

A Diagnostic Rule for Acute Gouty Arthritis in Primary Care Without Joint Fluid Analysis

Hein J. E. M. Janssens, MD; Jaap Fransen, PhD; Eloy H. van de Lisdonk, MD, PhD;
Piet L. C. M. van Riel, MD, PhD; Chris van Weel, MD, PhD; Matthijs Janssen, MD, PhD

Background: Most cases of acute gouty arthritis are diagnosed in primary care and without joint fluid analysis in many instances. Our objectives were to estimate the validity of this diagnosis by family physicians and to develop a diagnostic rule.

Methods: Patients with monoarthritis recruited in an open Dutch population with gout by family physician diagnosis were enrolled in a diagnostic study (March 24, 2004, through July 14, 2007). Validity variables were estimated using 2×2 tables, with the presence of synovial monosodium urate crystals as the reference test. For development of the diagnostic rule, clinical variables (including the presence of synovial monosodium urate crystals) were collected within 24 hours. Statistically significant variables and predefined variables were separately entered in multivariate logistic regression models to predict the presence of synovial monosodium urate crystals. Diagnostic performance of the models was tested by receiver operating characteristic curve analysis. The most appropriate model was transformed to a clinically useful diagnostic rule.

Results: Three hundred twenty-eight patients were included in the study. The positive and negative predictive values of family physician diagnosis of gout were 0.64 and 0.87, respectively. The most appropriate model contained the following predefined variables: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint (MTP1) involvement, hypertension or 1 or more cardiovascular diseases, and serum uric acid level exceeding 5.88 mg/dL (to convert serum uric acid level to micromoles per liter, multiply by 59.485). The area under the receiver operating characteristic curve for this model was 0.85 (95% confidence interval, 0.81-0.90). Performance did not change after transforming the regression coefficients to easy-to-use scores and was almost equal to that of the statistically optimal model (area under the receiver operating characteristic curve, 0.87; 95% confidence interval, 0.83-0.91).

Conclusions: The validity of family physician diagnosis of acute gouty arthritis was moderate in this study. An easy-to-use diagnostic rule without joint fluid analysis was developed for their use.

Arch Intern Med. 2010;170(13):1120-1126

GOUT IS A COMMON MEDICAL problem affecting many patients worldwide. The annual incidence ranges from 62 to 180 cases per 100 000^{1,2} and the annual prevalence from 940 to 1400 cases per 100 000,^{2,3} and approximately 6.1 million US adults 20 years or older have had gout.³ Primary care physicians diagnose and manage most patients with gout.^{4,5} Less than 10% of patients diagnosed as having gout are referred to rheumatologists.⁶ In primary care, this diagnosis is based on clinical signs and symptoms, usually without synovial fluid analysis for the presence of monosodium urate (MSU) crystals, which is the reference test for the diagnosis.⁴ We found no evidence to suggest that joint aspiration is unnecessary for diagnosis of gout in primary care.^{7,8}

The number of patients involved renders it more than a theoretical issue to gain

greater insight into the validity of gout diagnosed by physicians in primary care. Failure to diagnose gout and incorrect diagnosis of gout may have adverse consequences (equivalent to withholding appropriate management) for many patients.

Therefore, we studied the validity of acute gouty arthritis diagnosed by family physicians, with the presence of synovial MSU crystals as the reference test. From the signs and symptoms of patients, we developed and internally validated prediction models with the objective to develop a diagnostic rule without need for joint fluid analysis.

METHODS

DESIGN, DOMAIN, AND CONTEXT

We performed a prospective diagnostic study of patients in primary care with a high priori probability of acute gouty arthritis. These in-

Author Affiliations:

Departments of Primary and Community Care (Drs Janssens, van de Lisdonk, and van Weel) and Rheumatology (Drs Fransen and van Riel), Radboud University Nijmegen Medical Center, Nijmegen, and Department of Rheumatology, Rijnstate Hospital, Arnhem (Dr Janssen), the Netherlands.

cluded patients seen with signs and symptoms of monoarthritis by Dutch family physicians (FPs) irrespective of whether this was an index case of arthritis or a recurrent episode or whether a previous episode was considered gout. Within 24 hours of presentation to the FP, the affected joint was aspirated, and synovial fluid was analyzed for the presence of MSU crystals. In all eligible patients, gout diagnosis by participating FPs was evaluated using 2×2 tables, with the presence of MSU crystals as the reference test. After this, prediction models were developed and validated in patients with gout by FP diagnosis using multivariate logistic regression analysis by linking the presence of MSU crystals to clinical variables. The rationale was that further diagnostic procedures for detecting gout would generally only be pursued in patients who were suspected by physicians of having the disease.

The study was conducted in the eastern part of the Netherlands among a population of about 330 000 inhabitants (March 24, 2004, through July 14, 2007). The FP practices that eventually participated in the study covered 180 000 to 200 000 of this population. In the Netherlands, all inhabitants are registered with a personal FP who provides primary care for about 2000 to 3000 people and who refers patients for secondary medical care to a hospital if needed. After study inclusion, patients with the presence of MSU crystals were also invited to participate in a randomized clinical trial (Trial Registration: www.controlled-trials.com Identifier: ISRCTN14648181) on the effectiveness of prednisolone; the trial was approved by the regional ethics review committee (Arnhem-Nijmegen).⁹

PROCEDURES

We invited FPs to participate in the study personally and at regional educational meetings. We asked participating FPs to recruit consecutive patients with monoarthritis who were encountered and diagnosed in the setting of primary care during regular office hours (Monday through Friday, 8 AM to 6 PM). The FPs sent recruited patients to our regional hospital research center (Department of Rheumatology, Rijnstate Hospital, Arnhem, the Netherlands) with concealed information about their diagnosis.

To obtain clinical variables at the time of study inclusion, patients were evaluated in the research center by one of us (M.J., substituted in a few instances by a rheumatologist colleague) using a standard interview, physical examination, and laboratory testing within 24 hours of visiting the FP. The clinical variables were not collected by the FPs to avoid interference with their daily work. For practical reasons, the evaluation was combined with inclusion and informed consent procedures of the study. **Table 1** gives an overview of the collected clinical variables. Synovial fluid was aspirated from the affected joint of each patient and was microscopically analyzed to identify the presence of MSU crystals.

If MSU crystals could not be identified and other crystal-induced arthropathies and septic arthritis were excluded, patients were classified as meeting accepted diagnostic criteria for joint diseases, such as psoriatic arthritis and reactive arthritis, or as having arthritis of unknown cause. All patients with arthritis of unknown cause were followed up for at least 1 year until July 2007. In the event of recurrent episodes, patients were completely reevaluated, including synovial fluid analysis, at each recurrent episode. If MSU crystals were later identified during the follow-up period, the patient was then classified as having gout according to the reference test, with the initial false-negative MSU test result changed to a positive result.

Information about the FP diagnosis (gout or nongouty arthritis) remained concealed from the investigators until the final diagnosis or throughout the follow-up period if no diagnosis was established. Thereafter, FP diagnoses among patients

were evaluated to define samples and to develop and test the prediction models.

STATISTICAL ANALYSIS

Data were analyzed from all patients with signs and symptoms of monoarthritis. Family physician gout diagnosis (index test) was related to the presence of synovial MSU crystals (reference test) to evaluate diagnostic test characteristics (sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios) using 2×2 tables.

In patients with gout by FP diagnosis, signs and symptoms were analyzed using descriptive statistics (mean [SD] numbers and percentages) and univariate logistic regression (odds ratios, 95% confidence intervals, and *P* values), with the presence of MSU crystals as the dependent variable. The occurrence of missing values was evaluated. The following 3 multivariate logistic regression models, with the presence of MSU crystals as the dependent variable, were fitted to the data set of the sample: a statistically optimal model (model 1) and 2 predefined models (model 2 and model 3). In model 1, selection of predictor variables was based on statistical significance. In models 2 and 3, selection of predictor variables was based on external knowledge and on practical availability during regular patient care.

Model 1, the best model given the data, was used to gauge the performance of models 2 and 3, which were developed for convenient clinical use. Between models 2 and 3, the most appropriate regression model was chosen.

For model 1, all variables with $P < .20$ in the univariate logistic regression analysis and a plausible direction of the regression coefficient (based on generally accepted knowledge) were selected for inclusion in the full multivariate logistic regression model. This full model was subsequently reduced by stepwise exclusion of all variables with $P \geq .10$. For model 2, the following variables were selected: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint (MTP1) involvement, and hypertension or 1 or more cardiovascular diseases. Model 3 included the same variables as model 2 but also included the laboratory variable of serum uric acid level exceeding 5.88 mg/dL (to convert serum uric acid level to micromoles per liter, multiply by 59.485).

Diagnostic performance of the 3 models was evaluated using receiver operating characteristic (ROC) curve analysis (area under the curve), the fraction of variance by the model was explained (Nagelkerke R^2),¹⁰ and the model fit (with respect to the data) was assessed according to Hosmer-Lemeshow goodness-of-fit, *P* value, and calibration slope. The calibration slope is a measure of "extremeness" of the predictions: a slope of 1.0 indicates complete agreement between observed and predicted probabilities.¹¹ Calibration plots compared observed frequencies vs predicted probabilities of the presence of MSU crystals in deciles of the risk score.

The most appropriate model was then chosen between model 2 and model 3. The bootstrap method (ie, repeated sampling with replacement) with 300 repetitions without variable selection was used to determine the shrinkage factor.^{12,13} Variable selection was not included in the bootstrap procedure because we used a predefined model. The regression coefficients of the final model were multiplied by the shrinkage factor to reduce overoptimism of the model in new patients. The final model was then transformed to an easy-to-use diagnostic rule by rescaling the regression coefficients of the variables. The performance of this diagnostic rule was evaluated, and the prevalence of gout confirmed by the presence of MSU crystals was assessed at several cutoff points.

In secondary analyses, models were tested in all patients with monoarthritis, including those judged by FPs as having nongouty

Table 1. Potentially Diagnostic Variables in Patients With Presumed Gout in Primary Care

Variable	MSU Crystals		P Value ^a	Odds Ratio (95% Confidence Interval)
	Present (n=209)	Absent (n=119)		
Age, mean (SD), y	58.8 (12.9)	56.6 (14.4)	.15	0.99 (0.97-1.00)
Male sex, No. (%)	187 (89.5)	74 (62.2)	<.001	5.17 (2.90-9.20)
Onset, No. (%)				
Within hours	78 (37.3)	52 (43.7)	.26	0.77 (0.49-1.21)
Within 1 d	166 (79.4)	90 (75.6)	.42	1.24 (0.73-2.13)
Patient history, No. (%)				
Patient-reported arthritis attack	156 (74.6)	53 (44.5)	<.001	3.67 (2.27-5.91)
Arthritis always in the same joint	51 (32.7) ^b	25 (47.2) ^c	.06	0.54 (0.29-1.03)
Patient-reported gout	128 (61.2)	36 (30.3)	<.001	3.64 (2.25-5.89)
Medication use, No. (%)				
Diuretics	65 (31.1)	22 (18.5)	.01	1.99 (1.15-3.44)
Antiplatelet agents, acetylsalicylic acid	17 (8.1)	5 (4.2)	.27	1.24 (0.85-1.81)
Cardiovascular or antihypertensive drugs	128 (61.2)	44 (37.0)	<.001	2.69 (1.69-4.29)
Family history of gout, No. (%)	53 (25.9) ^d	32 (27.4) ^e	.77	0.93 (0.56-1.55)
Comorbidity, No. (%)				
Diabetes	16 (7.7)	9 (7.6)	.98	1.01 (0.43-2.37)
Hypertension	110 (52.6)	36 (30.3)	<.001	2.56 (1.59-4.12)
≥1 Cardiovascular diseases	64 (30.6)	17 (14.3)	.001	2.65 (1.47-4.79)
Hypertension or ≥1 cardiovascular diseases	133 (63.6)	43 (36.1)	<.001	3.09 (1.94-4.94)
Renal stones	19 (9.1)	7 (5.9)	.30	1.60 (0.65-3.93)
Recent joint trauma or surgery, No. (%)	6 (2.9)	3 (2.5) ^f	.86	1.13 (0.28-4.62)
Alcohol consumption, No. (%)		(n=118)		
Any	132 (63.2)	65 (55.1)	.26	1.31 (0.82-2.07)
Beer	95 (45.5)	25 (21.2)	<.001	3.10 (1.85-5.21)
Wine	28 (13.4)	32 (27.1)	.002	0.42 (0.24-0.73)
Liquor	26 (12.4)	14 (11.9)	.88	1.06 (0.53-2.11)
≥7 U/wk	98 (46.9)	50 (42.4) ^f	.39	1.22 (0.77-1.92)
Joint redness, No. (%)	187 (89.5)	91 (76.5)	.002	2.62 (1.42-4.82)
Location of affected joint, No. (%)				
First metatarsophalangeal joint	120 (57.4)	35 (29.4)	<.001	3.24 (2.00-5.23)
Foot or ankle	161 (77.0)	75 (63.0)	.007	1.97 (1.20-3.22)
Lower leg	179 (85.6)	94 (79.0)	.12	1.59 (0.88-2.85)
Tophus, No. (%)	27 (12.9)	0	NA	NA
Body mass index ^g		(n=118)		
Mean (SD)	29.7 (4.4)	28.7 (5.6)	.08	0.96 (0.91-1.00)
>30, No. (%)	85 (40.7)	38 (32.2)	.13	1.44 (0.90-2.32)
>25, No. (%)	187 (89.5)	89 (75.4)	.001	2.77 (1.51-5.09)
Blood pressure, mm Hg				
Systolic, mean (SD)	144.3 (22.6)	143.6 (22.1)	.78	1.00 (0.99-1.01)
Systolic >140, No. (%)	91 (43.5)	53 (44.5)	.86	0.96 (0.61-1.51)
Diastolic, mean (SD)	84.1 (12.7)	83.6 (14.7)	.73	1.00 (0.98-1.01)
Diastolic >90, No. (%)	57 (27.3)	31 (26.1)	.81	1.07 (0.64-1.77)
Serum uric acid level, mg/dL				
Mean (SD)	8.24 (1.51)	6.05 (2.01)	<.001	0.00 (0.00-0.00)
>7.06 For men or >5.72 for women, No. (%)	161 (77.0)	38 (32.2) ^f	<.001	7.06 (4.27-11.68)
>5.88, No. (%)	199 (95.2)	55 (46.6) ^f	<.001	22.80 (10.98-47.35)
Creatinine level, mg/dL		(n=117)		
Mean (SD)	1.12 (0.45)	0.91 (0.31)	<.001	0.98 (0.97-0.99)
>1.19, No. (%)	133 (65.2)	56 (49.1)	.002	2.82 (1.47-5.43)
Glomerular filtration rate, mL/min/1.73 m ²		(n=117)		
Mean (SD)	74.4 (24.4)	85.0 (21.9)	<.001	1.02 (1.01-1.03)
<90, No. (%)	148 (71.5)	61 (52.1)	.001	2.30 (1.44-3.69)
<60, No. (%)	54 (26.1)	13 (11.1)	.002	2.82 (1.47-5.43)
Erythrocyte sedimentation rate, mm/h		(n=117)		
Mean (SD)	23.6 (20.3)	20.4 (16.5)	.16	0.99 (0.98-1.00)
>20 For men or >30 for women, No. (%)	88 (42.7)	38 (32.5)	.07	1.55 (0.96-2.49)
C-reactive protein level, mg/dL		(n=114)		
Mean (SD)	27.0 (33.1)	20.6 (2.97)	.09	0.99 (0.99-1.00)
>1, No. (%)	133 (65.2)	56 (49.1)	.005	1.94 (1.22-3.09)

Abbreviations: MSU, monosodium urate; NA, not applicable because tophus presence completely coincided with MSU presence.

SI conversion factors: To convert serum uric acid level to micromoles per liter, multiply by 59.485; creatinine level to micromoles per liter, multiply by 88.4; C-reactive protein level to nanomoles per liter, multiply by 9.524.

^aBetween-group differences after univariate logistic regression analysis.

^bn=156.

^cn=53.

^dn=205.

^en=117.

^fn=118.

^gCalculated as weight in kilograms divided by height in meters squared.

arthritis. All analyses were performed using commercially available statistical software (SAS, version 8.1.2; SAS Institute, Cary, North Carolina).

RESULTS

Figure 1 shows the study profile. Ninety-three FPs recruited 381 patients with monoarthritis. Their mean age was 57.7 (13.6) years, and 285 patients (74.8%) were male. The presence of MSU crystals was identified in 216 patients (56.7%), 209 at the initial investigation and 7 during the follow-up period. A total of 328 patients (86.1%) had an index test diagnosis of gout. The reference test demonstrated index test sensitivity of 0.97 (209 of 216), specificity of 0.28 (46 of 165), positive predictive value of 0.64 (209 of 328), and negative predictive value of 0.87 (46 of 53). The derived positive likelihood ratio was 1.3, with a negative likelihood ratio 0.1.

Of 328 patients with an index test diagnosis of gout (included in the regression models), the mean age was 58.0 (13.5) years, 261 (79.6%) were male, and hypertension, 1 or more cardiovascular diseases, and diabetes were present in 146 (44.5%), 81 (24.7%), and 25 (7.6%), respectively. The presence of MSU crystals was identified in 209 patients (63.7%). Of 53 patients excluded from the regression models (with an index test diagnosis of nongouty arthritis), 24 (45.3%) were male, the mean age was 55.8 (14.2) years, and hypertension, 1 or more cardiovascular diseases, and diabetes were present in 16 (30.2%), 9 (17.0%), and 3 (5.7%), respectively. The presence of MSU crystals was identified in 7 nongouty patients (13.2%).

Table 1 summarizes findings of the descriptive statistics and univariate logistic regression analyses of diagnostic indicators and risk factors for the presence of MSU crystals among 328 patients who were included in the regression models. The number of missing values was low; therefore, missing values were not replaced.

After the univariate procedure and the multivariate logistic regression procedure that included stepwise exclusion of all variables with $P \geq 10$, model 1 (the statistically optimal model) consisted of 8 variables (including 2 laboratory values) that were independently predictive in multivariate logistic regression analysis. The equation for model 1 is as follows:

$$-4.66 \text{ (intercept)} + (0.92 \times \text{male sex}) + (1.02 \times \text{previous patient-reported arthritis attack}) + (1.83 \times \text{MTP1 involvement}) + (1.01 \times \text{hypertension or } \geq 1 \text{ cardiovascular diseases}) + (1.15 \times \text{beer consumption}) + (2.44 \times \text{serum uric acid level } > 5.88 \text{ mg/dL}) + (0.68 \times \text{erythrocyte sedimentation rate } > 20 \text{ mm/h for men or } > 30 \text{ mm/h for women}).$$

The eighth variable was the presence of tophus, which was 100% specific for the presence of MSU crystals in synovial joint fluid analysis. Therefore, a regression coefficient for this variable could not be calculated, but the variable was kept in the model by awarding the maximum risk score for patients with tophus.

Results of the multivariate logistic regression analysis in the predefined models (models 2 and 3) are given

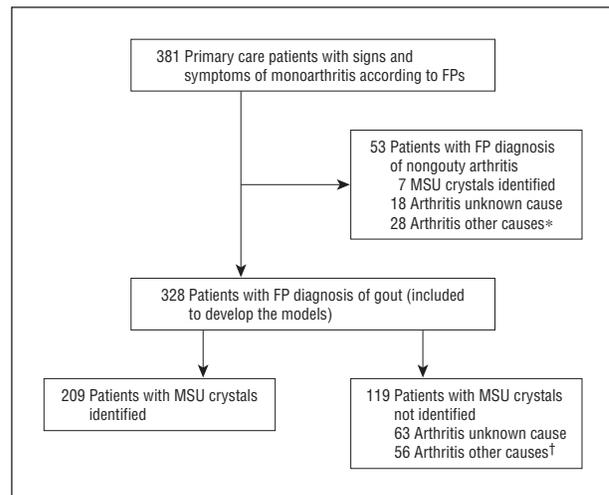


Figure 1. Study profile. FP indicates family physician; MSU, monosodium urate. *Tested positive for cyclic citrullinated peptide antibodies or rheumatoid factor positive or had progression to rheumatoid arthritis (2 patients), psoriatic arthritis (2 patients), pseudogout (5 patients), poststreptococcal reactive arthritis (2 patients), arthritis secondary to inflammatory bowel disease (1 patient), Lyme disease arthritis (1 patient), bacterial arthritis (1 patient), osteoarthritis (1 patient), or no arthritis (4 patients). †Tested positive for cyclic citrullinated peptide antibodies or rheumatoid factor positive or had progression to rheumatoid arthritis (10 patients), psoriatic arthritis (4 patients), pseudogout (9 patients), reactive arthritis (1 patient), poststreptococcal reactive arthritis (3 patients), arthritis secondary to inflammatory bowel disease (3 patients), Lyme disease arthritis (2 patients), bacterial arthritis (2 patients), palindromic rheumatism (5 patients), osteoarthritis (9 patients), or no arthritis (8 patients).

in **Table 2**. Except for onset within 1 day and joint redness, all other variables (male sex, previous patient-reported arthritis attack, hypertension or ≥ 1 cardiovascular diseases, MTP1 involvement, and serum uric acid level > 5.88 mg/dL) were independently predictive in multivariate regression analysis based on their respective P values.

Performance of the 3 models is summarized in **Table 3**. The area under the ROC curve for the statistically optimal model (model 1) was high, with the areas under the ROC curve for models 2 and 3 being slightly lower. Compared with model 2, the performance of model 3 was better based on area under the ROC curve, Nagelkerke R^2 , Hosmer-Lemeshow goodness-of-fit test, and calibration slope. Accordingly, model 3 was chosen as the final model. The areas under the ROC curve for models 1 and 3 are shown in **Figure 2**.

The regression coefficients of variables included in model 3 were first multiplied by a shrinkage factor of 0.81, and the regression coefficients were then rescaled to easy-to-use scores (**Table 4**). The area under the ROC curve for this diagnostic rule was 0.85 (95% confidence interval, 0.81-0.90). **Figure 3** shows the calibration plot of the rule. As confirmed by the presence of MSU crystals, the prevalences of gout at 3 cutoff scores (≤ 4 , > 4 to < 8 , and ≥ 8 points) on the final diagnostic rule were 2.2% (1 of 45), 31.2% (15 of 48), and 82.5% (193 of 234), respectively.

Among all patients with monoarthritis, including those judged by FPs as having nongouty arthritis, the area under the ROC curve for the diagnostic rule was 0.87 (95% CI, 0.84-0.91). As confirmed by the presence of MSU crystals, the prevalences of gout at the 3 cutoff scores (≤ 4 ,

Table 2. Results of Multivariate Logistic Regression Analysis of the Predefined Models (Model 2 Without Laboratory Testing and Model 3 With Laboratory Testing)^a

Variable	Model 2			Model 3		
	Regression Coefficient	OR (95% CI)	P Value	Regression Coefficient	OR (95% CI)	P Value
Male sex	1.90	6.67 (3.26-13.67)	<.001	1.25	3.50 (1.54-8.00)	.003
Previous patient-reported arthritis attack	1.42	4.13 (2.20-7.78)	<.001	1.17	3.24 (1.63-6.43)	.001
Onset within 1 d	0.30	1.35 (0.69-2.63)	.38	0.03	1.03 (0.50-2.14)	.93
Joint redness	0.45	1.57 (0.73-3.39)	.25	0.50	1.64 (0.73-3.72)	.23
MTP1 involvement	1.87	6.48 (3.37-12.46)	<.001	1.54	4.68 (2.34-9.35)	<.001
Hypertension or ≥ 1 cardiovascular diseases ^b	1.16	3.21 (1.81-5.69)	<.001	0.88	2.42 (1.30-4.50)	.005
Serum uric acid level > 5.88 mg/dL	2.28	9.81 (4.32-22.31)	<.001

Abbreviations: CI, confidence interval; ellipsis, not applicable; MTP1, metatarsophalangeal joint; OR, odds ratio.

SI conversion factor: To convert serum uric acid level to micromoles per liter, multiply by 59.485.

^aThe intercept of model 2 is -3.78 , and the intercept of model 3 is -4.49 .

^bAngina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease.

Table 3. Performance of the 3 Models Before Shrinkage by the Bootstrap Method

Model	Description	Area (95% Confidence Interval) Under the ROC Curve	Nagelkerke R^2	Hosmer-Lemeshow Goodness-of-Fit P Value	Calibration Slope (SE)
1 ^a	Statistically optimal model	0.89 (0.85-0.92)	0.57	.52	0.98 (0.11)
2	Predefined model without laboratory testing	0.82 (0.77-0.87)	0.41	.44	1.00 (0.12)
3	Predefined model with laboratory testing	0.85 (0.81-0.90)	0.51	.46	1.00 (0.11)

Abbreviation: ROC, receiver operating characteristic.

^aIncludes the variable of tophus, which was 100% specific for the presence of monosodium urate crystals in synovial joint fluid analysis.

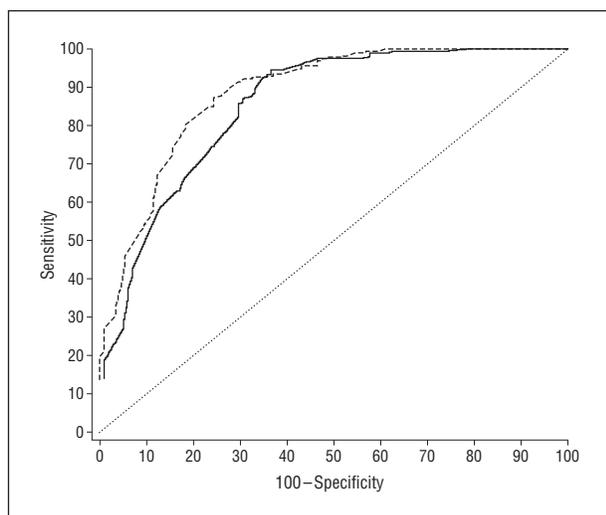


Figure 2. Areas under the receiver operating characteristic (ROC) curve for the statistically optimal model (model 1, broken line) and for the predefined (model 3) solid line. The diagonal line indicates the curve for a virtual model without predicting value (ROC of 0.5).

>4 to <8 , and ≥ 8 points) on the final diagnostic rule were 2.8% (2 of 72), 27.0% (17 of 63), and 80.4% (197 of 245).

COMMENT

To our knowledge, this diagnostic study is the first to develop a clinical prediction model for the diagnosis of acute

gouty arthritis in primary care. We present a model that showed a good internal validity and performed nearly equally as well as the statistically optimal model even after the correction for overoptimism of the model in new patients and the transformation of the regression coefficient to easy-to-use scores. The model contains a limited number of signs and symptoms and 1 laboratory test (serum uric acid level), predefined based on prior knowledge of their association with gout and their availability to primary care physicians in routine daily practice. This yielded a diagnostic rule that could discriminate patients with gout using scores for the following 7 variables that are easily ascertainable in primary care: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, MTP1 involvement, hypertension or 1 or more cardiovascular diseases, and serum uric acid level exceeding 5.88 mg/dL. The positive and negative predictive values of FP diagnosis of gout were moderate in our study. The presented diagnostic rule helps FPs to select patients with high vs low probability of gout and to restrict the use of joint fluid aspiration to test for the presence of MSU crystals for patients with remaining uncertainty about the diagnosis.

On the diagnostic rule, a score of 4 or less ruled out gout in almost 100% of patients. Diagnoses such as rheumatoid arthritis, pseudogout, psoriatic arthritis, and reactive arthritis must be considered in these patients. Among patients with a score of 8 or higher, gout was confirmed in more than 80%, indicating gout-specific management options such as systemic corticosteroid use (instead of non-steroidal anti-inflammatory drugs),⁹ uric acid-lowering

Table 4. Clinical Scores of the Final Diagnostic Rule After Transforming the Regression Coefficients Shrunk by the Bootstrap Method

Predefined Variable	Regression Coefficient After Shrinkage	Clinical Score
Male sex	1.01	2.0
Previous patient-reported arthritis attack	0.95	2.0
Onset within 1 d	0.03	0.5
Joint redness	0.40	1.0
MTP1 involvement	1.25	2.5
Hypertension or ≥ 1 cardiovascular diseases ^a	0.72	1.5
Serum uric acid level >5.88 mg/dL	1.85	3.5
Maximum score	6.21	13.0

Abbreviation: MTP1, metatarsophalangeal joint.

SI conversion factor: To convert serum uric acid level to micromoles per liter, multiply by 59.485.

^aAngina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischemic attack, or peripheral vascular disease.

therapy if indicated,¹⁴ and evaluation of gout-associated cardiovascular¹⁴⁻¹⁷ and renal¹⁸ diseases. At this score range, a false-positive diagnosis of gout was found in 17% of patients, which is better than the FP false-positive diagnosis rate of 36.3%. However, the risk of missing other important conditions remains. Thirty-two patients with false-positive results according to the diagnostic rule were classified as having arthritis of unknown cause, and only 1 patient was classified as having a possible prestage of rheumatoid arthritis. None had septic arthritis (data not shown). This implies that the false-positive outcomes only occasionally missed important diagnoses at a cutoff score of 8 or higher on the diagnostic rule. In addition, development of another disease over time must be noted if the arthritis continues, deteriorates, or recurs. A midrange score (>4 to <8) leaves uncertainty about the diagnosis (with gout confirmed in about 30%). In these patients, analysis of synovial fluid from the affected joint for the presence of MSU crystals should be considered if necessary for future management. With the help of a computer program or calculator, the original untransformed (shrunk) regression coefficients of the final model can be applied to more accurately predict gout diagnosis for an individual patient compared with the simple scores of the diagnostic rule.

We used a model with predefined variables rather than a data-derived model. Fitting such an optimal model using variables based on statistical significance in small data sets such as ours has the following risks: a few patients can alter the model (unstable selection), variables may be nonsignificant due to chance processes, standard errors and *P* values are underestimated, and power to select important variables is limited.¹² Our strategy to fit a model with predefined variables (based on external knowledge independent of statistical significance and shrunk by the bootstrap method to correct for overoptimism of the model in new patients) is considered the most obvious choice in this situation.¹² Despite this, overoptimism of the model may occur among new patients. Therefore, our diagnostic rule needs to be validated in other primary care populations before definitive implementa-

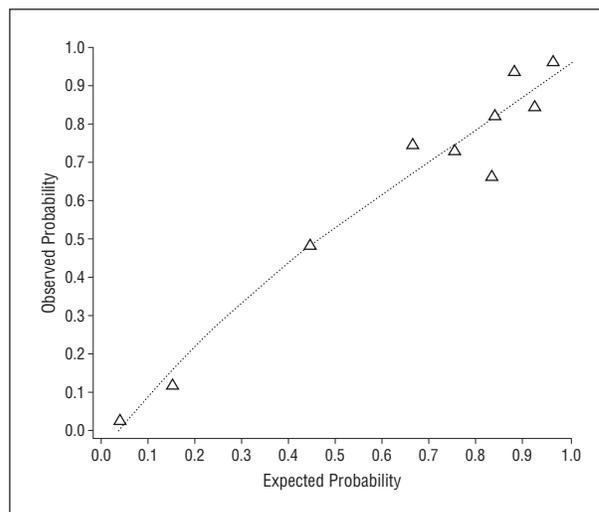


Figure 3. Calibration plot of the final diagnostic rule. Every triangle is a decile of observed score (expected probability) plotted against the observed fraction with the presence of monosodium urate crystals (observed probability).

tion in daily practice, as the application in a single data set may not indicate its performance among future patients.¹³

Because most patients with gout are diagnosed (and subsequently managed) in primary care, the setting of our study was relevant for investigating gout.^{4,5} The included patients had a high priori probability of physician-diagnosed gout in the general population.

There are several limitations of the study. The clinical variables were not assessed by the participating FPs but by one of us (M.J.) according to the study protocol. Although this may have limited the generalizability of our results, we believe that the variables in the proposed diagnostic rule can be reliably assessed by FPs as well.

Because the diagnostic rule was developed in a population of patients with monoarthritis seen by FPs, its application pertains to them and not to patients with oligoarticular and polyarticular arthritis. However, the prevalence of oligoarticular and polyarticular (gout) arthritis is low among primary care patients.¹⁹ Because monoarthritis was the inclusion criterion, the probability of gout was raised among the studied patients. Rather than (possible) selection bias, this reflects the population of interest in whom FPs diagnose acute gouty arthritis. As a consequence, there is little risk that this aspect of patient recruitment biased our findings. Bias at the testing stage (eg, verification bias) was another risk of our study. However, participating FPs were invited to send all patients with presumed monoarthritis even when referral was not needed from the perspective of regular primary care. There were no exclusion criteria, and all patient data were evaluated without delay, which could have diluted the association between presenting signs and symptoms and MSU crystal identification.

Aspirated joint fluid was thoroughly searched for MSU crystals (sensitive detection), and detected crystals were specifically identified by rheumatologists (M.J. and colleague) with experience in synovial fluid analysis. The sensitivity of crystal detection is estimated to be higher than 95%, with a specificity higher than

97%, even by trained observers who had no previous experience in synovial fluid analysis.²⁰ In addition, study patients with identified MSU crystals were eligible to participate in a randomized clinical trial accompanying the present study.⁹

However, in 63 patients (19.2%), no MSU crystals were detected and no other joint diagnosis established. Our study findings would have differed if patients with arthritis of unknown cause had turned out to have true gout diagnoses after our follow-up period of 1 to 3 years. Most gouty reattacks would have occurred within the follow-up period, and (as expected) this did not happen frequently. In addition, the proportion of patients with arthritis of unknown cause in our study was low compared with the proportion of patients with undifferentiated arthritis reported in population surveys or investigations among patients at early-arthritis clinics.^{21,22}

Although it is not difficult to obtain the variables to compute the diagnostic rule score, time constraints in busy practices and perceived complexity may prevent the use of the model. To alleviate this, an online calculator is available on the Internet (<http://www.umcn.nl/goutcalc>).

In conclusion, our study using an unequivocal reference test for the presence of synovial MSU crystals elucidates the validity of clinical signs and symptoms for diagnosing acute gouty arthritis in primary care. We developed and validated a diagnostic rule without joint fluid analysis for use by FPs. The rule may also be helpful in defining eligible patients with gout for participation in research settings vs other clinical criteria such as those of the American College of Rheumatology,²³ which appear recently to have limited validity.^{24,25}

Accepted for Publication: July 12, 2009.

Correspondence: Hein J. E. M. Janssens, MD, Department of Primary and Community Care, Radboud University Nijmegen Medical Center, PO Box 9101, 6500 HB Nijmegen, the Netherlands (h.janssens@elg.umcn.nl).

Author Contributions: *Study concept and design:* Janssens, Fransen, van de Lisdonk, van Riel, van Weel, and Janssen. *Acquisition of data:* Janssens and Janssen. *Analysis and interpretation of data:* Janssens and Fransen. *Drafting of the manuscript:* Janssens, Fransen, and van de Lisdonk. *Critical revision of the manuscript for important intellectual content:* Fransen, van de Lisdonk, van Riel, van Weel, and Janssen. *Statistical analysis:* Fransen. *Administrative, technical, and material support:* Janssens and van de Lisdonk. *Study supervision:* Janssens, van de Lisdonk, van Riel, van Weel, and Janssen.

Financial Disclosure: None reported.

Additional Contributions: Tonnie Berends; Carla De Gendt, MD; Alphons de Jong, MD, PhD; Henk Visser, MD, PhD; Twanny Jeijmsman-Rouwhorst; and Jan van Doremalen, MSc, helped collect data. We thank the 93 family physicians who selected the patients, as well as the patients for their willingness to participate in the study.

REFERENCES

1. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? *J Rheumatol*. 2002;29(11):2403-2406.
2. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990-1999. *Ann Rheum Dis*. 2005;64(2):267-272.
3. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41(5):778-799.
4. Zhang W, Doherty M, Pascual E, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout, part I: diagnosis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCI-SIT). *Ann Rheum Dis*. 2006;65(10):1301-1311.
5. Rott KT, Agudelo CA. Gout. *JAMA*. 2003;289(21):2857-2860.
6. Pal B, Foxall M, Dysart T, Carey F, Whittaker M. How is gout managed in primary care? a review of current practice and proposed guidelines. *Clin Rheumatol*. 2000;19(1):21-25.
7. Gorter KJ, Tan G, Verstappen WHJM, et al. NHG-standaard Jicht [NHG practice guideline "gout"]. *Huisarts Wet*. 2001;44:304-313.
8. Rainer TH, Graham CA. A significant step forward for gout. *Lancet*. 2008;371(9627):1816-1818.
9. Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet*. 2008;371(9627):1854-1860.
10. Nagelkerke NJ. A note on a general definition of the coefficient of determination. *Biometrika*. 1991;78:691-692.
11. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema DF. Validity of prognostic models: when is a model clinically useful? *Semin Urol Oncol*. 2002;20(2):96-107.
12. Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD. Prognostic modeling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med*. 2000;19(8):1059-1079.
13. Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol*. 2003;56(9):826-832.
14. Zhang W, Doherty M, Bardin T, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR evidence based recommendations for gout, part II: management: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCI-SIT). *Ann Rheum Dis*. 2006;65(10):1312-1324.
15. Janssens HJ, van de Lisdonk EH, Bor H, van den Hoogen HJ, Janssen M. Gout, just a nasty event or a cardiovascular signal? a study from primary care. *Fam Pract*. 2003;20(4):413-416.
16. Krishnan E, Baker JF, Furst DE, Schumacher HR. Gout and the risk of acute myocardial infarction. *Arthritis Rheum*. 2006;54(8):2688-2696.
17. Fox R. Management of recurrent gout. *BMJ*. 2008;336(7639):329.
18. Petersel D, Schlesinger N. Treatment of acute gout in hospitalized patients. *J Rheumatol*. 2007;34(7):1566-1568.
19. Lawry GV II, Fan PT, Bluestone R. Polyarticular versus monoarticular gout: a prospective, comparative analysis of clinical features. *Medicine (Baltimore)*. 1988;67(5):335-343.
20. Lumbrellas B, Pascual E, Frasquet J, González-Salinas J, Rodríguez E, Hernández-Aguado I. Analysis for crystals in synovial fluid: training of the analysts results in high consistency. *Ann Rheum Dis*. 2005;64(4):612-615.
21. Savolainen E, Kaipainen-Seppänen O, Kröger L, Luosujärvi R. Total incidence and distribution of inflammatory joint diseases in a defined population: results from the Kuopio 2000 Arthritis Survey. *J Rheumatol*. 2003;30(11):2460-2468.
22. 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.
23. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20(3):895-900.
24. Malik A, Schumacher HR, Dinnella JE, Clayburne GM. Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. *J Clin Rheumatol*. 2009;15(1):22-24.
25. Janssens HJ, Janssen M, van de Lisdonk EH, Fransen J, van Riel PL, van Weel C. Limited validity of the American College of Rheumatology criteria for classifying patients with gout in primary care [published ahead of print March 16, 2010]. *Ann Rheum Dis*. <http://ard.bmj.com/content/early/2010/03/12/ard.2009.123687.extract>. Accessed April 22, 2010.