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Diagnostic accuracy of a clinical prediction rule (CPR) for identifying patients with recent-onset undifferentiated arthritis who are at a high risk of developing rheumatoid arthritis: A systematic review and meta-analysis

Emma McNally[a,b,1], Claire Keogh, PhD[a,1], Rose Galvin, PhD[a,*], Tom Fahey, MD[a]

[a] Department of General Practice, Royal College of Surgeons in Ireland, HRB Centre for Primary Care, 123 St Stephen's Green, Dublin 2, Ireland
[b] School of Medicine, Trinity College Dublin, Dublin 2, Ireland

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ABSTRACT

Objectives: The Leiden clinical prediction rule (CPR) was developed in 2007 to predict disease progression in patients with recent-onset undifferentiated arthritis (UA). This systematic review and meta-analysis investigates the predictive ability of the rule at identifying patients who are at a high risk of developing rheumatoid arthritis (RA).

Methods: A systematic review of the literature search was conducted from 2007 to May 2013 to identify studies that validated the rule. This study adhered to the PRISMA guidelines. The methodological quality of studies was assessed using the QUADAS-2 tool. Pooled sensitivity and specificity values for each of the cut points were generated using a bivariate random-effects model. Heterogeneity was assessed using the variance of logit-transformed sensitivity and specificity. Bayes' theorem was used to calculate post-test probability of progression from UA to RA.

Results: The search identified four relevant studies, resulting in six data sets ($n = 1084$). A cut point of ≥ 9 was identified as the optimal cut point for determining progression to RA. It is associated with a greater pooled specificity (0.99, 95% CI 0.95–1.00) than sensitivity (0.31, 95% CI 0.24–0.37). Using Bayes' theorem, a score of ≥ 9 points increased the pre-test probability from 40.04% to 93.63%. A less stringent cut-off of ≥ 8 also identified a significant proportion of patients at risk of RA who have a high likelihood of progressing to RA (LR + 9.5, 95% CI 6.21–14.54).

Conclusion: A cut point of ≥ 9 offers an optimal estimate for identifying patients with UA who are at a high risk of developing RA and warrant intervention. However, a number of methodological limitations identified across studies suggest that the results should be interpreted cautiously and that further validation of the Leiden CPR is necessary.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting 0.2–1% of the population worldwide and is associated with progressive destruction of the joints [1,2]. Several research studies indicate the benefits of early aggressive treatment in patients with early signs of RA, in terms of delaying or diminishing the effects of disease progression (e.g., joint damage and functional disability) [3–9]. Undifferentiated arthritis (UA) is defined as an early form of arthritis that does not meet the required classification criteria for a more definitive arthritis diagnosis. It is estimated that one-third of patients with UA will progress to rheumatoid arthritis (RA), while approximately 40–50% of patients will experience spontaneous remission [4,10]. The remaining patients develop other conditions, for example, osteoarthritis, psoriatic arthritis and reactive arthritis [11]. Therefore, it is important to be able to identify the patients with UA who will progress to RA to ensure that those who will benefit from early intervention receive appropriate treatment, as well as to prevent unnecessary overtreatment of those patients who will not develop RA.

A clinical prediction rule (CPR) was developed in 2007 to estimate the likelihood of progression from UA to RA [5]. The model was constructed using the Leiden Early Arthritis Cohort, and the resulting CPR consists of nine clinical variables (both continuous and categorical) including age, sex, localisation of symptoms,

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* Corresponding author.
E-mail address: rosegalvin@rcsi.ie (R. Galvin).
[1] Both authors contributed equally to the preparation of this manuscript.

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morning stiffness, tender joint count, swollen joint count, C-reactive protein (CRP) level, IgM rheumatoid factor (IgM–RF) positivity and the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies. Different clinical variables are associated with different scores (see Fig. 1 for an outline of the prediction rule). Total prediction scores range from 0 to 14, with higher scores associated with increasing probability of developing RA at 1 year [5]. A cut point of ≤ 6 is used to identify patients who are at a low risk of developing RA, while a cut point of ≥ 8 is applied to identify those who are at a high risk of developing RA. However, no adequate prediction could be made for patients with a score of 7. The aim of this systematic review and meta-analysis is to determine the predictive accuracy of the Leiden CPR at identifying patients with UA who are at a high risk of progressing to RA. Specifically, we wanted to determine the optimal cut point to rule in (specificity) and rule out (sensitivity) RA in patients with UA.

1. What is the age in years? (Multiply by 0.02)
2. What is the sex?

   In case female: (1 point)
3. What is the distribution of involved joints?

   In case of small joints hands/feet: (0.5 point)

   In case of symmetric: (0.5 point)

   In case of upper extremities: (1 point)

   In case of upper and lower extremities: (1.5 points)
4. What is the score for morning stiffness on a 100-mm VAS score?

   In case of 26-90-mm: (1 point)

   In case of >90-mm: (2 points)
5. What is the number of tender joints?

   In case of 4-10: (0.5 point)

   In case of 11 or more: (1 point)
6. What is the number of swollen joints?

   In case of 4-10: (0.5 point)

   In case of 11 or more: (1 point)
7. What is the C-reactive protein level?

   In case of 5-50 mg/litre: (0.5 point)

   In case of 51 mg/ litre or higher: (1.5 points)
8. Is the patient Rheumatoid Factor positive?

   If yes: (1 point)
9. Are the anti- CCP antibodies positive?

   If yes: (2 points)

Fig. 1. The Leiden CPR for progression from undifferentiated arthritis to rheumatoid arthritis.

Methods

Search strategy

The PRISMA guidelines for the conduct and reporting of systematic reviews and meta-analysis were followed for this review [12]. The Cochrane handbook for diagnostic test accuracy studies was also referenced [13]. A search string was developed to search the MEDLINE database using the PubMed search engine to identify the Leiden CPR ('Leiden arthritis clinic cohort', 'EAC cohort' and 'Leiden early arthritis'), arthritis ('undifferentiated arthritis' and 'rheumatoid arthritis') and the aim of the study ('predict*' and 'validat*'). The search string was restricted to humans. No restrictions were placed on language, clinical setting or study design. The search period ranged from January 2007 to May 2013 (as the Leiden CPR was published in 2007). The Cochrane Library, EMBASE and Cinahl databases were searched in a similar manner. The search was supplemented by hand searching references of retrieved articles and searching in the Google Scholar database.

Study selection

Inclusion criteria for the systematic review were as follows: (i) *Patient population*: patients with recent-onset UA who meet the following inclusion criteria; >16 years of age, symptom duration of 6 weeks to 12 months and synovitis in at least one joint and/or present with two or more swollen joints. (ii) *Index test*: Leiden CPR applied. Since the rule was derived, a number of validation studies have been conducted. In some of these validation studies, the duration of morning stiffness as opposed to the severity of morning stiffness was recorded when applying the rule. As duration of morning stiffness was found to be a slightly less powerful predictor than severity of morning stiffness, the maximal prediction score for duration of morning stiffness was adjusted to 1 (compared with a maximal score of 2 in the original CPR) [10]. The modified rule was compared to the original rule and the difference in predictive value was minimal. Studies using both the original or modified version of the rule were eligible for inclusion here. (iii) *Reference standard*: progression to RA as defined by the American College of Rheumatology criteria published in 1987 (ACR 1987 criteria) [14].

Data extraction

The titles and abstracts for each article retrieved by the electronic search were independently screened by two researchers (E.M. and C.K.). The full-text article was obtained for any study that was considered potentially relevant. Each full-text article was independently read and considered for inclusion by two researchers (E.M. and C.K.). Disagreements were resolved by a third reviewer (R.G.). Additional data was requested from the authors wherever necessary. For each study, data was extracted for each cut point in the rule.

Quality assessment

Quality assessment was independently performed by two researchers (E.M. and R.G.) following the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, a validated tool for the quality assessment of diagnostic accuracy studies [15]. This checklist assesses the risk of bias in papers on four domains including patient selection, index test, reference standard and flow and timing. The first three of these domains are also assessed in terms of applicability.