Point-of-Care Guides

Predicting Rheumatoid Arthritis Risk in Adults with Undifferentiated Arthritis

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This guide is one in a series that offers evidence-based tools to assist family physicians in improving their decision making at the point of care.

A collection of Point-of-Care Guides published in *AFP* is available at http://www.aafp.org/afp/poc.

Clinical Question

Which adults with undifferentiated arthritis have a high risk of developing rheumatoid arthritis (RA)?

Evidence Summary

Early use of disease-modifying antirheumatic drugs (DMARDs) markedly reduces inflammation and joint destruction associated with RA.[1,2] Therefore, with early diagnosis of RA and appropriate use of DMARDs, there is a window of opportunity to change the clinical course of this disabling disease.

However, diagnosing RA in the early stages of the disease is difficult. Many patients who are diagnosed with RA presented earlier with undifferentiated arthritis to a primary care physician. Undifferentiated arthritis is diagnosed when signs, symptoms, and laboratory test results do not meet the American College of Rheumatology's (formerly the American Rheumatism Association) classification for a definitive diagnosis of RA *(Table 1[3])*.

Among patients initially diagnosed with undifferentiated arthritis, 28 percent develop RA.[4] Successfully predicting which patients with undifferentiated arthritis have a high risk of developing RA would help primary care physicians identify appropriate candidates for DMARD therapy early in the disease.

Clinics for early arthritis have been established to carefully monitor potential clinical signs and biomarkers that may help identify patients with the highest risk of RA. Researchers from these clinics have published two clinical rules to predict which patients with undifferentiated arthritis will develop RA. One rule focuses on predicting self-limited, persistent, or erosive arthritis in patients with more advanced clinical symptoms.[5] The other rule was developed specifically for patients with recent-onset undifferentiated arthritis.[6] The study results from which the latter rule was developed are most relevant for answering the clinical question presented in this article.

The study, conducted at the Leiden Early Arthritis Clinic in the Netherlands, included 570 patients with recent-onset undifferentiated arthritis. Patients were monitored for one year. During the first year, 177 patients developed RA, 150 achieved remission, and 94 developed another rheumatologic disorder; the remaining 149 patients had not reached one year of follow-up.[6] Regression analysis using a combination of questionnaires, physical examination findings, and blood test results identified nine independent clinical findings that predict the risk of developing RA at one year. The logistic regression model was then converted into a simpler prediction rule that used an additive point score.

The 14-point rule *(Table 2)* was cross-validated in the original population and in a new group of 55 patients; using the rule, a score of 0 represents the lowest risk of RA, and a score of 14 represents the highest risk.[6] In both validation groups, the score performed well as measured by the area under the receiver operating characteristic curve (0.87 and 0.97, respectively, where 0.5 is least accurate and 1.0 is most accurate). None of the patients with a score of 3 or less was diagnosed with RA, and the risk steadily became greater with increasing score.[6]

Based on these findings, patients with a score of 6.51 or more should be referred to a rheumatologist for evaluation and

consideration of DMARD therapy, whereas patients with a score of 6.5 or less are at low risk of progression and may be followed regularly by their primary care physician. If symptoms or risk score worsens at any time, the patient should be promptly referred for evaluation.

Applying the Evidence

A 48-year-old woman presents to her primary care physician with a three-week history of painful, swollen hands and moderate morning stiffness, which she rates as 50 mm on a 100-mm visual analog scale. Physical examination revealed slight tenderness and mild

Table 1. Accuracy of Individual Elements of the American College of Rheumatology* Criteria for the Classification of Rheumatoid Arthritis

				Percentage with rheumatoid arthritis if sign or symptom is present or absent†	
Sign or symptom	*Definition*	*LR+*	*LR–*	*Present*	*Absent*
Morning stiffness	Stiffness in or around the affected joints for at least one hour after initiating movement	1.9	0.5	39	14
Arthritis of three or more joint areas	Three or more of the following joints noted to be fluid-filled or have soft-tissue swelling: wrist, PIP, MCP, elbow, knee, ankle, MTP	1.4	0.5	32	13
Hand joint involvement	Wrist, MCP, or PIP joints among the symptomatic joints observed	1.5	0.4	33	12
Symmetric arthritis	Right and left extremities involved for one or more of following joints: wrist, PIP, MCP, elbow, knee, ankle, MTP‡	1.2	0.6	29	17
Rheumatoid nodules	Subcutaneous nodules in regions surrounding joints, extensor surfaces, or bony prominences	3.0	0.98	50	25
Serum rheumatoid factor test result positive	Positive result using any laboratory test that has a positive predictive value of 95 percent or more (i.e., is positive in no more than 5 percent of patients without rheumatoid arthritis)	8.4	0.4	74	13
Radiographic changes	Hand and wrist films show typical changes of erosions or loss of density adjacent to affected joints	11	0.8	79	21

NOTE: *A patient is classified as having rheumatoid arthritis if four criteria are present and the first four criteria have been present for at least six weeks.*

LR+ = positive likelihood ratio; LR– = negative likelihood ratio; PIP = proximal interphalangeal; MCP = metacarpophalangeal; MTP = metatarsophalangeal.

**—Formerly the American Rheumatism Association.*
†—Assumes overall probability of rheumatoid arthritis of 30 percent.
‡—PIP, MCP, and MTP joints need not be absolutely symmetric.

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swelling over all proximal interphalangeal and metacarpophalangeal joints and in both wrists. No lower-extremity joint involvement or rheumatoid nodules were observed. Her serum rheumatoid factor and anticyclic citrullinated peptide antibody test results were negative, but she had a C-reactive protein (CRP) level of 600 mg per dL (60 mg per L). Radiography of her hands showed no erosions or unequivocal bony decalcifications.

Answer: Using *Table 2*,[6] the patient receives 8.46 points (0.96 points for age, 1.0 for female sex, 0.5 for small joints of the hand, 0.5 for symmetry, 1.0 for upper extremity besides the hand [the wrist], 1.0 for intensity of morning stiffness, 2.0 for the number of tender and swollen joints, and 1.5 for CRP level); the score is rounded to 8.5. You tell the patient that her risk of RA is approximately six out of 10. You discuss with her the results of recent studies about the risks and benefits of DMARDs for treating RA and refer her to a rheumatologist at an early arthritis clinic for further evaluation.

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Author disclosure: Nothing to disclose.

Table 2. Clinical Rule for Predicting the Risk of Rheumatoid Arthritis in Patients with Undifferentiated Arthritis

Patient characteristics	*Points*
Age	Years multiplied by 0.02
Female sex	1.0
Distribution of involved joints (patient may receive points for more than one item)	
Small joints of the hands or feet	0.5
Symmetrical	0.5
Upper extremities	1.0
Upper and lower extremities	1.5
Score for morning stiffness on a 100-mm visual analog scale	
26 to 90 mm	1.0
> 90 mm	2.0
Number of tender joints	
4 to 10	0.5
≥ 11	1.0
Number of swollen joints	
4 to 10	0.5
≥ 11	1.0
C-reactive protein level	
50 to 500 mg per dL (5 to 50 mg per L)	0.5
≥ 510 mg per dL (51 mg per L)	1.5
Rheumatoid factor test result positive	1.0
Anticyclic citrullinated peptide antibody test result positive	2.0
Total:	_____

*Score**	*Number with RA*	*Number without RA*	*Likelihood ratio*	*Percentage with RA at one year*
0 to 3.5	0	109	0	0
3.51 to 6.5	41	214	0.42	16
6.51 to 8.5	71	53	3.0	57
≥ 8.51	63	11	12.7	85

RA = rheumatoid arthritis.

**—Scores are rounded to the nearest number ending in .0 or .5.*

Adapted with permission from van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum. *2007;56(2):436.*

REFERENCES

1. Neil VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology.* 2004;43(7):906-914.
2. Vital EM, Emery P. Advances in the treatment of early rheumatoid arthritis. *Am Fam Physician.* 2005;72(6):1002-1004.
3. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. *Am Fam Physician.* 2005;72(6):1037-1047.
4. van Aken J, van Dongen H, le Cessie S, Allaart CF, Breedveld FC, Huizinga TW. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: an observational cohort study. *Ann Rheum Dis.* 2006;65(1):20-25.
5. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JMW. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum.* 2002;46(2):357-365.
6. van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum.* 2007;56(2):433-440. ■