7–5.6)	1.142
Difficulty with making a fist	1.5 (1.0–2.1)	0.372

Legend:

Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

S5 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable.

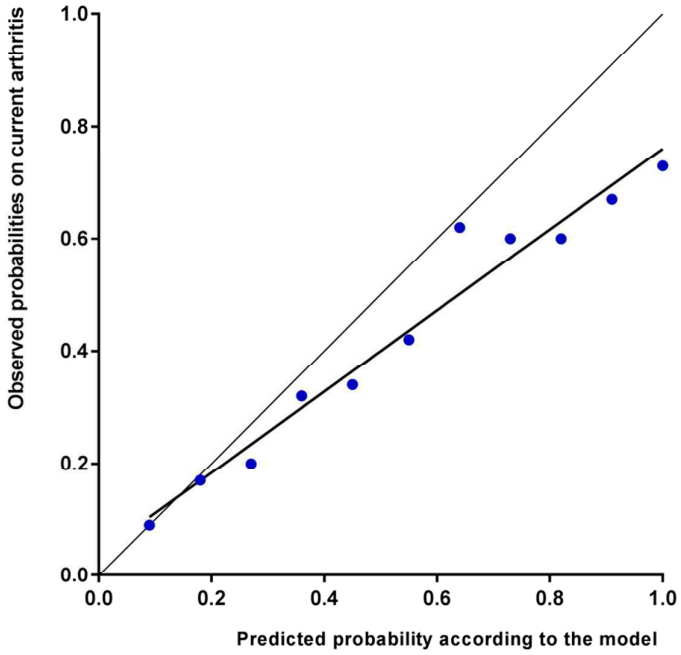
	Derivation (N=644)		
	OR (95%CI)	**B**	**points**
Male	1.7 (1.1–2.5)	0.517	0.5
Age, years			
0 – 59.9	*(ref)*	(*ref*)	0
≥ 60	2.1 (1.4–3.1)	0.750	0.5
Symptom duration, weeks			
< 6	3.6 (2.2–6.0)	1.279	1.5
6–51.9	2.2 (1.4–3.6)	0.797	1
≥ 52	*(ref)*	(*ref*)	0
Acute onset of complaints	0.99 (0.66–1.5)	-0.015	0
Morning stiffness >60 min	1.6 (0.91–2.9)	0.485	0.5
Number of painful joints			
0	*(ref)*	(*ref*)	0
1–3	10.0 (1.2–83.4)	2.300	2.5
≥ 4	4.5 (0.54–37.1)	1.497	1.5
Number of swollen joints			
0	*(ref)*	(*ref*)	0
≥ 1	3.5 (1.9–6.6)	1.253	1.5
Difficulty with making a fist	1.6 (0.99–2.6)	0.467	0.5

Legend:

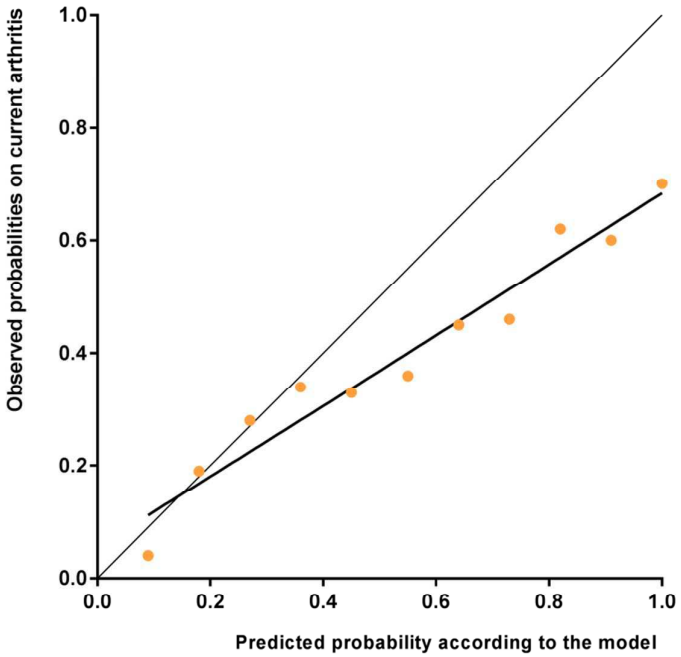
Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

S6 Appendix. Calibration plot showing the observed probabilities on current inflammatory arthritis in the derivation (A) and validation dataset (B) versus the predicted probabilities according to the model.

A.



B.



Legend:

Predicted probabilities using the final fitted multivariable model in the validation dataset were partitioned in 10 equally sized groups. In each group, the average predicted probability on inflammatory arthritis was compared with observed prevalence of inflammatory arthritis in the validation dataset. Regression lines were fitted to the calibration plot and revealed a coefficient of 0.73 and an intercept of 0.03 in the derivation dataset and a coefficient of 0.62 and an intercept of 0.061 in the validation dataset.

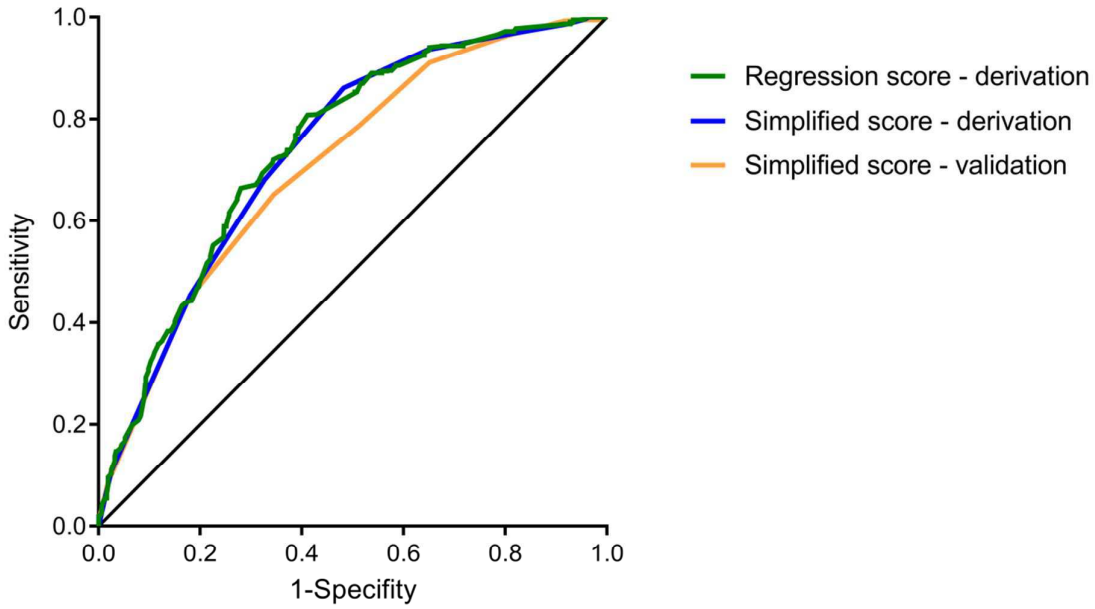
S7 Appendix. Test characteristics of the simplified model in both the derivation and validation dataset with presence of synovitis upon joint examination as outcome.

	Derivation (N=644)		Validation (N=644)	
Cut-off (≥)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
1	100	0.8		
2	99.9	3.3	99.5	1.5
3	98.7	7.7	99.3	7.8
4	93.6	35.6	90.8	35.9
4.5	85.8	52.8	78.1	50.0
5	67.6	68.0	63.9	67.0
5.5	45.0	82.7	43.5	83.4
6	23.1	92.1	21.6	92.8
7	2.5	99.4	2.1	99.7

Legend:

Sensitivity was obtained by calculating the probability that the Clinical Arthritis RulE indicated 'disease' positive among those actually identified with inflammatory by the rheumatologist. Specificity was obtained by calculating the fraction of those without inflammatory arthritis that had a negative test result on the Clinical Arthritis RulE.

S8 Appendix. Receiver operator characteristics curves for the logistic regression models with presence of synovitis upon joint examination as outcome, showing sensitivity and specificity of both regression score and simplified tool score in the derivation and validation dataset.



Legend:

The Area Under Receiver Operator Curve (AUC) for the different models was: for the regression model in the derivation dataset 0.75 (95%CI 0.70–0.79), for the simplified score in the derivation dataset 0.74 (95%CI 0.70–0.78), and for the simplified score in the validation dataset 0.71 (95%CI 0.67–0.75).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[The design of the study is described in the abstract, see Page 2; Methods and Findings]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Page 2; Methods and Findings]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Page 4-5; Introduction describes that scientific background]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 5; Introduction. "We have developed and validated a rule composed of clinical characteristics (….) which may assist in the decision-making process in patients with musculoskeletal symptoms with suspected IA at other places, in order to promote early identification of IA."]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 5–10; Methods.]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 5–7; Methods. Setting: "the Early Arthritis *Recognition* Clinic" at the "Leiden University Medical Center". Relevant dates: "All patients that visited the EARC between 2010 and September 2015 were studied." Data collection: "At the EARC, patients completed a short questionnaire about their joint symptoms, after which they were seen by an experienced rheumatologist."]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **[Page 5,6; Methods, section Study population]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 7–9; Methods, sections Data collection and Derivation and validation of the model]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Page 7–9; Methods, sections Data collection and Derivation and validation of the model]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 7; Methods, section Derivation and validation of the model.]**
Study size	10	Explain how the study size was arrived at **[Page 10; Results: "1,288 patients in whom GPs were unsure about the presence of IA visited the EARC between 2010 and 2015"]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 7–9; Methods, section Derivation and validation of the model]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		[Page 7–9; Methods, section Derivation and validation of the model]
		(*b*) Describe any methods used to examine subgroups and interactions **[N/A]**
		(*c*) Explain how missing data were addressed **[Page 7; Methods: "To prevent exclusion of patients with one or more missing variables, we imputed missing values using chained equations."]**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 10; Results: "1,288 patients in whom GPs were unsure about the presence of IA visited the EARC between 2010 and 2015"]]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 10; Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[S2 Appendix]**
Outcome data	15*	Report numbers of outcome events or summary measures **[Page 11 and S3 Appendix; "41% had synovitis at joint examination"]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Page 10–11; Table 2; Table 3]**
		(*b*) Report category boundaries when continuous variables were categorized **[Page 7–8; 10–11; Table 2; Table 3]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 12–13; Discussion]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 14–15; "A disadvantage of our setting is that the data were not collected in primary care itself, but in a setting intermediary between primary and secondary care."]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,

		multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 15–16; "In conclusion, this study developed a clinical rule that supports the identification of patients suspected of having IA by physicians that feel insufficiently experienced in assessment of synovitis by joint examination."]**
Generalizability	21	Discuss the generalizability (external validity) of the study results **[Page 15–16; "(…)We expect that our rule (Clinical Arthritis RulE - CARE) might support GPs and other health care professionals in the decision-making process in patients with musculoskeletal symptoms in whom they suspect IA, regardless of the region. (…)"]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Entered through the online submission system]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Development and validation of a clinical rule for recognition of early inflammatory arthritis

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Research Article

Development and validation of a clinical rule for recognition of early inflammatory arthritis

Short title: A clinical rule that supports identification of patients suspected of having IA

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ABSTRACT

Objectives: National and international guidelines recommend prompt referral of patients presenting with inflammatory arthritis (IA), but general practitioners (GPs) feel uncertain in their proficiency to detect synovitis through joint examination, the method of choice to identify IA. Our objective was to develop and validate a rule composed of clinical characteristics to assist GPs and other physicians in identifying IA when in doubt.

Design: Split-sample derivation and validation study.

Setting: The Leiden Early Arthritis *Recognition* Clinic (EA*R*C); a screening clinic for patients in whom GPs suspected but were unsure of the presence of IA.

Participants: 1,288 consecutive patients visiting the EA*R*C .

Primary and secondary outcome measures: Associations of clinical characteristics with presence of IA were determined using logistic regression in 644 patients, while validating the results in the other 644 patients (split-sample validation). To facilitate application in clinical practice, a simplified rule (with scores ranging 0 to 7.5) was derived and validated.

Results: IA was identified by a rheumatologist in 41% of patients. In univariable analysis, male gender, age ≥60 years, symptom duration <6 weeks, morning stiffness >60 minutes, a low number of painful joints (1-3 joints), presence of patient-reported joint swelling, and difficulty with making a fist were associated with IA in the derivation dataset. Using multivariable analysis, a simplified rule consisting of these seven items was derived and validated, yielding an Area Under the Receiver Operator Characteristic curve (AUC) of 0.74 (95%CI 0.70-0.78) in the derivation dataset. Validation yielded an AUC of 0.71 (95%CI 0.67-0.75). Finally, the model was repeated to study predicted probabilities with a lower prevalence of inflammatory arthritis to simulate performance in primary care settings.

Conclusions: Our rule, composed of clinical parameters, had reasonable discriminative ability for IA and could assist physicians in decision-making in patients with suspected IA, increasing appropriateness of health care utilization.

KEYWORDS:

Inflammatory Arthritis, General Practitioners, Early Recognition, Clinical Decision Rule, Rheumatoid Arthritis

Strengths and limitations of this study

- A clinical rule could help to select patients to refer for additional investigations (laboratory or imaging) or to secondary care. This could promote early identification of inflammatory arthritis and increase appropriateness of health care utilization.
- Data were collected prospectively in a population of patients in which general practitioners had doubt on the presence of inflammatory arthritis.
- The main limitation is that data were not collected in primary care itself, but in a setting intermediary between primary and secondary care. Further external validation in GP settings is therefore required.

BACKGROUND

Early initiation of disease modifying anti-rheumatic drugs is strongly associated with improved outcomes of rheumatoid arthritis (RA).[1] National and international guidelines attempt to facilitate this by emphasizing prompt referral of patients presenting with inflammatory arthritis (IA) to a rheumatologist. The European League Against Rheumatism (EULAR) taskforce for the management of early IA recommends referral within 6 weeks of onset of symptoms[2], while in the United Kingdom (UK) the National Institute for Health and Care Excellence (NICE) guidelines advises referral to a rheumatologist in patients with new, persistent (>3–4 weeks) synovitis within three working days.[3] However, it was demonstrated that this referral timeline is achieved in only 17% of patients.[4] On average, RA patients are seen four (and sometimes more than eight) times by general practitioners (GPs) before they refer to secondary care[5-8], which may reflect the difficulty of differentiating patients with early IA from patients with other types of common musculoskeletal symptoms. A recent qualitative study revealed that GPs acknowledge the importance of early detection and referral, but feel uncertain in their proficiency to detect synovitis through joint examination, the method of choice to identify IA.[2,9] As a consequence, the referral to a rheumatologist may be delayed, which contributes to overall treatment delay in early RA, as observed in Europe.[10,11]

This is further complicated by the high incidence of consultations for various common musculoskeletal symptoms and the low incidence of early IA in primary care.[12] The consultation prevalence of any musculoskeletal symptom in primary care in the UK approximates 2405 per 10,000 per year [13], making it the most common organ system consulted for at GP practices.[12-14] Although musculoskeletal symptoms are common, GPs

suspect IA (based on pattern recognition) in only a very small minority of patients.[5] In these patients, GPs often lack confidence in joint assessment for synovitis.

To support early detection, several initiatives have been developed, including triage systems. The best studied triage system (the Early Inflammatory Arthritis Questionnaire) was developed and validated for patients attending secondary and tertiary care.[15-17] Furthermore, several referral guidelines for GPs[6,18-22], and public awareness campaigns have been developed, for instance one attempting to simplify pattern recognition to the "S-Factor": Stiffness, Swelling, Squeezing. However, none of these initiatives were designed using primary care data, and all assume that GPs can differentiate between the presence and absence of joint swelling[6,18-20], which continues to be a barrier to the early detection of IA.

Altogether there is a contradiction with the need to refer as quickly as possible while evidence who must be referred or, in line with this, in whom additional investigations are appropriate is lacking. To solve the issue, we have developed and validated a rule composed of clinical characteristics, by taking advantage of data from a setting intermediate between primary and secondary care. This intermediate setting of an the Early Arthritis *Recognition* Clinic was a local solution to promote early referrals and is not easy implementable in other regions. The clinical rule derived from these data however, is easy to apply and may assist in the decision-making process in patients with musculoskeletal symptoms with suspected IA at other places, in order to promote early identification of IA.

METHODS

Study population

To promote early recognition of early IA, the Early Arthritis *Recognition* Clinic (EA*R*C) was initiated in September 2010 in Leiden, the Netherlands. The outpatient clinic of the department of Rheumatology of the Leiden University Medical Centre (LUMC) is the only referral centre in a healthcare region of ~400,000 people. GPs were instructed to refer patients to the EA*R*C in whom they were unsure about the presence of IA (instead of a 'wait-and-see' approach or performing additional tests). The EA*R*C system has reduced referral delay from 8 to 2 weeks, and improved early identification of IA.[11,23] To emphasize the importance of early identification of IA and aiming to inform on the purpose of the EA*R*C, a region-wide educational campaign was conducted among regional GPs.

In addition to (and distinct from) the EA*R*C, the LUMC also has an Early Arthritis Clinic (EAC). The EAC was established in 1993 to include and follow patients with early arthritis and to offer the possibility of rapid access to rheumatology care, usually within a week of referral. To differentiate between the clinics, GPs were instructed to refer to the EAC if there was a clear synovitis or very high suspicion of IA (i.e. to continue as they had before, since there was no benefit for such patients to go the EA*R*C first) and to refer to the EA*R*C when in doubt about the presence of IA (i.e. to not 'wait-and-see' or order additional tests). Thus, patients included in this study represent the difficult group in whom GPs were uncertain of the presence of suspected IA; patients with a very high degree of suspicion were referred directly to the EAC.

The EA*R*C screening clinic was held twice a week between 2010–2014 and once a week from 2014 onwards. After GP referral, patients can visit the EA*R*C without an appointment. All patients that visited the EA*R*C between 2010 and September 2015 were studied.

Data collection

At the EA*R*C, patients completed a short questionnaire about their joint symptoms, after which they were seen by an experienced rheumatologist (AvdHvM or other senior rheumatologists) who performed a full 66-joint examination. If synovitis was determined by physical examination, patients were fast-tracked to visit the EAC within 1 week for further evaluation and treatment. Patients without IA were discharged to primary care. The questionnaire completed by patients, provided in S1 Appendix, contained questions on age, gender, date of symptom onset, date of first visit to GP, presence of a (sub)acute symptom onset (versus a gradual symptom-onset), morning stiffness (duration in minutes), which part of the day symptoms were worst, and whether they had difficulty with making a fist. Patients were asked to indicate on a 52-joint mannequin which joints were painful and which joints they considered to be swollen. IA, defined as synovitis confirmed by the rheumatologist at physical examination, was used as outcome.

Collected data was anonymized and entered in a research database at chronological order of visiting the EA*R*C. The local medical ethical committee approved this study.

Derivation and validation of the model

We used half of the dataset for derivation and the other half for validation of results (split-sample validation). To prevent bias by (unknown) effects of inclusion period, patients with odd ID-numbers (1,3,etc) were included in the derivation dataset and those with even ID-numbers (2,4,etc) were used for validation.

To prevent exclusion of patients with one or more missing variables, we imputed missing values using chained equations[24]; frequencies of missing variables are presented in S2 Appendix. The variables 'difficulty with making a fist' and 'self-reported joint swelling' were most frequently missing as these were added to the questionnaire after April 1st 2012, thus absence of these data was considered to occur completely at random.

We conducted logistic regression analysis modelling with presence of IA (defined as rheumatologist-confirmed synovitis on physical examination) as dependent variable. Continuous variables were categorized using clinically relevant cut-offs: age: <40 / 40–59.9 / ≥60 years; duration of symptoms: <6 / 6–11 / 12–51.9 / ≥52 weeks; duration of morning stiffness: ≤60 / >60 minutes; number of painful joints: 0 / 1–3 / 4–10 / ≥11; number of swollen joints: 0 / 1–3 / 4–10 / ≥11. We performed univariable logistic regression to evaluate associations between dependent variables and presence of IA. Variables with p-values <0.05 in univariable analyses were entered in multivariable regression analyses (enter model) to obtain a model with a small number of variables. If several categories within a variable had similar regression coefficients in multivariable modelling, we pooled these categories and repeated the analysis. In sub-analysis, we also performed a multivariable logistic regression model with the pooled categories using backward selection.

To obtain a simplified rule applicable in daily care, we rounded the regression coefficients of the final multivariable logistic regression model to the nearest 0.5 (irrespective of p-value). This resulted in an easily calculable risk score. For each value of the risk score, we determined test characteristics (i.e. sensitivity and specificity) and predicted probabilities of the presence of inflammatory arthritis.

We evaluated the overall discriminative ability of the models using the Area Under the Receiver Operating Characteristic curve (AUC). The model's calibration was assessed by generating a calibration plot to measure goodness of fit, where the data was partitioned in 10 equally sized groups based on the predicted probabilities using the final fitted multivariable model. In each group, the average predicted probability on current IA was compared with the observed prevalence, both in the derivation and validation dataset. Additionally, the Hosmer-Lemeshow statistic was calculated.

To estimate performance of our simplified rule in a setting with a different prevalence of IA (e.g. primary care), a simulation was performed. Accurate data on prevalence of IA in GP practices is lacking, and therefore an estimation was made based on previous literature. One study revealed that 27% assigned with the International Classification of Primary Care-1 code for suspected IA in their medical record had confirmed RA (n=38), polyarthritis (n=5), or oligoarthritis (n=8) following rheumatologist's assessment. Another study among GPs found that 18% of patients with suspected IA was referred; though data on rheumatologists' diagnoses was not provided.[25] Guided by these scarce data obtained in GP practices, performance of the model was simulated with an estimated prevalence of 20%.[5] The intercept of the regression model was adjusted as described in [26,27] and we plotted average estimated predicted probabilities against the regression and simplified risk score.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 23.0). P-values <0.05 were considered significant.

Patient involvement

Patient research partners agreed with the pathway of care at the EA*R*C. They also provided feedback on the questionnaire, which was expanded in 2012 with two questions.

RESULTS

Patients

1,288 patients in whom GPs were unsure about the presence of IA visited the EA*R*C between 2010 and 2015; of these, 41% had synovitis at joint examination. The frequency of inflammatory arthritis was stable throughout the study years (S3 Appendix). Baseline characteristics of patients in both derivation and validation dataset are presented in Table 1.

Model derivation

In univariable analyses, male gender, age ≥60 years, symptom duration of <6 weeks, an acute onset of symptoms, morning stiffness >60 minutes, a low number of painful joints (1–3 joints), presence of patient-reported joint swelling (1–3 joints), and difficulty with making a fist were associated with the presence of IA in the derivation dataset (Table 2). 'Symptoms worst in the early morning' was not associated with IA and therefore not included in multivariable analysis. Two multivariable models were created with categorized variables; first a model with categories similar to the univariable analysis (Table 3, model 1), and secondly a model pooling categories per variable with similar regression coefficients (Table 3, model 2). Performing this second model in the derivation dataset revealed that male gender, age ≥60 years, symptom duration of <6 weeks, a low number of painful joints (1–3 joints), and presence of patient-reported joint swelling were independently associated with the presence of IA (Table 3). The AUC of model 2 was 0.75 (95%CI 0.70–0.79) in the

derivation dataset. In sub-analysis, model 2 was repeated with a backward selection procedure, showing similar regression coefficients (S4 Appendix).

Generation of a simplified rule

In order to facilitate usage in routine clinical practice, a simplified model was generated (S5 Appendix). The obtained regression coefficient of acute onset of symptoms in multivariable modelling was -0.015, yielding 0 points. Also after exclusion of this variable, the regression coefficients of the other seven variables in the model did not change yielding similar points. This resulted in a simplified rule consisting of seven scored items and a total score ranging from 0 to 7.5 with corresponding predicted risks (Figure 1). Risks of IA predicted by the model as a function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates) are presented in Figure 2A; as shown, simplification did not majorly affect the predicted risks. The calibration plot shows that predicted probabilities correlated well with the observed proportions of patients with IA (S6 Appendix). The Hosmer-Lemeshow test for the derivation dataset yielded a P-value of 0.36. If cut-offs are required and a highly sensitive approach is preferred (>90% sensitivity), this is obtained by a cut-off score of ≥4. When a highly specific approach is preferred (>90% specificity), this is obtained by a cut-off score of ≥6. Test characteristics for all cut-off points are presented in S7 Appendix. The AUC of the simplified score, measuring discrimination, was 0.74 (95%CI 0.70–0.78; S8 Appendix).

Validation

The final multivariable model (model 2) was applied in the validation dataset, revealing similar results (Table 3). The AUC was 0.72 (95%CI 0.68–0.77). Figure 2A shows the predicted probabilities of the simplified rule are almost similar to those obtained in the

derivation data. The AUC of the simplified rule was 0.71 (95%CI 0.67–0.75) in the validation dataset. The calibration plot is shown in S6 Appendix, the Hosmer-Lemeshow test for the validation dataset yielded a P-value of 0.43.

Simulation of accuracy in a setting with a lower prevalence of IA

In contrast to test characteristics, predicted probabilities depend on the prior risk (i.e. prevalence) of IA. The frequency of IA among primary care patients with GP-determined clinical suspicion of IA may be different than that observed in the EA*R*C. Based on observations in GP practices[5,25], a simulation was run for the regression and simplified score with a prevalence of inflammatory arthritis set at 20%. Estimated predicted probabilities for different scores of the multivariable model and simplified rule (in derivation and validation datasets) are presented in Figure 2B.

Our simplified rule was implemented in a web application that provides predictions on the presence of current IA for individual patients; a screenshot is presented in Figure 3. The web application is accessible online at http://caretool.eu/

DISCUSSION

GPs play a crucial role in the early identification of RA and often lack confidence in detecting joint synovitis.[9] In an attempt to solve the contradiction between the need to refer very early and absence of evidence who must be referred, we provided an evidence-based and simple method to identify the presence of IA in patients in whom IA is suspected. This clinical rule helps to select patients to refer for additional investigations (laboratory or

imaging) or to secondary care. Hence, the Clinical Arthritis RulE could increase appropriateness of health care utilization.

This study is different from studies that derived tools to facilitate triage of patients that have been referred to secondary or tertiary care[15-17] as our study did not aim to prioritize patients that are already referred. In addition, we aimed to facilitate recognition of IA (as this would necessitate prompt referral to a rheumatologist) and did not perform a longitudinal study to predict development of specific diagnoses (e.g. RA) later-on. This explains why several factors were found to be associated with presence of IA that are not generally considered typical for RA (male gender, a low number of painful joints, a short symptom duration). GPs generally do well in identifying those at high risk for development of RA (i.e. women with subacute smouldering polyarticular, symmetric complaints), and therefore we aimed this tool to assist GPs in decision-making for more atypical or non-classical presentations of IA (e.g. due to overlap of symptoms with other diagnoses) leading to doubt. Indeed, many of the patients that did not have synovitis at the EA*R*C had symptoms due to diagnoses that are characterized by longstanding or extensive joint pain (e.g. osteoarthritis, fibromyalgia), explaining higher scores for a short symptom duration or a low number of symptomatic joints.

Adding other clinical variables might increase the discriminative ability of the model. Potential examples include the squeeze test of the metacarpophalangeal joints (although the diagnostic accuracy was shown to be only moderate[28]), information on family history, or functional impairments. These items were not routinely collected before December 2015. Adding data on laboratory investigations to our rule could potentially also increase its

discriminative ability. However, our data do not permit us to evaluate this, as additional investigations were done afterwards and only in patients with synovitis at joint examination.

A strength of our EA*R*C for the purpose of this study is that GPs in our region are familiar with the need for early referral and that regional healthcare logistics make rheumatology care rapidly available for patients with arthritis, with the EA*R*C as ultimate service for patients in whom GPs suspect (but are unsure about) IA. With the availability of the EA*R*C every week and lack of any waiting list for the EA*R*C, we assume a low number of patients not showing up at the EA*R*C despite being encouraged by their GP to visit the EA*R*C. As the EA*R*C serves as a unique bridge between primary and secondary care, its patients closely resemble the population GPs have contact with and have doubts about. Although the EA*R*C is successful in our region[11,23], this approach may be more difficult to implement in other centres or regions due to a shortage of rheumatologists, or long traveling distances to rheumatology outpatient clinics, and as such a different system is needed to aid GPs in identifying IA. This prompted us to derive a validated rule composed of clinical characteristics that could assist GPs in decision-making for more atypical or non-classical (but nevertheless suspect) presentations of IA, as classical presentations usually don't cause GPs concern.

GPs were discouraged (both by our local communication with GPs and according to national guidelines for GPs) to perform autoantibody testing.[29] Autoantibody testing in primary care in this region was infrequent[5], unlike in other parts of the world. Autoantibody testing may falsely reassure doctors and patients, especially when results are negative, and as such we believe a model based on clinical presentation is more appropriate to facilitate rapid referral. Another strength is that we studied patients in whom the GPs have indicated a lack of confidence to identify the presence of synovitis. Patients with clinically obvious IA had early

access to rheumatologic care already. This may enhance the generalizability of the present data to the setting of doubt in primary care. Furthermore, the use of real-life observational data in our study may boost external validity of the results.

A disadvantage of our setting is that the data were not collected in primary care itself, but in a setting intermediary between primary and secondary care. Although musculoskeletal symptoms are a very common reason for consulting primary care, suspected IA is relatively unusual, and the average full-time GP diagnoses only one new patient with RA each year.[30] Additionally, although the EA*R*C is easily accessible on a weekly basis, the exact number of patients that were referred but did not visit the EA*R*C is unknown. Validation in primary care is required. We studied 'the difficult group' of patients in whom GPs were uncertain of the presence of suspected IA. The prevalence of such patients in primary care may be higher and as a consequence the actual prevalence of IA among suspected IA patients may be lower than 41% in primary care. Since the post-test probabilities strongly depend on the prevalence (i.e. pre-test probability), a simulation was performed with an estimated prevalence of IA that was half of the prevalence as observed in our data (20%). The choice of 20% was based on literature from primary care; although not much is known about suspected IA in primary care, two study suggested a prevalence of IA among suspected patients of 18-27%[5, 25]. We demonstrated the predictive accuracy of the model using a simulated prevalence of 20%. Because of the limitation that no other data are available on the prevalence of IA when GPs suspect IA, this estimated prevalence could be an overestimation. However, the observed data could also be an underestimation as in our setting GPs were instructed to refer patients with high suspicion/definite arthritis to the regular outpatient clinic. Further external validation in GP settings is therefore required.

GPs in our region are well informed about the importance of the early detection of IA, but the GPs in our region feel that their actual detection skills are not different from that of GPs elsewhere. However if the detection skills of our GPs are different from that of GPs in other regions, a lower prevalence of IA (and therefore lower pre-test probabilities) may be present. As a consequence, the rule may yield lower post-test probabilities. This effect may have been dealt with in the simulation analysis but still external validation in primary care and preferably in different regions or countries is necessary.

We expect that our rule (Clinical Arthritis RulE - CARE) might support GPs and other health care professionals in the decision-making process in patients with musculoskeletal symptoms in whom they suspect IA, regardless of the region. Of course, the consequences of an increased score will likely depend on the setting and relation with secondary care: it can either influence the decision to directly refer a patient or to first ask for additional laboratory tests (e.g. acute phase reactants or autoantibodies; Figure 4). A clinical decision aid may be of value to this end as well, as for most laboratory investigations the diagnostic accuracy depends on the prior risk. Using a simple clinical decision aid first may be more cost-effective than performing additional investigations in all patients in whom there is doubt about IA. Depending on the setting and consequences of a high score, either a sensitive method or a specific method may be preferred; for this reason cut-offs for both situations are provided. The web application, also easily assessable by phone, facilitates implementation of the Clinical Arthritis RulE by GPs, physicians, and other health care professionals such as physiotherapists in their daily work.

CONCLUSION

In conclusion, this study developed a clinical rule that supports the identification of patients suspected of having IA by physicians that feel insufficiently experienced in assessment of synovitis by joint examination. We hope the current data are a prelude to a data-driven method that supports GPs, physicians, and other health care professionals in decision-making in patients with suspected early IA.

LIST OF ABBREVATIONS

AUC = Area Ander the Curve

CARE = Clinical Arthritis Rule

EAC = Early Arthritis Clinic

EA*R*C = Early Arthritis Recognition Clinic

GPs = General Practitioners

IA = Inflammatory Arthritis

LUMC = Leiden University Medical Centre

MCP = Metacarpophalangeal

NICE = National Institute for Health and Care Excellence

RA = Rheumatoid Arthritis

UK = United Kingdom

DECLARATIONS

Ethics approval and consent to participate

The medical ethical committee of the Leiden University Medical Centre ("Commissie Medische Ethiek") approved the study.

Consent for publication

Not applicable.

Availability of data and material

The calculator presented in this paper is available online at http://caretool.eu. Statistical code and dataset are available from R.M. ten Brinck (e-mail; r.m.ten_brinck@lumc.nl) at reasonable request.

Competing interests

The authors declare that they have no competing interests. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work. The disclosure forms are available at request.

Patient consent

Obtained.

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Authors' contributions

RtB, BvD, and AvdHvM designed the study. RtB, BvD, and SlC conducted the statistical analysis. RtB, BvD and AvdHvM conducted the literature search and wrote the article. RtB, BvD, HvS, SlC, MN, SH, CM and AvdHvM contributed intellectually to the writing or revising of the manuscript, and approved the final version.

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Table 1. Characteristics of patients visiting the Early Arthritis *Recognition* Clinic

	Derivation (N=644)	Validation (N=644)	P-value**
Male, n (%)	190 (30)	198 (31)	0.62
Age in years, mean ± SD	52 ± 16	51 ± 17	0.27
Symptom duration in weeks, median (IQR)	10 (3–45)	12 (4–45)	0.18
Acute onset of symptoms *, n (%)	252 (39)	238 (37)	0.45
Symptoms worst in the early morning, n (%)	372 (58)	351 (55)	0.10
Morning stiffness in minutes, median (IQR)	10 (0–30)	10 (0–30)	0.33
Number of painful joints, median (IQR)	7 (2–15)	6 (3–15)	0.69
Number patient-reported swollen joints, median (IQR)	2 (1–5)	2 (1–5)	0.19
Difficulty with making a fist, n (%)	329 (51)	301 (47)	0.06
Arthritis present at joint examination by experienced rheumatologist, n (%)	271 (42)	252 (39)	0.28

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Abbreviations: IQR = interquartile range; SD = standard deviation. ** Unpaired t-tests, chi-squared tests and Mann-Whitney U tests were used as appropriate.

Table 2. Univariable logistic regression in the derivation dataset with presence of synovitis upon joint examination as outcome.

		Arthritis (N=271)	No arthritis (N=373)	OR (95% CI)
Male, n (%)		104 (38)	86 (23)	2.1 (1.5–2.9)
Age, n (%)	<40	49 (18)	104 (28)	*(ref)*
	40–59.9	109 (40)	172 (46)	1.3 (0.89–2.0)
	≥60	113 (42)	97 (26)	2.5 (1.6–3.8)
Symptom duration in weeks, n (%)	<6	124 (46)	103 (28)	3.8 (2.4–5.9)
	6–11	38 (14)	62 (17)	1.9 (1.1–3.9)
	12–51.9	66 (24)	75 (20)	2.7 (1.7–4.5)
	≥52	43 (16)	132 (36)	*(ref)*
Acute onset of symptoms *, n (%)		122 (45)	131 (35)	1.5 (1.1–2.1)
Symptoms worst in early morning, n (%)		158 (58)	214 (57)	1.1 (0.69–1.6)
Morning stiffness >60 min, n (%)		45 (17)	40 (11)	1.7 (1.03–2.7)
Number of painful joints, n (%)	0	1 (0)	10 (3)	*(ref)*
	1–3	110 (41)	82 (22)	13.2 (1.7–105.5)
	4–10	76 (28)	123 (33)	6.1 (0.77–49.0)
	≥11	84 (31)	158 (42)	5.2 (0.65–41.3)
Number of patient-reported swollen joints, n (%)	0	18 (7)	71 (19)	*(ref)*
	1–3	115 (42)	119 (32)	3.7 (2.0–6.9)
	4–10	87 (32)	115 (31)	2.9 (1.5–5.5)
	≥11	51 (19)	68 (18)	2.9 (1.4–5.9)
Difficulty with making a fist, n (%)		156 (58)	172 (46)	1.6 (1.1–2.4)

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Abbreviations: CI = confidence interval; OR = odds ratio.

Table 3. Multivariable logistic regression analyses with synovitis upon joint examination as outcome. Model 1 includes categories of clinically applicable cut-offs; if within variables several categories had similar regression coefficients, categories were pooled (Model 2).

		Model 1		Model 2		
		Derivation		**Derivation**		**Validation**
			OR (95% CI)		**OR (95% CI)**	**B**	**OR (95% CI)**
Male			1.7 (1.1–2.5)		1.7 (1.1–2.5)	0.517	1.7 (1.1–2.4)
Age (years)	<40	*(ref)*	0–59.9	*(ref)*	(*ref*)	*(ref)*
	40–59.9	1.5 (0.96–2.5)	≥60	2.1 (1.4–3.1)	0.750	2.1 (1.5–3.0)
	≥60	2.9 (1.7–4.8)				
Symptom duration (weeks)	<6	3.8 (2.3–6.4)	<6	3.6 (2.2–6.0)	1.279	3.4 (2.0–5.7)
	6–11	1.7 (0.92–3.1)	6–51.9	2.2 (1.4–3.6)	0.797	1.9 (1.2–3.0)
	12–51.9	2.9 (1.7–5.0)	≥52	*(ref)*	(*ref*)	*(ref)*
	≥52	*(ref)*				
Acute onset of symptoms*			1.0 (0.67–1.5)		0.99 (0.66–1.5)	-0.015	1.0 (0.70–1.5)
Morning stiffness (minutes)	>60	1.6 (0.88–2.9)	>60	1.6 (0.91–2.9)	0.485	1.2 (0.62–2.3)
Number of painful joints	0	*(ref)*	0	*(ref)*	(*ref*)	*(ref)*
	1–3	9.3 (1.1–78.2)	1–3	10.0 (1.2–83.4)	2.300	7.9 (0.91–68.6)
	4–10	4.5 (0.53–37.6)	≥4	4.5 (0.54–37.1)	1.497	5.2 (0.61–45.1)
	≥11	3.3 (0.39–28.4)				
Number of patient-reported swollen joints	0	*(ref)*	0	*(ref)*	(*ref*)	*(ref)*
	1–3	3.2 (1.6–6.4)	≥1	3.5 (1.9–6.6)	1.253	3.7 (1.9–7.0)
	4–10	3.4 (1.7–7.0)				
	≥11	4.3 (1.9–10.0)				
Difficulty with making a fist			1.6 (0.97–2.5)		1.6 (0.99–2.6)	0.467	1.4 (0.91–2.2)
Intercept			-4.8			-4.6	-4.6
AUC			0.76 (0.71–0.80)		0.75 (0.70–7.79)		0.72 (0.68–0.77)

Legend:

* Patients were asked to define onset of symptoms; either acute onset of symptoms or gradual onset of symptoms, see S1 Appendix. Variables with p-values <0.05 in univariable analysis in the derivation set were entered in multivariable regression analyses. Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

Figure 1. The Clinical Arthritis RulE (CARE) and corresponding predicted risks of the presence of inflammatory arthritis per score.

Legend:

Observed risks of current inflammatory arthritis were obtained by calculating the proportion of patients with a positive outcome (rheumatologist-confirmed synovitis) for each value of the risk score in the derivation dataset.

Figure 2. The Clinical Arthritis RulE (CARE) and presentation of the predicted probabilities of the presence of current inflammatory arthritis based on the regression model, and the simplified score as observed in the derivation and validation datasets (A), and estimated predicted probabilities in a simulation with a pre-test probability (i.e. prevalence) of inflammatory arthritis of 20% (B).

Legend:

Predicted probabilities of the final multivariable logistic regression model, fitted in the derivation set as function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates (green line)). Furthermore, for each value of the simplified score the mean predicted probability is plotted in the derivation and validation dataset (blue and orange dots).

FIGURE 3. A stylized representation of the Clinical Arthritis RulE, to be used in patients in whom GPs doubt about the presence of inflammatory arthritis.

Legend:

The web application that provides predictions on the predicted risk of inflammatory arthritis for individual patients as can be accessed at http://caretool.eu/

FIGURE 4. Flowchart of decision-making in patients with suspected early IA based on clinical characteristics and the role of the Clinical Arthritis RulE

OVERVIEW OF SUPPORTING INFORMATION

S1 Appendix. The questionnaire (in Dutch) completed by patients at the Early Arthritis *Recognition* Clinic (EA*R*C).

S2 Appendix. Frequencies of missing variables.

S3 Appendix. Frequency of synovitis at joint examination per number of visits per year.

S4 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable using backward stepwise logistic regression.

S5 Appendix. Simplified model based on the derivation dataset, with synovitis upon joint examination as dependent variable.

S6 Appendix. Calibration plot showing the observed probabilities on current inflammatory arthritis in the derivation (A) and validation dataset (B) versus the predicted probabilities according to the model.

S7 Appendix. Test characteristics of the simplified model in both the derivation and validation dataset with presence of synovitis upon joint examination as outcome.

S8 Appendix. Receiver operator characteristics curves for the logistic regression models with presence of synovitis upon joint examination as outcome, showing sensitivity and

specificity of both regression score and simplified tool score in the derivation and validation dataset.

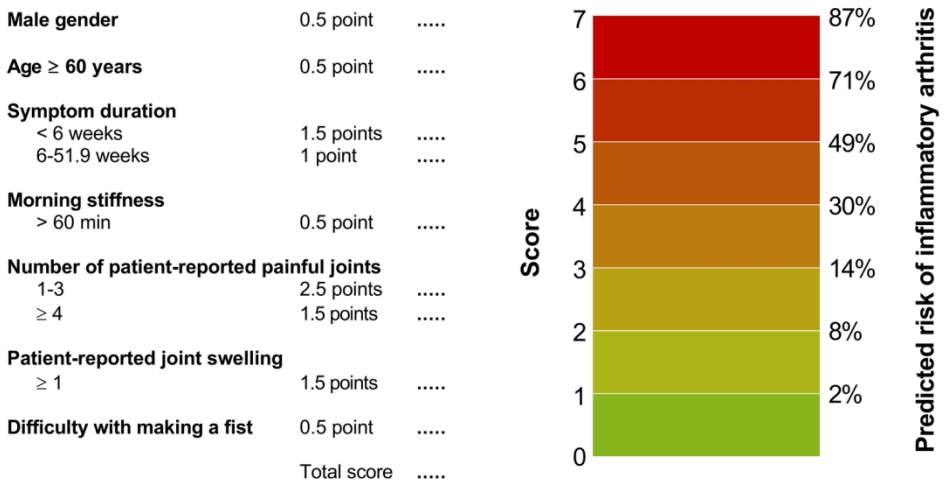
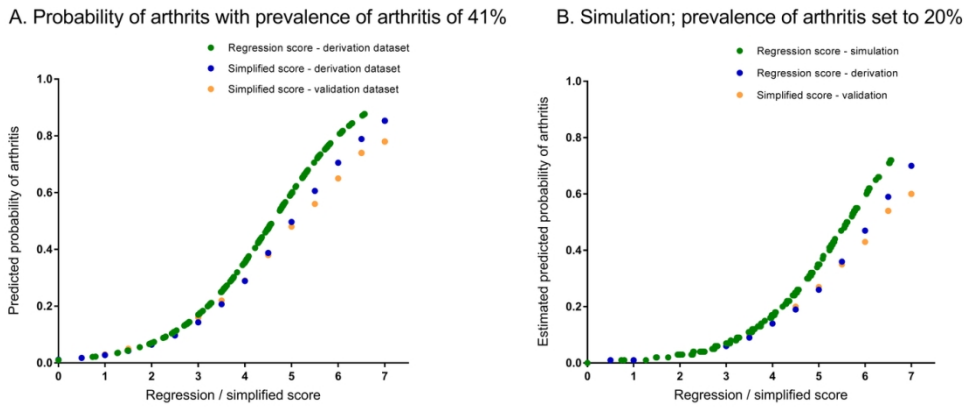


Figure 1. The Clinical Arthritis RulE (CARE) and corresponding predicted risks of the presence of inflammatory arthritis per score.

Legend:
Observed risks of current inflammatory arthritis were obtained by calculating the proportion of patients with a positive outcome (rheumatologist-confirmed synovitis) for each value of the risk score in the derivation dataset.

143x78mm (300 x 300 DPI)



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Legend:
Predicted probabilities of the final multivariable logistic regression model, fitted in the derivation set as function of the regression score (i.e. the sum of the regression coefficients times the value of the corresponding covariates (green line)). Furthermore, for each value of the simplified score the mean predicted probability is plotted in the derivation and validation dataset (blue and orange dots).

122x53mm (300 x 300 DPI)

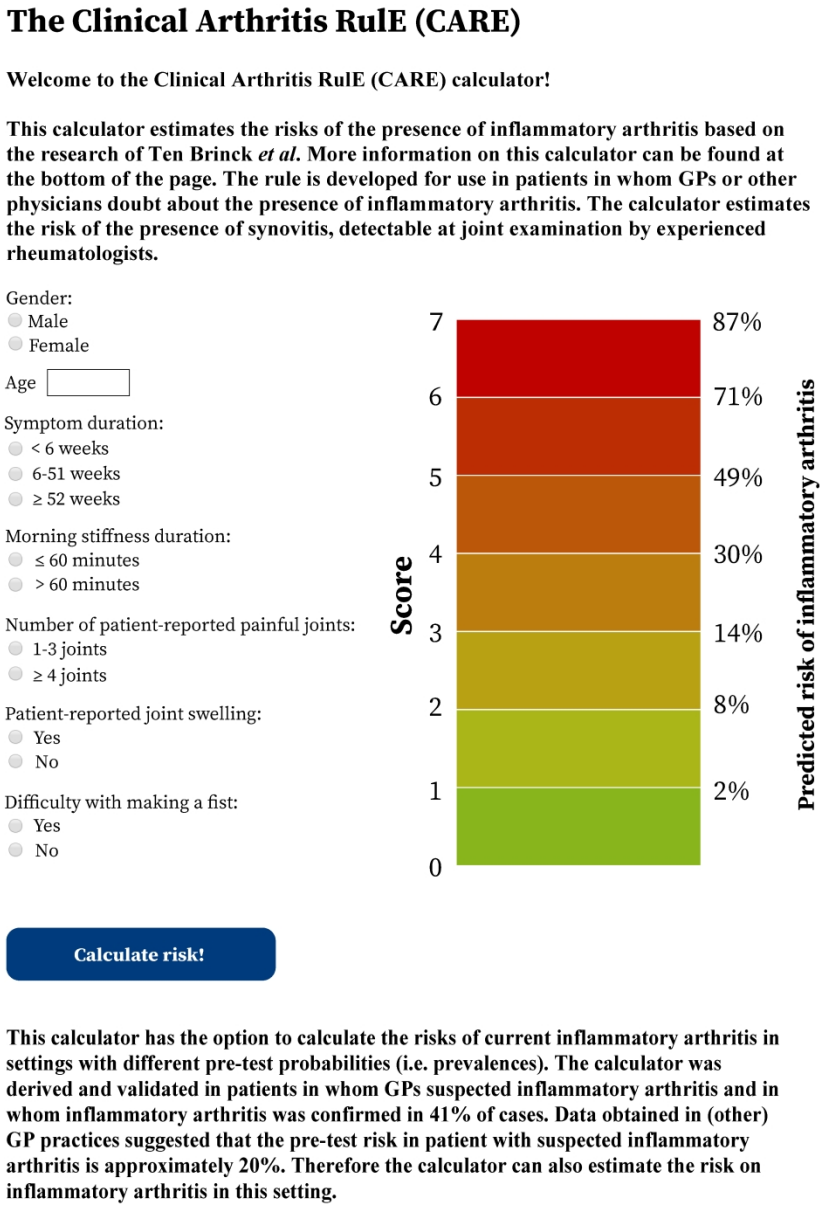


Figure 3. A stylized representation of the Clinical Arthritis RulE, to be used in patients in whom GPs doubt about the presence of inflammatory arthritis.

Legend:
The web application that provides predictions on the predicted risk of inflammatory arthritis for individual patients as can be accessed at http://caretool.eu/

263x386mm (300 x 300 DPI)

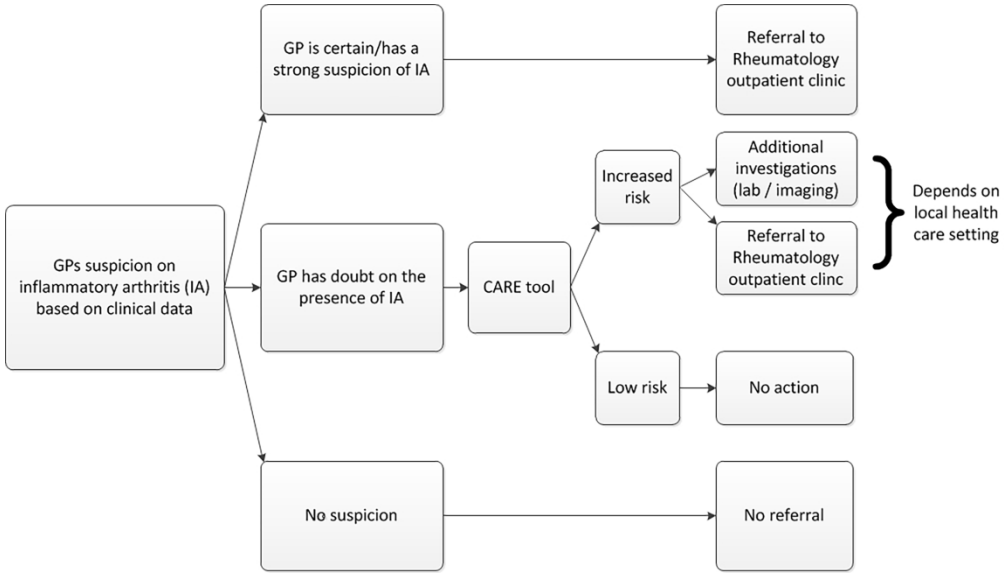


FIGURE 4. Flowchart of decision-making in patients with suspected early IA based on clinical characteristics and the role of the Clinical Arthritis RulE

274x155mm (300 x 300 DPI)

S1 Appendix. The questionnaire (in Dutch) completed by patients at the Early Arthritis Recognition Clinic (EARC).

EARC vragenlijst

U komt bij de reumatoloog aan de beurt als u deze vragenlijst heeft ingevuld.

Heeft u een **LUMC** nummer? Zo ja: wat is uw LUMC nr: ☐☐☐☐☐☐☐

Wat is uw geboortedatum: ☐☐-☐☐-☐☐☐☐

Wat is uw geslacht: ☐ vrouw ☐ man

Wat is de datum van uw eerste klacht? ☐☐-☐☐-☐☐☐☐

Wat is de datum van uw eerste bezoek aan de huisarts in verband met uw gewrichtsklachten? ☐☐-☐☐-☐☐☐☐

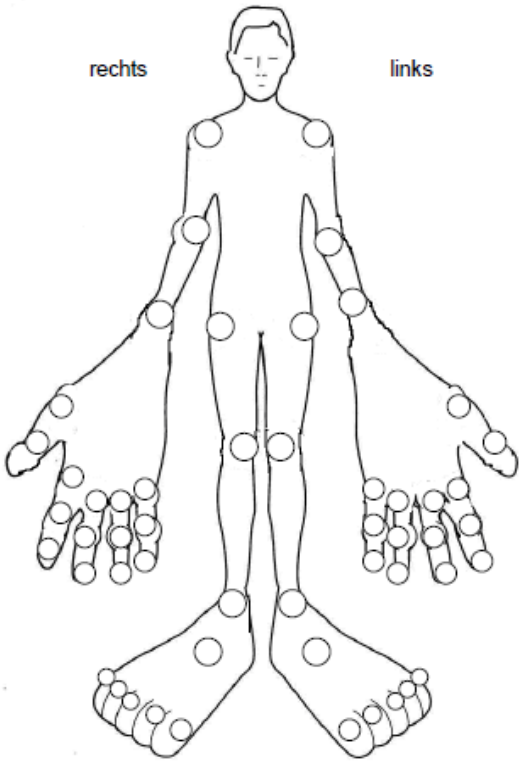
Ontstonden uw klachten plotseling of geleidelijk? (kies één van de twee) ☐ plotseling ☐ geleidelijk

Heeft u last van stijfheid als u 's morgens opstaat? ☐ nee ☐ ja; hoeveel minuten? ☐☐☐

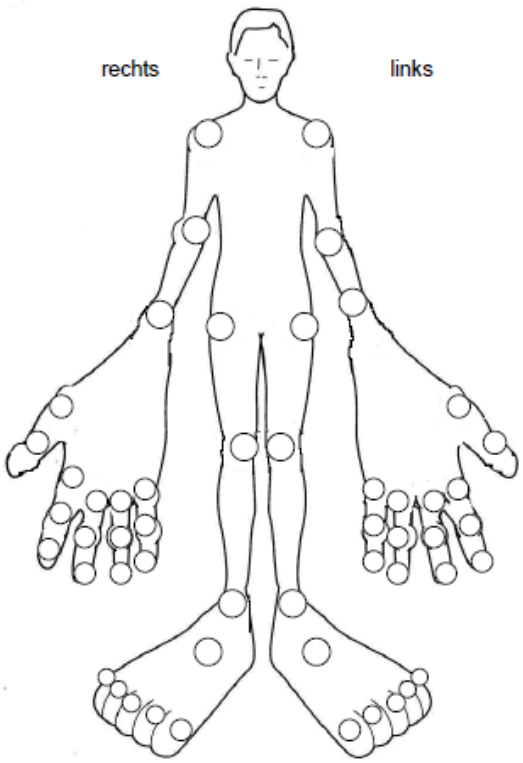
Kost het u moeite om een vuist te maken? ☐ nee ☐ ja

Wanneer heeft u de meeste last van uw gewrichtsklachten? (kies één van de twee) ☐ vroege ochtend ☐ einde van de dag

Wilt u in de pop (in de rondjes) aankruisen in welke gewrichten u **pijn** heeft?



Wilt u in de pop (in de rondjes) aankruisen welke gewrichten u **gezwollen** vindt?



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Legend:

Patients filled this questionnaire at the Early Arthritis *Recognition* Clinic, before they were seen for joint examination by a rheumatologist. This version was used from April 2012 onwards. The question on 'difficulty with making a fist' and the mannequin for 'self-reported joint swelling' were added to the questionnaire at April 1st 2012 and were not included before this date. All other questions were similar before and after April 2012.

S2 Appendix. Frequencies of missing variables.

	Derivation (N=644)	Validation (N=644)
Gender	0 (0)	0 (0)
Age	0 (0)	0 (0)
Symptom duration	48 (8)	32 (5)
Acute onset of symptoms	12 (2)	17 (3)
Morning stiffness in minutes	95 (15)	79 (12)
Number of painful joints	5 (1)	7 (1)
Number of swollen joints	234 (36)	238 (37)
Difficulty with making a fist	249 (39)	254 (39)
Arthritis present	0 (0)	0 (0)

Legend:

Variables are indicated as number of patients with missing data (percentage) unless otherwise indicated. Patient reported swollen-joint count and difficulty with making a fist were added to the questionnaire after April 1st 2012; therefore these missing data was completely at random.

S3 Appendix. Frequency of synovitis per number of visits per year.

	Nr. of visits	**Arthritis present (% of visits per year)**
2010 (starting from 31 August)	136	61 (45)
2011	264	103 (39)
2012	296	132 (45)
2013	252	105 (42)
2014	203	72 (36)
2015 (up to and including 24 September)	137	50 (37)
Total	**1288**	**523 (41)**

S4 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable using backward stepwise logistic regression.

Step 2.	Derivation (N=644)	
	OR (95%CI)	**B**
Male	1.7 (1.1–2.4)	0.503
Age, years		
0 – 59.9	*(ref)*	(*ref*)
≥ 60	2.1 (1.5–3.2)	0.762
Symptom duration, weeks		
< 6	3.5 (2.1–5.6)	1.246
6–51.9	2.2 (1.4–3.5)	0.783
≥ 52	*(ref)*	(*ref*)
Acute onset of complaints	*Excluded at step 1*	*N/A*
Morning stiffness >60 min	1.7 (1.0–2.7)	0.523
Number of painful joints		
0	*(ref)*	(*ref*)
1–3	10.6 (1.3–87.8)	2.361
≥ 4	4.6 (0.56–37.7)	1.527
Number of swollen joints		
0	*(ref)*	(*ref*)
≥ 1	3.1 (1.7–5.6)	1.142
Difficulty with making a fist	1.5 (1.0–2.1)	0.372

Legend:

Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

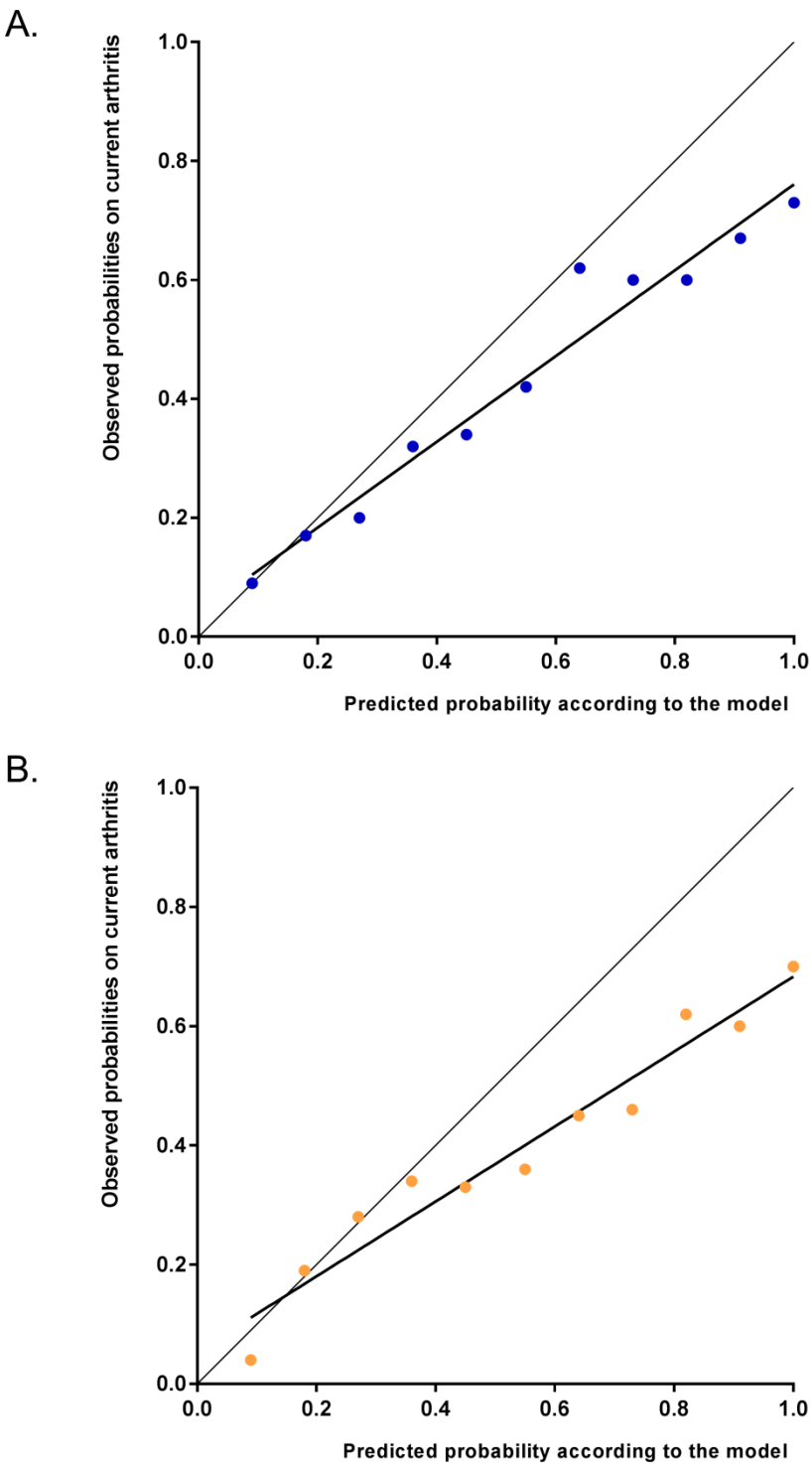
S5 Appendix. Simplified model based on the derivation dataset, with arthritis upon examination as dependent variable.

	Derivation (N=644)		
	OR (95%CI)	**B**	**points**
Male	1.7 (1.1–2.5)	0.517	0.5
Age, years			
0 – 59.9	*(ref)*	(*ref*)	0
≥ 60	2.1 (1.4–3.1)	0.750	0.5
Symptom duration, weeks			
< 6	3.6 (2.2–6.0)	1.279	1.5
6–51.9	2.2 (1.4–3.6)	0.797	1
≥ 52	*(ref)*	(*ref*)	0
Acute onset of complaints	0.99 (0.66–1.5)	-0.015	0
Morning stiffness >60 min	1.6 (0.91–2.9)	0.485	0.5
Number of painful joints			
0	*(ref)*	(*ref*)	0
1–3	10.0 (1.2–83.4)	2.300	2.5
≥ 4	4.5 (0.54–37.1)	1.497	1.5
Number of swollen joints			
0	*(ref)*	(*ref*)	0
≥ 1	3.5 (1.9–6.6)	1.253	1.5
Difficulty with making a fist	1.6 (0.99–2.6)	0.467	0.5

Legend:

Abbreviations: B = beta; CI = confidence interval; OR = odds ratio.

S6 Appendix. Calibration plot showing the observed probabilities on current inflammatory arthritis in the derivation (A) and validation dataset (B) versus the predicted probabilities according to the model.



Legend:

Predicted probabilities using the final fitted multivariable model in the validation dataset were partitioned in 10 equally sized groups. In each group, the average predicted probability on inflammatory arthritis was compared with observed prevalence of inflammatory arthritis in the validation dataset. Regression lines were fitted to the calibration plot and revealed a coefficient of 0.73 and an intercept of 0.03 in the derivation dataset and a coefficient of 0.62 and an intercept of 0.061 in the validation dataset.

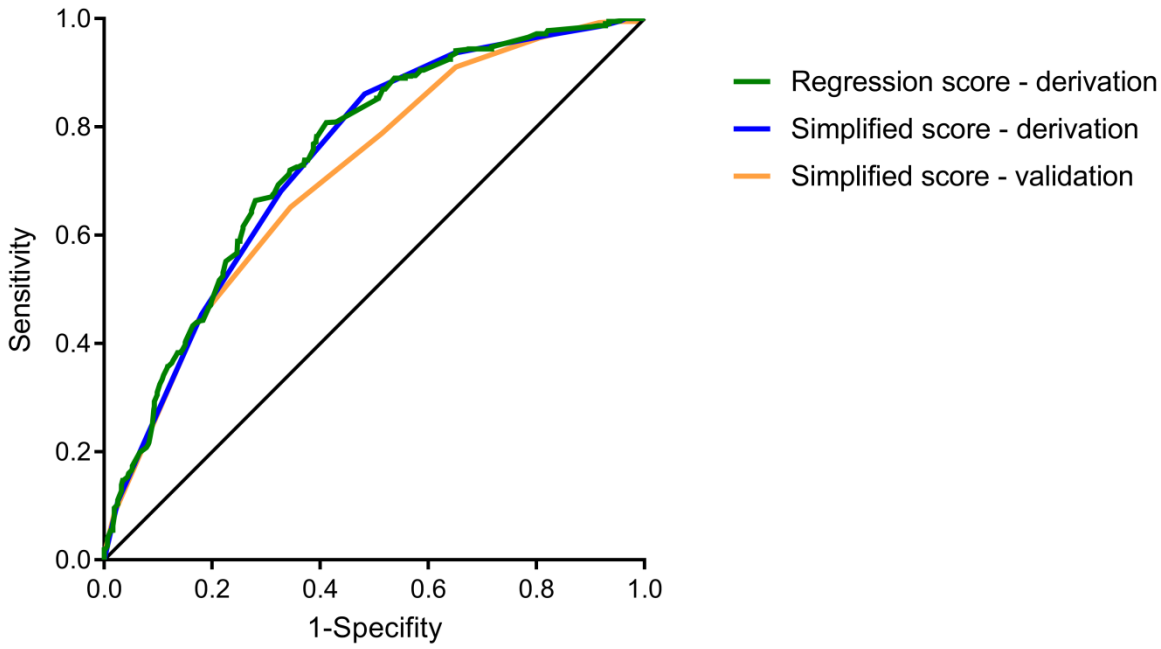
S7 Appendix. Test characteristics of the simplified model in both the derivation and validation dataset with presence of synovitis upon joint examination as outcome.

	Derivation (N=644)		Validation (N=644)	
Cut-off (≥)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
1	100	0.8		
2	99.9	3.3	99.5	1.5
3	98.7	7.7	99.3	7.8
4	93.6	35.6	90.8	35.9
4.5	85.8	52.8	78.1	50.0
5	67.6	68.0	63.9	67.0
5.5	45.0	82.7	43.5	83.4
6	23.1	92.1	21.6	92.8
7	2.5	99.4	2.1	99.7

Legend:

Sensitivity was obtained by calculating the probability that the Clinical Arthritis RulE indicated 'disease' positive among those actually identified with inflammatory by the rheumatologist. Specificity was obtained by calculating the fraction of those without inflammatory arthritis that had a negative test result on the Clinical Arthritis RulE.

S8 Appendix. Receiver operator characteristics curves for the logistic regression models with presence of synovitis upon joint examination as outcome, showing sensitivity and specificity of both regression score and simplified tool score in the derivation and validation dataset.



Legend:

The Area Under Receiver Operator Curve (AUC) for the different models was: for the regression model in the derivation dataset 0.75 (95%CI 0.70–0.79), for the simplified score in the derivation dataset 0.74 (95%CI 0.70–0.78), and for the simplified score in the validation dataset 0.71 (95%CI 0.67–0.75).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[The design of the study is described in the abstract, see Page 2; Methods and Findings]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Page 2; Methods and Findings]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Page 4-5; Introduction describes that scientific background]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Page 5; Introduction. "We have developed and validated a rule composed of clinical characteristics (….) which may assist in the decision-making process in patients with musculoskeletal symptoms with suspected IA at other places, in order to promote early identification of IA."]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Page 5–10; Methods.]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Page 5–7; Methods. Setting: "the Early Arthritis *Recognition* Clinic" at the "Leiden University Medical Center". Relevant dates: "All patients that visited the EARC between 2010 and September 2015 were studied." Data collection: "At the EARC, patients completed a short questionnaire about their joint symptoms, after which they were seen by an experienced rheumatologist."]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **[Page 5,6; Methods, section Study population]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Page 7–9; Methods, sections Data collection and Derivation and validation of the model]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[Page 7–9; Methods, sections Data collection and Derivation and validation of the model]**
Bias	9	Describe any efforts to address potential sources of bias **[Page 7; Methods, section Derivation and validation of the model.]**
Study size	10	Explain how the study size was arrived at **[Page 10; Results: "1,288 patients in whom GPs were unsure about the presence of IA visited the EARC between 2010 and 2015"]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Page 7–9; Methods, section Derivation and validation of the model]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		[Page 7–9; Methods, section Derivation and validation of the model]
		(*b*) Describe any methods used to examine subgroups and interactions **[N/A]**
		(*c*) Explain how missing data were addressed **[Page 7; Methods: "To prevent exclusion of patients with one or more missing variables, we imputed missing values using chained equations."]**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **[N/A]**
		(*e*) Describe any sensitivity analyses **[N/A]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Page 10; Results: "1,288 patients in whom GPs were unsure about the presence of IA visited the EARC between 2010 and 2015"]]**
		(b) Give reasons for non-participation at each stage **[N/A]**
		(c) Consider use of a flow diagram **[N/A]**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Page 10; Table 1]**
		(b) Indicate number of participants with missing data for each variable of interest **[S2 Appendix]**
Outcome data	15*	Report numbers of outcome events or summary measures **[Page 11 and S3 Appendix; "41% had synovitis at joint examination"]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[Page 10–11; Table 2; Table 3]**
		(*b*) Report category boundaries when continuous variables were categorized **[Page 7–8; 10–11; Table 2; Table 3]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[N/A]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[N/A]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Page 12–13; Discussion]**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Page 14–15; "A disadvantage of our setting is that the data were not collected in primary care itself, but in a setting intermediary between primary and secondary care."]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,

		multiplicity of analyses, results from similar studies, and other relevant evidence **[Page 15–16; "In conclusion, this study developed a clinical rule that supports the identification of patients suspected of having IA by physicians that feel insufficiently experienced in assessment of synovitis by joint examination."]**
Generalizability	21	Discuss the generalizability (external validity) of the study results **[Page 15–16; "(…)We expect that our rule (Clinical Arthritis RulE - CARE) might support GPs and other health care professionals in the decision-making process in patients with musculoskeletal symptoms in whom they suspect IA, regardless of the region. (…)"]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Entered through the online submission system]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.