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

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CRD summary
The authors concluded that a cut-off point of ≥9 or ≥10 on the Leiden clinical prediction rule may be optimal in identifying patients with undifferentiated arthritis at high risk of developing rheumatoid arthritis, but the results should be interpreted with caution. Limitations of the evidence suggest the findings may be overestimated, and the recommendation for cautious interpretation seems appropriate.

Authors' objectives
To assess the accuracy of the Leiden clinical prediction rule in identifying patients with an early form of arthritis who are at high risk of developing rheumatoid arthritis.

Searching
MEDLINE, EMBASE, CINAHL and The Cochrane Library were searched from 2007 to May 2013 without language restrictions. Search terms were reported. In addition, Google Scholar was searched and reference lists of retrieved articles were manually searched for additional articles.

Study selection
Eligible for inclusion in the review were all studies that assessed the accuracy of the original or a modified version of the Leiden clinical prediction rule in identifying patients (older than 16 years) who are at high risk of developing rheumatoid arthritis. Eligible patients had to have recent-onset undifferentiated arthritis. Symptoms had to have been present for between six weeks and 12 months, and include synovitis in at least one joint and/or two or more swollen joints. The comparator (reference) test was progression to rheumatoid arthritis as defined by the American College of Rheumatology criteria (ACR 1987).

Included studies were conducted in The Netherlands, Canada, UK, Germany and Japan. Most studies were conducted in early arthritis clinics, with one based in a hospital setting. Some patients were receiving or had received disease-modifying antirheumatic drugs, and a small proportion of patients were also receiving glucocorticoids. The mean age of participants ranged between 45 and 52.5 years, and most participants were female. The proportion of participants developing rheumatoid arthritis ranged from 31.14% to 76.19%.

Study inclusion criteria varied across studies, as did definitions for undifferentiated arthritis, where this was reported. Four cohorts used the modified version of the Leiden clinical prediction rule.

Two reviewers independently screened studies for inclusion; discrepancies were resolved by a third reviewer.

Assessment of study quality
Two reviewers independently assessed study risk of bias according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Criteria related to patient selection, index test, reference standard, flow and timing, and applicability.

Data extraction
True and false positives and true and false negatives were extracted for each clinical prediction rule cut-off point, and presented in 2x2 tables.

Primary authors were contacted for additional data where necessary. The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
A bivariate random-effects model was used to calculate summary estimates of sensitivity (the proportion of patients correctly identified as progressing to rheumatoid arthritis) and specificity (the proportion of patients correctly identified as not progressing to rheumatoid arthritis), along with their 95% confidence intervals. Summary estimates were used to plot a summary receiver operating characteristics (sROC) curve.

Statistical heterogeneity was assessed using variance of logit-transformed sensitivity and specificity and visual inspection of sROC plots. Bayes’ theorem was used to estimate the post-test probability of progressing from undifferentiated to rheumatoid arthritis (as described in the review).

Sensitivity analyses were undertaken to explore the effect of duration of follow-up and the effect of the modified version of the prediction rule on the accuracy of the Leiden clinical prediction rule.

**Results of the review**

Four studies (six cohorts; 1,084 participants, range 34 to 562) were included in the review. Follow-up duration ranged from six to 30 months. Studies were reported to be at low to moderate risk of bias, with minimal concerns about applicability. However, all studies were at unclear risk of bias in relation to the index and comparator tests.

A cut-off score of ≥5 was judged to have a good balance between sensitivity (94%, 95% CI 90 to 96; 741 patients), and specificity (49%, 95% CI 41 to 56). A cut-off point of ≥8 had higher specificity (95%, 95% CI 92 to 97; 253 patients), but sensitivity was 49% (95% CI 43 to 55). Sensitivities and specificities for other cut-off points were reported in the review, where sufficient data were available to calculate these.

Assessment for statistical heterogeneity suggested little heterogeneity between studies. Sensitivity analyses did not significantly alter the findings. Leiden clinical prediction rule scores of ≥9 (93.63%) or ≥10 (93.39%) had the highest post-test probabilities for progression to rheumatoid arthritis.

**Authors’ conclusions**

A cut-off point of ≥8 on the Leiden clinical prediction rule was associated with good predictive value in identifying patients who are at high risk for developing rheumatoid arthritis. However, a cut-off point of ≥9 or ≥10 may offer a more conservative approach to determine initiation of treatment. The results should be interpreted with some caution given the methodological limitations identified.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. A satisfactory literature search was undertaken without language restrictions, thereby reducing the risk of bias. Action was taken to reduce reviewer error and bias for study selection and quality assessment, but it was unclear whether this was true for data extraction. Study quality was assessed and suggested some potential for risk of bias.

Appropriate statistical methods were used to pool the data. The authors highlighted some of the limitations of the evidence, including potential issues with the reference standard, and potential for overestimation of the predictive ability of the clinical prediction rule. Other limitations included the small number of included studies and small sample sizes, and the poor trade-off between sensitivity and specificity. There was also insufficient data to determine the accuracy of the prediction rule at certain cut-off points.

This was a generally well conducted review, but the limitations of the evidence and the poor trade-off between sensitivity and specificity suggest the findings may be overestimated. Therefore, the authors’ recommendations to interpret the findings with caution seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that a cut-off point of ≥9 or ≥10 offered the highest level of certainty of developing rheumatoid arthritis and may be a more robust marker for determining initiation of an intervention. However, a cut-off point of ≥8 will identify a significant proportion of patients who are at high risk of developing rheumatoid arthritis and may merit intervention. The authors also stated that patients classified in the intermediate clinical prediction rule category (6 to 7 points) may warrant a watchful waiting period, but clinicians must consider individual patient symptoms before deciding not to intervene. Further implications were reported in the review.
Research: The authors stated that further assessment of the Leiden clinical prediction rule is necessary before widespread implementation, including the assessment of its use in different clinical settings, and if the ACR European League Against Rheumatism (EULAR) 2010 criteria are routinely used in clinical practice.

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