The GOUT-36 prediction rule for inpatient gout flare in people with comorbid gout: derivation and external validation

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Abstract

Objectives: To develop and validate a gout flare risk stratification tool for people with gout hospitalised for non-gout conditions.

Methods: The prediction rule for inpatient gout flare was derived from a cohort of 625 hospitalised people with comorbid gout from New Zealand. The rule had four items: (1) no pre-admission GOut flare prophylaxis, (2) no pre-admission Urate-lowering therapy, (3) Tophus and (4) pre-admission serum urate >0.36 mmol/L within the previous year (GOUT-36 rule). Two or more items are required for the classification of high risk for developing inpatient gout flare. The GOUT-36 rule was validated in a prospective cohort of 284 hospitalised people with comorbid gout from Thailand and China.

Results: The GOUT-36 rule had a sensitivity of 75%, specificity of 67% and AUC of 0.71 for classifying people at high risk for developing inpatient gout flare. Four risk groups were developed: low (no items), moderate (one item), high (two items) and very high risk (three or four items). In a population with frequent (overall 34%) in-hospital gout flare, 80% of people with very high risk people developed flare, while 11% of low-risk people had inpatient flare.

Conclusion: GOUT-36 rule is simple and sensitive for classifying people with high risk for inpatient gout flare. The rule may help inform clinical decision and future research on the prevention of inpatient gout flare.

Key message

- GOUT-36 rule helps identify people at high risk of developing gout flare during hospital stay

Introduction

Gout flare is an important problem in hospital-based practice, with prevalence between 14% and 35% in people with comorbid gout who were hospitalised for reasons other than gout.(1-3) Inpatient gout flare adds three to six days to hospital length of stay(4, 5) and is associated with higher inpatient healthcare cost.(6) However, a clinical tool to identify people at high risk for inpatient gout flare has not been developed, partly contributing to a lack of evidence-based recommendations for prevention of inpatient gout flare.

In this study, we aimed to develop a simple prediction rule to help clinicians identify people at high risk of gout flare during hospital admission using data from a cohort in New Zealand.(1) The prediction rule was then validated in an independent cohort from Thailand and China.

Methods

Development of the prediction rule

The prediction rule was developed from a set of nine previously identified predictors of inpatient gout flare in people with comorbid gout.(1) The predictors and their corresponding regression coefficients were derived from a logistic regression analysis of 625 hospitalised people with comorbid gout from New Zealand (derivation cohort). The derivation cohort had 87 inpatient gout flare episodes (14%) and was predominantly male (78%) and European (60%).(1) Four predictors were readily assessable at the time of hospital admission so were categorised as 'pre-admission domain'. The remaining five were categorised as 'in-admission domain' as they occur during admission (**Supplementary Table S1,** available from *Rheumatology* online).

Three candidate prediction rules were initially developed (**Supplementary Table S1,** available from *Rheumatology* online): the regression coefficient (β)-based rule, the simple

rule and the first-day rule. The β-based rule contained nine items, each assigned with a score derived by rounding each predictor's β value to the closest integer.(7) The simple rule also had nine items, but all items were assigned a score of one point. The first-day rule only contained the four items from the pre-admission domain to facilitate early risk stratification and to avoid the need for repeat assessment during hospital stay which may not be feasible for real-world hospital practice. The cut-off for each candidate rule was determined by the maximum Youden index (**Supplementary Table S2,** available from *Rheumatology* online), which represented the point on the receiver operating characteristic (ROC) curve with the highest sensitivity and specificity.(8) The cut-off as well as the performance characteristics of each candidate rule in the derivation cohort are shown in **Supplementary Table S1,** available from *Rheumatology* online.

For the selection of the final prediction rule, it was stipulated that the rule must have a sensitivity of 0.80 or more to ensure that people at high-risk were correctly identified with reasonable accuracy. The selected rule was also required to be as user-friendly as possible to facilitate wide use in routine hospital-based practice. Based on these criteria, the first-day rule was chosen for its high sensitivity (84%) and simplicity (only four items). The first-day rule also had the practical advantage of early risk assessment at admission without requiring repeat evaluation during hospitalisation. We renamed the first-day rule as the GOUT-36 rule as an acronym for 'no pre-admission GOut flare prophylaxis', 'no pre-admission ULT', 'Tophus' and 'pre-admission serum urate >0.36 mmol/L within the previous year' (**Table 1**).

External validation

The GOUT-36 rule was validated in an independent cohort prospectively recruited between 12 December 2019 and 31 December 2020 from two hospitals in Thailand (Thammasat and Naresuan University Hospital) and one in China (Peking University

International Hospital). The validation cohort included all hospitalised people aged 18 years or older with comorbid gout, defined as having received a diagnosis of gout by a doctor before the current hospital admission. Exclusion criteria included people who were hospitalised with gout as the primary admission diagnosis and people who received a gout diagnosis for the first time in the current admission. For people who were hospitalised more than once in the study period, only data from the first admission were collected.

We identified potential participants through usual rheumatology services and by daily manual screening of the hospital admission database for people who had gout as a comorbid condition in their previous outpatient notes or hospital discharge letters (**Supplementary Figure S1,** available from *Rheumatology* online). Investigators approached the potential participants to confirm their eligibility and invited them to participate in the study. After obtaining informed consent, the investigators collected data by conducting interview (demographics), physical examination (tophus), and review of medical records (admission data, past prescriptions and the items from GOUT-36 rule). After the first data collection, the participants were followed daily until hospital discharge for the development of inpatient gout flare. Gout flare was defined as a new episode of joint pain and swelling judged to be gout by an attending doctor or consultant rheumatologist. For participants who had more than one flare episode in the same hospital admission, only data prior to the first flare episode were collected. A full list of variables and their definitions are shown in **Supplementary Table S3,** available from *Rheumatology* online.

Statistical analysis

Validation of a regression-based model requires at least 81 events to detect a change of 0.1 in the value of area under the ROC curve (AUC) with 80% power.(9) Recruitment of at

least 200 hospitalised people with comorbid gout (100 flares and 100 non-flares) was therefore planned.

The performance of the GOUT-36 rule was determined in both derivation and validation cohorts, with inpatient gout flare (yes/no) as the primary outcome. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratios (LR+), negative likelihood ratios (LR-), AUC and the calibration slope were calculated. An ideal prediction rule should have sensitivity, specificity, PPV and NPV as close to 1.0 as possible. An ideal prediction rule is expected to have LR+ higher than 1.0 and LR- lower than 1.0. AUC is the ability to discriminate high-risk from low-risk people, which ranges between 0.5 (performing no better than chance) and 1.0 (perfect discrimination). A calibration plot was determined by plotting the predicted probability of flare against the observed probability of flare. An ideal model would have a calibration slope of 1.0, indicating a perfect agreement between the predicted and observed probability of flare. Statistical analysis was performed using IBM SPSS Statistics (Version 16) and MedCalc (Version 19.5.3).

Ethical approval

The Human Research Ethics Committee, University of Otago, reviewed and approved the study protocol (reference number H18/012) for the New Zealand (derivation) cohort, in compliance with the Helsinki Declaration. This was a retrospective, chart-review, cohort study for which informed consent was not required. For the validation cohort, the study protocol was reviewed and approved by the institutional ethics committee of Thammasat University (reference number MTU-EC-IM-1-185/62), Naresuan University (reference number P3-0011/2563) and Peking University International Hospital (reference number

2020-032-BMR). All participants in the validation cohort provided informed consent before joining the study.

Results

For the validation cohort, 431 admissions were screened and 284 admissions (for 284 people) were analysed. There were 96 flare episodes (34%). The majority of the participants were male (81%) and Asian (99%) (**Supplementary Tables S4** and **S5,** available from *Rheumatology* online).

Compared to the derivation cohort, the GOUT-36 rule in the validation cohort had lower sensitivity (75% vs. 84%) but superior specificity (67% vs. 50%) and superior AUC (0.71 vs. 0.67). The GOUT-36 rule had a PPV of 0.54, NPV of 0.84, LR+ of 2.27, LR- of 0.37 in the validation cohort (**Table 2**). Calibration slopes for the GOUT-36 rule in the derivation and validation cohorts were 0.95 and 1.40, respectively (**Table 2** and **Supplementary Figure S2,** available from *Rheumatology* online).

Four risk groups were developed based on the GOUT-36 rule: low risk (no item), moderate risk (one item), high risk (two items) and very high risk (three or four items). In the validation cohort, 11% of low-risk group developed gout flare and 80% of the very high-risk group had a flare during admission (**Table 2** and **Supplementary Figure S3,** available from *Rheumatology* online).

Discussion

We developed and validated a prediction rule for inpatient gout flare in people with comorbid gout. The rule was intended to help hospital-based clinicians identify people who are at high risk of developing gout flare during hospital admission. The GOUT-36 rule

contains only four items, which could be easily assessed by medical records review (prescription history of gout flare prophylaxis and ULT, and serum urate results) and physical examination (tophus). The rule also allows risk assessment on the first day of admission by relying only on pre-admission data. To ensure consistent performance across different populations, the rule was validated in a prospectively recruited cohorts from Thailand and China.

The GOUT-36 rule had a sensitivity of 75% to 84% (**Table 2**). High sensitivity was prioritised during the development to ensure that the rule identified as many high-risk people as possible. However, maximising the sensitivity may have resulted in a relatively lower specificity (up to 67%), which we considered an acceptable trade-off. Misclassifying low-risk people as high risk is unlikely to lead to serious adverse events, but failing to identify high-risk people would make the prediction rule less clinically useful. PPV of 0.54 indicated that over half of people classified as high-risk would eventually develop flare, while NPV of 0.84 indicated that the majority of people who were classified as low/moderate risk would not develop flare. These results further support the satisfactory performance of the GOUT-36 rule in the validation cohort.

There were some limitations to the validation of the GOUT-36 rule. Participants in the validation cohort were identified by manual screening of admission database and through rheumatology services, potentially leading to selection bias towards people with gout flare who required rheumatologist input. The majority of participants were recruited from hospitals in major urban areas, which may not be representative of the general gout population being cared for in the community hospitals. Further validation in community settings is therefore encouraged. We did not used Gaffo's definition of flare to support the presence of gout flare in the validation cohort.(10) However, gout flare was confirmed by a specialist physician in our study. This definition was considered the gold standard when Gaffo's definition was

developed and validated, so we believe that our approach is valid. It was possible that other types of arthritis with similar natural course to gout (e.g., calcium pyrophosphate arthritis) could have been mistakenly included in the flare group. The possible presence of non-gout episodes in the flare group, however, should have led to worse performance of the GOUT-36 rule because the items in the rule were highly specific to gout. Finally, we were unable to test the performance of GOUT-36 rule in specific subgroups (e.g., people with coexisting cardiovascular disease, people with acute kidney injury), because there were insufficient number of flare event for such analyses.

Regarding the generalizability, the GOUT-36 rule was developed and validated in general inpatient populations from New Zealand, Thailand and China. These three countries have widely different health care systems, gout prevalence and ethnicities. This provides some evidence in support of the generalizability of the rule. The study results, however, cannot be extrapolated to primary care or outpatient settings. Furthermore, GOUT-36 rule should be used only in people already diagnosed with gout and should not be used for the diagnosis of an arthritis episode occurring in an inpatient setting.

The GOUT-36 rule can only help identify individuals with high risk for flare, but cannot dictate what preventive actions should be taken. Until there is sufficient evidence, what to do with high-risk individuals should be decided on a case-by-case basis. Potential preventive strategies may include ensuring continuation of existing gout medications and close monitoring for signs of flare The clinical usefulness of GOUT-36 rule in hospital practice requires further study. For example, a randomized trial could be set up to compare rates of inpatient gout flare in high-risk individuals receiving short course of prophylactic colchicine compared to high-risk individuals receiving placebo (i.e., usual care).

In conclusion, the GOUT-36 rule is a practical and sensitive risk stratification tool for inpatient gout flare. The rule may help clinicians identify people with high risk for inpatient flare on the first day of hospital admission and help promote the concept that gout flare prevention is included in the overall plan for that particular hospital event.

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Contributors

KJ and WJT designed the study. KJ, RL, PH, PT and LS collected the data for the validation cohort. KJ, RG, ND and WJT were involved in the prediction rule development and data analysis. All authors were involved in data interpretation and manuscript preparation and have given approval to the submitted version of the manuscript.

Data availability statement: The data underlying this article are available in the article and in its online supplementary material.

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Table 1. The GOUT-36 prediction rule for inpatient gout flare and definitions

GOUT-36 rule	**Definitions**[a]
Entry criteria	A person must have gout, defined as having received a diagnosis of gout by a doctor before the current hospital admission.
Classification*	A person with two or more of the following four items is classified as having high risk for inpatient gout flare.
Criteria	
(1) No GOut flare prophylaxis	No pre-admission gout flare prophylaxis medication according to medical records. Gout prophylaxis flare includes colchicine, oral NSAIDs and oral corticosteroids.
(2) No Urate-lowering therapy	No pre-admission urate-lowering therapy (ULT) according to medical records. ULT includes allopurinol, febuxostat, probenecid, benzbromarone or sulfinpyrazone.
(3) Tophus[b]	Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles).
(4) Serum urate >0.36 mmol/L	Highest serum urate level tested within 12 months before admission greater than 0.36 mmol/L (6 mg/dL).

[a]Evaluation should take place on the first day of hospital admission.

[b]Based on the 2015 ACR/EULAR gout classification criteria.(11)

Table 2. Performance characteristics of the GOUT-36 rule and the prevalence of gout flare according to risk groups

Cohort	**Derivation cohort (New Zealand)**	**Validation cohort (Thai-Chinese)**
Number of participants (flare)	625 (87 flares)	284 (96 flares)
Performance characteristics		
Sensitivity (95%CI)	0.84 (0.75 to 0.91)	0.75 (0.65 to 0.83)
Specificity (95%CI)	0.50 (0.46 to 0.54)	0.67 (0.60 to 0.74)
Positive predictive value (95%CI)	0.21 (0.19 to 0.24)	0.54 (0.48 to 0.59)
Negative predictive value (95%CI)	0.95 (0.92 to 0.97)	0.84 (0.79 to 0.88)
Positive likelihood ratio (95%CI)	1.68 (1.48 to 1.90)	2.27 (1.80 to 2.87)
Negative likelihood ratio (95%CI)	0.32 (0.20 to 0.52)	0.37 (0.26 to 0.54)
AUC (95%CI)	0.67 (0.61 to 0.73)	0.71 (0.65 to 0.77)
Calibration slope (95%CI)	0.95 (0.53 to 1.37)	1.40 (0.14 to 2.66)
Prevalence of inpatient gout flare by risk group		
Low risk (0 item)	3% (1/37)	11% (4/38)
Moderate risk (1 item)	5% (13/246)	18% (20/112)
High risk (2 items)	16% (41/263)	43% (40/94)
Very high risk (3 or 4 items)	41% (32/79)	80% (32/40)

AUC, area under the receiver operating characteristic curve; CI: confidence interval