The validation of a diagnostic rule for gout without joint fluid analysis: a prospective study

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Abstract

Objective. The gold standard for diagnosing gout is the identification of MSU crystals in joint fluid. In secondary care, the facilities or expertise to analyse joint fluid are not always available and gout is diagnosed clinically. To improve the predictive value of the clinical diagnosis of gout in secondary care, a diagnostic rule developed in primary care could be helpful. The aim of this study was to validate this diagnostic rule in a secondary care population with the gold standard as reference test.

Methods. Three hundred and ninety patients with monoarthritis were included. The variables of the diagnostic rule (male sex, previous arthritis attack, onset <1 day, joint redness, involvement of the first MTP joint, hypertension or one or more cardiovascular disease, and serum uric acid >5.88 mg/dl) were collected and scored. The affected joint was aspirated and joint fluid was analysed for the presence of MSU crystals.

Results. In 219 patients (56%) MSU crystals were found. The positive predictive value of a score of ≥8 points was 0.87, the negative predictive value of a score of ≤4 points was 0.95. The area under the receiver operating characteristic curve for the diagnostic rule was 0.86 (95% CI 0.82, 0.89). The Hosmer-Lemeshow goodness-of-fit test showed that the difference between the expected and the observed probability was non-significant (P = 0.64), indicating good agreement.

Conclusion. An easy-to-use diagnostic rule for gout developed in primary care shows good performance in secondary care and improves the predictive value of the clinical diagnosis of gout when joint fluid analysis is not available.

Key words: gout, diagnosis, diagnostic rule, joint fluid, synovial fluid.

Introduction

Gout is a common problem that affects 1.4% of the population [1]. The gold standard for diagnosing gout is the identification of MSU crystals in joint fluid by polarization microscopy [2, 3]. Although this is the gold standard, in some patients joint fluid analysis is not performed. Joint fluid analysis requires skills in arthrocentesis, the availability of polarization microscopy and familiarity with the use of this microscope. In primary care [4], but also in secondary care at emergency or other non-rheumatology departments, the facilities or expertise to analyse joint fluid are not always available. Even rheumatologists often lack these facilities or expertise [5, 6]. In that case gout is diagnosed based on clinical signs and symptoms only.

However, it has been shown that the validity of the clinical diagnosis of gout in primary care is limited [positive predictive value (PPV) 0.64 and negative predictive value (NPV) 0.87] [7]. To improve the predictive value of the clinical diagnosis of gout in primary care, a diagnostic rule (gout calculator) was developed [7]. This diagnostic rule includes scores for the following seven variables: male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, involvement of the first MTP joint (MTP-1), hypertension or one or more cardiovascular diseases and serum uric acid exceeding 5.88 mg/dl (equal to 0.35 mmol/l). The total score of the
variables of four or fewer of these variables ruled out gout in 97%. Gout was confirmed by MSU crystal identification in 80% of the patients with a score ≥8. A midrange score (between 4 and 8), leaving uncertainty about the diagnosis, was found in ~15% of the patients and the authors suggested that joint fluid analysis be performed for this group [7]. A valid diagnosis is of clinical importance in providing the right therapeutic measures, correct information to the patient and correct estimation of the prognosis (especially with respect to cardiovascular risks and morbidity) [8–12].

An easy-to-use diagnostic rule without joint fluid analysis developed in a primary care population showed a clinically highly relevant validity [7]. If the same validity could be shown in secondary care patients, the diagnostic rule may have clinical relevance for this population as well. The objective of this study was to validate this diagnostic rule for patients with monoarthritis diagnosed at a rheumatology department (secondary care).

Methods

Patient selection

This was a prospective diagnostic validation study performed from 1 January 2011 until 8 May 2013 in the eastern part of the Netherlands. Adult patients who were diagnosed in our regional gout research centre (Department of Rheumatology, Rijnstate Hospital, Arnhem) with signs and symptoms of monoarthritis at their first visit, who conceivably could have gout, were included upon referral. These patients were considered as persons with a prior probability of acute gout arthritis (the research source population). For this reason patients with previously MSU crystal–proven gout were not included. Patients were referred by general practitioners, emergency care physicians, cardiologists, internists, orthopaedic surgeons and other secondary care physicians. According to the nature of this study (observing anonymously regular secondary care diagnostic interventions), and Dutch law on performing medical research on humans [Medical Research Involving Human Subjects Act (WMO)], ethics committee approval was not required.

Baseline assessment

Patients were examined by physicians at the research centre (L.B.E.K. and M.J., and in a few patients substituted by a colleague rheumatologist). Data for all seven variables of the diagnostic rule were collected. The seven variables are male sex (score 2 points), previous patient-reported arthritis attack (score 2 points), onset within 1 day (score 0.5 points), joint redness (score 1 point), involvement of the MTP-1 joint (score 2.5 points), hypertension or one or more cardiovascular diseases (angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease; score 1.5 points) and serum uric acid exceeding 5.88 mg/dl (equal to 0.35 mmol/l; score 3.5 points) [7]. The affected joint was aspirated and the joint fluid was analysed with a polarization microscope for the presence of MSU crystals. When no joint fluid could be collected during arthrocentesis the patient was classified as having non-gout. When MSU crystals could not be identified, additional clinical and laboratory evaluations were performed to diagnose or exclude other forms of arthritis, including the identification of other joint fluid crystals, assessment of IgM RF and anti-CCP antibody, radiographic evaluation, and, on indication, assessment of ANA, anti-streptolysin titre, anti-DNase B or Borrelia IgM and IgG antibodies. Should there be a definite diagnosis fulfilling the accepted criteria of rheumatic diseases other than gout, the follow-up period was stopped.

Finally, for each patient the score of the diagnostic rule was calculated after the follow-up period. The physicians who performed the joint fluid analysis and who collected data on the variables of the diagnostic rule were blinded for the score.

Follow-up

In the case of unspecified arthritis, the patient was followed up at the regional gout research centre until 31 July 2013 and was re-evaluated, including joint fluid analysis for the presence of MSU crystals, if a new episode of any arthritis occurred. If MSU crystals were identified during the follow-up period, the patient was retrospectively classified as already having had gout at the baseline assessment. The initial negative result for gout of the joint fluid analysis was then changed to a positive result.

Statistical analysis

Differences in the seven variables of the diagnostic rule between the gout and non-gout groups at baseline were analysed using the chi-squared test. The score of the diagnostic rule was calculated for each patient and the mean scores of the group of patients with and without gout were compared using the Mann–Whitney U test.

A gout diagnosis according to the diagnostic rule was considered as the index test, with the identification of MSU crystals as the reference test. The performance of the diagnostic rule was evaluated by assessing the PPV, NPV, area under the receiver operating characteristic (ROC) curve, fit according to the Hosmer–Lemeshow goodness-of-fit test and a calibration plot. The PPV (the number of patients with a positive index and reference test as a proportion of all patients with a positive index test) and NPV (the number of patients with a negative index and reference test as a proportion of all patients with a negative index test) were calculated for the three original cut-off scores using 2 × 3 tables.

Missing data were handled by multiple imputation analysis with five imputed data sets. All statistical tests were performed using PASW Statistics 18 (SPSS, Chicago, IL, USA).
Results

Four hundred and forty-four patients with signs and symptoms of monoarthritis were examined. Fifty-four patients (12%) were excluded because arthrocentesis was not performed. The completeness of the baseline data for the 390 included patients varied between 91% for serum uric acid >5.88 mg/dl and 100% for sex and MTP-1 involvement.

The mean age of the included patients was 61.0 years (S.D. 14.0) and 274 (70%) of them were male. The affected joints were MTP-1 (29%), knee (26%), ankle (17%), wrist (10%), elbow (4%), first IP joint of the foot (4%), PIP joint of the hand (3%) and other joints (7%). At baseline, MSU crystals were identified in 49% (191/390) of patients. During follow-up, MSU crystals were found in joint fluid during a recurrent arthritis in an additional 28 patients, resulting in 56% (219/390) who were classified as having gout. Twenty-two per cent (86/390) fulfilled the criteria for other rheumatic diseases and 22% (85/390) had unspecified arthritis. Table 1 shows the variables of the diagnostic rule in the gout and non-gout groups.

The mean scores of the diagnostic rule were 8.6 (S.D. 2.1) and 5.2 (S.D. 2.5) (P < 0.001) in the gout and non-gout groups, respectively, with median scores of 8.5 (IQR 7.1–10.5) and 5.1 (IQR 3.5–7.0). The area under the ROC curve for the diagnostic rule was 0.86 (95% CI 0.82, 0.89) (see Fig. 1). The Hosmer-Lemeshow goodness-of-fit test showed that the difference between the expected and the observed probability was non-significant (P = 0.64), indicating a good fit. Fig. 2 shows the calibration plot of the diagnostic rule. The triangles show the observed and expected probabilities for having gout per decile of the predicted score. The triangles appear close to the line of identity, pointing to good fit and no systematic under- or overestimation. The PPV for a score of ≥8 points was 0.87 and the NPV for a score of ≤4 points was 0.95.

Discussion

According to the results of this study, the diagnostic rule for diagnosing gout without joint fluid analysis, which was developed and validated in primary care, appeared to be valid in a secondary care population of monoarthritis patients as well. The diagnostic rule discriminated well between patients with and without MSU crystals in their joint fluid, according to the area under the ROC curve. Moreover, the predicted probability for the presence of MSU crystals agreed well throughout the range of the score with the observed probability of MSU crystals being present. It is an easy-to-use tool for practitioners that has been proved to be a valid instrument for diagnosing gout in primary and secondary care. It helps practitioners to select patients with a high or low probability of gout among patients with monoarthritis when joint fluid analysis is not possible or available. By using the diagnostic rule, the PPV of the clinical diagnosis may improve from 0.64 to 0.87 and the NPV from 0.87 to 0.95 [7].

The study in primary care patients in which the diagnostic rule was developed showed an area under the ROC curve of 0.85 (95% CI 0.81, 0.90) [7]. The PPV for a score of ≥8 points was 0.83 and the NPV for a score of ≤4 points was 0.95.

Table 1 The seven variables of the diagnostic rule in patients with and without gout

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gout (n = 219)</th>
<th>Non-gout (n = 171)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>Total, n</td>
<td>n (%)</td>
<td>Total, n</td>
</tr>
<tr>
<td></td>
<td>219</td>
<td>173 (79)</td>
<td>171</td>
</tr>
<tr>
<td>Previous patient-reported arthritis attack</td>
<td>217</td>
<td>176 (81)</td>
<td>168</td>
</tr>
<tr>
<td>Onset within 1 day</td>
<td>211</td>
<td>175 (83)</td>
<td>154</td>
</tr>
<tr>
<td>Joint redness</td>
<td>215</td>
<td>184 (86)</td>
<td>154</td>
</tr>
<tr>
<td>MTP-1 involvement</td>
<td>219</td>
<td>84 (38)</td>
<td>171</td>
</tr>
<tr>
<td>Hypertension or one or more cardiovascular diseasesa</td>
<td>219</td>
<td>161 (74)</td>
<td>171</td>
</tr>
<tr>
<td>Serum uric acid &gt;5.88 mg/dlb</td>
<td>207</td>
<td>197 (95)</td>
<td>148</td>
</tr>
</tbody>
</table>

a Angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease. b A serum uric acid level of 5.88 mg/dl is equal to 0.35 mmol/l. MTP-1: first MTP joint.
points was 0.98. Our validation study showed similar results.

In clinical practice the diagnostic rule can be used in patients with monoarthritis (see Fig. 3). When the rule indicates a low probability of gout (a score ≤4), the practitioner should consider a diagnosis other than gout, such as calcium pyrophosphate dihydrate arthritis, reactive arthritis, septic arthritis, RA, OA or PsA. When it indicates a high probability (a score ≥8), the practitioner can consider that the monoarthritis is caused by gout, implying the specific management options for this disease, including the evaluation of cardiovascular risk factors [13]. When there is uncertainty about the diagnosis (a score between 4 and 8), the patient should (still) be referred for joint fluid analysis. If joint fluid analysis is not possible or available, patients should be followed extensively for recurrent (gout) attacks or the occurrence of other specific rheumatic diseases. At all scores clinical re-evaluation of the patient is advisable in the case of a recurrent arthritis, because there always remains a risk of missing other important rheumatic diagnoses if patients are false-positively classified as gout by the diagnostic rule.

If MSU crystals were identified during the follow-up period, the patient was retrospectively classified as already having had gout at the baseline assessment. On the one hand, the possibility remains that the initial arthritis attack was caused by a monoarticular rheumatic disease other than gout, which can be expected to be rare. On the other hand, the probability that the initial flare was caused by gout when MSU crystals are found in the recurrent flare is much higher, which was underscored by the finding that the same joint was affected at baseline and at follow-up arthrocentesis in 17 of the 28 patients (61%; results not shown).

Fig. 2 Calibration plot of the diagnostic rule

Every triangle is a decile of the score of the diagnostic rule (expected probability) plotted against the proportion of patients with the presence of MSU crystals in that decile (observed probability).

Fig. 3 Use of the diagnostic rule in clinical practice

**Indicates angina pectoris, myocardial infarction, heart failure, cerebrovascular accident, transient ischaemic attack or peripheral vascular disease. **Indicates a serum uric acid level of 5.88 mg/dl (equal to 0.35 mmol/l). CPPD: calcium pyrophosphate dihydrate deposition disease.
When no joint fluid was collected during arthrocentesis (inadequate reference test), we classified these patients \((n = 12)\) as non-gout, because no MSU crystals could be identified. A different option would have been to exclude these patients from the analysis. However, although not excluding could bias the performance of the rule, we do not expect a substantial change; a second arthrocentesis was successful during follow-up in 5 of 12 patients (results not shown) in which no joint fluid could be collected during arthrocentesis at baseline, leaving seven patients without an adequate reference test.

The ACR criteria for classifying patients with gout were compared with the gold standard and they showed limited validity in two studies with a PPV of 0.66–0.80 and an NPV of 0.65–0.82 [14, 15]. The Chronic Gout Diagnosis (CGD) criteria developed for patients with chronic gout [16] compared with a clinical diagnosis of gout by a rheumatologist as reference test showed a PPV of 0.95 and an NPV of 0.98. There was good correlation between the CGD criteria and the diagnostic rule \((r = 0.95, P < 0.001)\) [17]. However, the controls were patients with a form of arthritis not mimicking gout and thus were not representative of the population of patients who are normally referred to secondary care and conceivably could have gout. The diagnostic value of the CGD criteria could therefore be overrated. The diagnostic rule has shown good performance in distinguishing between acute gout arthritis and septic arthritis [18].

A strength of our diagnostic study is the prospective design with a long follow-up period in which patients with unspecified arthritis were re-evaluated in the case of any new arthritis. Not excluding patients with unspecified arthritis is consistent with clinical practice in which unspecified monoarthritis is prevalent.

A possible limitation is that the observer of the joint fluid, the assessor of the reference test, was not fully blinded for the clinical data used for scoring the index test. However, there was blindness for the weights of the separate scores (from 0.5 to 3.5) and the sum total for the final score of the diagnostic rule, because both were calculated after the follow-up period. A second limitation is that MSU crystals might have been missed during joint fluid analysis, thus patients may have been falsely classified as non-gout. However, besides the fact of a long follow-up of those of our patients with negative joint fluid analysis, the sensitivity of crystal detection is 0.96 with a specificity of 0.87 in trained observers without previous experience in joint fluid analysis. The sensitivity of MSU crystal identification is 0.95 with a specificity 0.97 [19]. Our study was performed in a research centre for gout with experienced joint fluid researchers. This makes missing MSU crystals less likely. A third limitation might be that 54 patients eligible for inclusion were excluded because arthrocentesis was not performed. However, we think that the exclusion of these patients did not bias our results substantially, as the patients included appeared to be highly representative of secondary care patients with monoarthritis, who conceivably could have gout. A fourth limitation might be that the diagnostic rule was developed and validated in patients with monoarthritis, who are, after excluding patients with oligo- or polyarthritis, not fully representative of patients with gout in the secondary care population. However, we feel confident that the rule will also work in patients with oligo- or polyarthritis suspected of gout because of the strength of its performance in patients with monoarthritis. The diagnostic rule has been developed and now validated for the primary and secondary population in the eastern part of the Netherlands, which might affect its validity in other populations. Validation of the diagnostic rule in other countries in primary care as well as secondary care would be welcome, to determine whether the diagnostic performance remains robust.

In conclusion, a diagnostic rule for diagnosing gout without joint fluid analysis in patients with monoarthritis, which was developed in a primary care population, has good performance in a secondary care population. This easy-to-use rule helps to improve the predictive value of the clinical diagnosis of gout when joint fluid analysis is not possible or available.

### Rheumatology key messages

- A diagnostic rule for gout without joint fluid analysis has been developed for use in primary care.
- This easy-to-use diagnostic rule for gout shows good performance in secondary care.
- The diagnostic rule improves the predictive value of the clinical diagnosis of gout.

### Acknowledgements

We thank Dr. J. D. Macfarlane, rheumatologist, for correcting the English text.

**Funding:** None.

**Disclosure statement:** The authors have declared no conflicts of interest.

### References


