ORIGINAL ARTICLE
Immunology, Allergic Disorders & Rheumatology

JKMS

http://dx.doi.org/10.3346/jkms.2015.30.6.700 • J Korean Med Sci 2015; 30: 700-704

Application of a Novel Diagnostic Rule in the Differential Diagnosis between Acute Gouty Arthritis and Septic Arthritis

Kwang-Hoon Lee,[1] Sang-Tae Choi,[2] Soo-Kyung Lee,[1] Joo-Hyun Lee,[3] and Bo-Young Yoon[3]

[1]Division of Rheumatology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang; [2]Division of Rheumatology, Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul; [3]Division of Rheumatology, Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea

Received: 11 September 2014
Accepted: 20 January 2015

Address for Correspondence:
Kwang-Hoon Lee, MD
Department of Internal Medicine, Dongguk University College of Medicine, 27 Dongguk-ro, Ilsandong-gu, Goyang 410-773, Korea
Tel: +82.31-961-7741, Fax: +82.31-961-7009
E-mail: lkh24217@hanmail.net

Funding: This work was supported by the Dongguk University Research Fund of 2012.

Septic arthritis and gout are major diseases that should be suspected in patients with acute monoarthritis. These two diseases are clinically similar and often indistinguishable without the help of synovial fluid analysis. Recently, a novel diagnostic rule for gout without synovial fluid analysis was developed and showed relevant performances. This study aimed to determine whether this diagnostic rule could perform well in distinguishing gout from septic arthritis. The diagnostic rule comprises 7 clinical and laboratory variables, each of which is given a specified score. The probability of gout is classified into 3 groups according to the sum of the scores: high (≥ 8), intermediate (> 4 to < 8) and low probability (≤ 4). In this retrospective study, we applied this diagnostic rule to 136 patients who presented as acute monoarthritis and were subsequently diagnosed as acute gout (n = 82) and septic arthritis (n = 54) based on synovial fluid analysis. The mean sum of scores of acute gout patients was significantly higher than that of those with septic arthritis (8.6 ± 0.2 vs. 3.6 ± 0.32, $P < 0.001$). Patients with acute gout had significantly more 'high', and less 'low' probabilities compared to those with septic arthritis (Eta[η]: 0.776). The prevalence of acute gouty arthritis, as confirmed by the presence of monosodium crystal, was 95.5% (61/64), 57.5% (19/33), and 5.1% (2/39) in high, intermediate and low probability group, respectively. The recently introduced diagnostic rule properly discriminates acute gout from septic arthritis. It may help physicians diagnose gout in cases difficult to be differentiated from septic arthritis.

Keywords: Gout; Arthritis, Infectious; Diagnosis, Differential; Diagnostic Test

INTRODUCTION

Acute gout and septic arthritis are the major diseases that should be suspected in patients presenting as acute monoarthritis (1). The differential diagnosis of these two diseases is important because incorrect diagnosis and misled treatment can lead to undesirable outcomes such as joint destruction or unnecessary surgical debridement. However, differentiating acute gout from septic arthritis can be difficult on clinical examination since they are clinically similar. Both of these two diseases commonly involve a single joint and accompany severe joint inflammation. Septic arthritis often accompany systemic features such as fever and chilling (1), which can also be seen in patients with gout, though they are not as common in gout as in septic arthritis. Diagnosis of both gout and septic arthritis can be established by synovial fluid analysis: demonstrating monosodium urate crystal (MSU) for gout by a polarized microscope and bacteria by Gram staining or culture in the case of septic arthritis. However, synovial fluid analysis is often impractical in real practice and the differential diagnosis between gout and septic arthritis might be problematic without the help of synovial fluid analysis. Recently, a novel diagnostic rule for acute gout without joint fluid analysis was introduced and showed a good performance in predicting the possibility of gout (2). However, the first study validating this rule included only 2 cases with septic arthritis. We applied this diagnostic rule to the patients with gout and those with septic arthritis and determined whether this rule properly diagnoses gout and excludes septic arthritis in the setting of acute monoarthritis.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of adult (age > 18 yr) patients who were diagnosed with acute gout or septic arthritis between January 2006 and December 2012 in Dongguk University Ilsan Hospital in Goyang, Korea. We searched in the electronic medical recording system for patients with an International Classification of Diseases (ICD)-10 code of gout (M10) or pyogenic arthritis (M00). After searching for such cases, in order to secure the certainty of diagnosis, we excluded patients who did not undergo synovial fluid analysis and only included

© 2015 The Korean Academy of Medical Sciences.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

pISSN 1011-8934
eISSN 1598-6357

those who were diagnosed by synovial fluid analysis (presence of monosodium urate [MSU] crystal in the case of gout and presence of bacteria in Gram stain or culture in the case of septic arthritis), which are the gold standards in the diagnosis of these two diseases.

Diagnostic rule

The diagnostic rule proposed by Janssens et al. (2) gives different scores to 7 clinical and laboratory variables: male sex = 2, previous patient-reported arthritis attack = 2, onset within a day = 0.5, joint redness = 1, 1st metatarsophalangeal (MTP) joint involvement = 2.5, hypertension or at least one cardiovascular disease = 1.5, serum uric acid level greater than 5.88 mg/dL = 3.5. The probability of acute gout is high if the sum of the scores is 8 and over, intermediate if between 4 and 8 and low if below 4. We scored the patients in these two groups (acute gouty arthritis and septic arthritis) based on this diagnostic rule and classified them into 3 groups (high, intermediate and low probability of gout) according to their total scores.

Evaluation of the performance of the diagnostic rule

To evaluate the performance of this diagnostic rule, we compared the mean total scores and the proportion of the 3 gout probability groups of each group (gout and septic arthritis) and assessed the significance of the association between the 3 gout probabilities and the actual diagnosis (gout or septic arthritis) by eta statistics which is useful in evaluating the associations between binominal and polynominal variables. Positive predictive value (PPV) and negative predictive value (NPV) were calculated for high probability (≥ 8) and low probability (< 4) score, respectively. The area under the receiver operating characteristic (ROC) curve for the diagnostic rule was calculated. Additionally, we conducted a sub-analysis excluding cases with podagra to determine whether this diagnostic rule performs well even in such a situation.

Table 1. Patient characteristics

Parameters	Acute gouty arthritis (n = 82)	Septic arthritis (n = 54)	*P* value
Age (mean ± SD, yr)	49.1 ± 18.0	58.6 ± 18.8	0.004
Male sex, No. (%)	76 (92.6)	31 (57.4)	< 0.001
WBC (mean ± SD, /μL)	8,898 ± 2,473	11,425 ± 4,333	< 0.001
ESR (mean ± SD, mm/hr)	34.0 ± 23.1	54.4 ± 32	< 0.001
CRP (mean ± SD, mg/dL)	4.4 ± 5.4	11.7 ± 8.9	< 0.001
Uric acid (mean ± SD, mg/dL)	7.8 ± 1.8	5.4 ± 1.8	< 0.001
Affected joints*			
1st MTP, No. (%)	36 (43.9)	None	
Knee, No. (%)	28 (34.1)	45 (83.3)	
Ankle, No. (%)	17 (20.7)	None	
Other joints, No. (%)	1 (1.7)	9 (16.7)	
Pathogens*			
Staphylococcus aureus, No. (%)		30 (55.5)	
Streptococcus pneumoniae, No. (%)		10 (18.5)	
Streptococcus pyogenes, No. (%)		7 (12.9)	
Coagulase (-) staphylococci, No. (%)		6 (11.1)	
Escheria coli, No. (%)		1 (1.8)	

SD, standard deviation; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MTP, metatarsophalangeal joint.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0. Student's *t*-test was used to compare continuous variables, Mann Whitney-U-test to compare nonparametric variables and chi-square test and eta (η) statistics to assess the association between ordinal (gout probability) and nominal (gout and septic arthritis) variables.

Ethics statement

This study was approved by the institutional review board of Donnguk University Ilsan Hospital (IRB number: 2014-80). Due to the retrospective nature of this study, informed consent was waived by the IRB.

RESULTS

Patient characteristics

There were several significant clinical and laboratory differences between patients with gout and septic arthritis as shown in Table 1. Patients with acute gout were significantly younger, more likely to be male, and had higher levels of serum uric acid with the first MTP joints affected more frequently compared to those with septic arthritis. Patients with septic arthritis had significantly higher levels of inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and white blood cell count with knee joints most frequently affected compared to those with gout. The positive rates of the 7 variables of this diagnostic rule in each group are presented in Table 2.

Discrimination between acute gouty arthritis and septic arthritis

As shown in Table 3, the mean total score of the patients with acute gout was significantly higher than that of those with septic arthritis (8.6 ± 0.2 vs. 3.6 ± 0.32, $P < 0.001$). In 82 patients with acute gout, the diagnostic rule classified 61 (74.4%) patients as

Table 2. Comparison of the positive rates of the variables of the diagnostic rule

Variables (score)	Acute gouty arthritis (n = 82)	Septic arthritis (n = 54)
Male sex (2), No. (%)	76 (92.6)	31 (57.4)
Previous arthritis attack (2), No. (%)	46 (56)	10 (18.5)
Onset within a day (0.5), No. (%)	68 (82.9)	12 (22.2)
Joint redness (1), No. (%)	54 (65.8)	22 (40.7)
1st MTP involvement (2.5), No. (%)	38 (46.3)	0 (0)
HTN or at least one CVD (1.5), No. (%)	21 (25.6)	23 (42.5)
Serum uric acid level > 5.88 mg/dL (3.5), No. (%)	70 (85.3)	14 (25.9)

MTP, metatarsophalangeal joint; HTN, hypertension; CVD, cardiovascular disease.

Table 3. Association of probability scores with gout diagnosis

Scores	Acute gouty arthritis (n = 82)	Septic arthritis (n = 54)	*P* value	Eta
Total score (mean ± SD)	8.6 ± 0.2	3.6 ± 0.32	< 0.001	
Low, No. (%)	2 (2.4)	37 (68.5)		
Intermediate, No. (%)	19 (23.2)	14 (25.9)	< 0.001	0.776
High, No. (%)	61 (74.4)	3 (5.6)		
	Acute gouty arthritis (n = 46) (*podagra excluded*)			
Total score (mean ± SD)	7.6 ± 0.3	3.6 ± 0.3	< 0.001	
Low, No. (%)	2 (4.3)	37 (68.5)		
Intermediate, No. (%)	16 (34.8)	14 (25.9)	< 0.001	0.715
High, No. (%)	28 (60.9)	3 (5.6)		

SD, standard deviation.

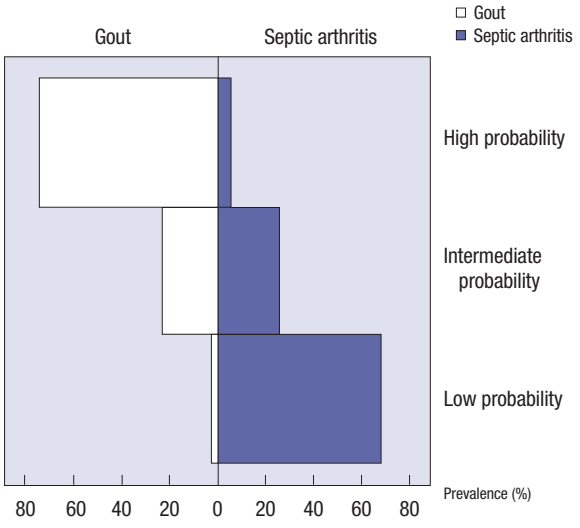

Fig. 1. Histogram of the proportion of 3 probability groups in patients with gout and septic arthritis.

high, 19 (23.2%) as intermediate and 2 (2.4%) as low probability, whereas in 54 patients with septic arthritis, it classified only 3 (5.6%) as high, 14 (25.9%) as intermediate and 37 (68.5%) as low probability. A histogram for this result is presented in Fig. 1. If these two groups are taken together, the prevalence of gout, as confirmed by the presence of MSU crystal, was 95.3% (61/64), 57.5% (19/33) and 5.1% (2/39) in high, intermediate and low gout probability group, respectively. PPV for high probability score (≥ 8) was 95.3% and NPV for low probability score (< 4) was 94.8%. Patients with gout had more 'high' and less 'low' probabilities than those with septic arthritis and this association was statistically significant (eta = 0.776). The area under the ROC curve for the diagnostic rule was 0.933 (95% confidence interval, 0.895-0.972).

Discrimination between gout without the first MTP involvement and septic arthritis

Acute monoarthritis involving the first MTP joint can easily be diagnosed as gout and be distinguished from septic arthritis. To examine whether this diagnostic rule performs well even in patients without the first MTP involvement, we excluded patients with a podagra and performed the same analysis. Of the 46 patients with acute gout without the first MTP involvement, 28 patients had arthritis in the knee, 17 in the ankle and 1 in the tarsal joint. As shown in Table 2, the diagnostic rule showed similar performances. The PPV for high probability score was 90.3% and the NPV for low probability score was 94.8%.

DISCUSSION

In this study, the diagnostic rule properly predicted the possibility of acute gout among patients with gout and those with septic arthritis in the setting of acute monoarthritis. It also discriminated acute gout and septic arthritis fairly well since most of the patients with septic arthritis were, at least, not classified as high probability group. The sub-analysis excluding cases with a podagra, a situation which may confuse physicians, also demonstrated similar performances.

The performance of the extremes of this diagnostic rule (high and low probability) was powerful. The PPV for high probability score was 95.3%, which demonstrates its usefulness in diagnosing gout. However, it should be noted that the rule classified 3 cases with septic arthritis as high probability group. The NPV for low probability score was 94.8%. This suggests that the rule may be useful in excluding gout from septic arthritis

The proportion of intermediate probability group was 24.2% and the prevalence of gout in the intermediate probability group was 57.5%. It is uncertain whether patients with scores within these ranges may have gout or not and a considerable number of patients with septic arthritis are included in this group. Therefore, within the framework of differential diagnosis between gout and septic arthritis, patients with intermediate scores should undergo further investigations such as synovial fluid analysis.

Differentiating gout and septic arthritis in the setting of acute monoarthritis on a clinical basis can be difficult because both gout and septic arthritis frequently involve a single joint and accompany severe joint inflammation. Several predisposing factors for septic arthritis such as age greater than 80 yr, diabetes mellitus, rheumatoid arthritis, prosthetic joint, and previous in-

http://dx.doi.org/10.3346/jkms.2015.30.6.700

tra-articular corticosteroid injection were identified, but they have only a modest impact on the risk of septic arthritis (4, 5). There were also significant differences between patients with gout and those with septic arthritis in the baseline characteristics in this study. However, these differences are insufficient evidences to establish the diagnosis.

The diagnostic rule showed proper performances in the differential diagnosis between gout and septic arthritis especially in the case of high and low probability score. This rule may particularly be helpful in conditions where a physician encounters a patient with acute monoarthritis in whom gout is suspected, but septic arthritis cannot be ruled out, and vice versa. High probability scores would support the possibility of gout, whereas low probability scores would support non-gout diagnosis, which is septic arthritis in this study. Patients with intermediate probability scores may not benefit from this diagnostic rule because both diseases are possible. Of note, it should be noted that septic arthritis, a medical emergency which should never be missed, was present in all possibility groups. The diagnostic rule may aid the physician to reach the correct diagnosis, but cannot be diagnostic references.

Several classification criteria for gout have been developed since the 1960s. The early ones of Rome and New York criteria (6) deal with key features of gout, but were not based on prospective data and tested to a limited extent. In addition, confirmation of MSU was one of the items of the Rome criteria. The American College of Rheumatology (ACR) criteria (7), which were introduced in 1977, comprise several clinical and radiologic variables and do not require confirmation of MSU. However, 1977 ACR criteria chose the physician diagnosis of gout as the gold standard and showed limited performance in the external validation studies using MSU crystal confirmed cases (8, 9). Recently, the ACR criteria was modified by Pelaez-Ballestas et al. (10) based on the frequency of the items of ACR criteria and the modified criteria showed better performance compared to the ACR criteria. However, they had limitations such as that the non-gout controls did not undergo synovial fluid analysis and that the rate of tophi in the gout cases was relatively high (81%).

The diagnostic rule proposed by Janssens et al. does not require synovial fluid analysis, comprises simple clinical and laboratory variables, the information of which can easily be obtained in primary care settings. It showed good performances in predicting the possibility of gout in the setting of acute monoarthritis in primary care setting (2). The prevalence of gout, as confirmed by the presence of MSU crystal, was 82.5%, 31.2%, and 2.2% in high, intermediate and low probability group, respectively. It was recently evaluated in a secondary care setting and also showed proper performances. The PPV of high probability score was 87% and the NPV was 95%, which is similar to our results (11).

This study has several limitations. First, this study was retrospective in nature and it is not clear how patients were indicated to undergo synovial fluid analysis, which suggests that this study may have a risk of a selection bias. Second, the number of subjects included was relatively limited. Thirdly, the conclusions may be limited to the findings of this study. The setting was a tertiary referral medical center and the patient selection was very specific based on synovial fluid diagnosis. Further studies may be needed in the future dealing with other situations related with this issue: concurrent cases with both gout and septic arthritis or cases with synovial fluid analysis results negative for MSU or bacteria.

In this study, the diagnostic rule proposed by Janssens et al. showed a good performance in predicting the possibility of gout and discriminating it from septic arthritis. Though the rule is not an absolute standard, it might be a useful tool in distinguishing these two diseases in the absence of a polarized microscope.

ACKNOWLEDGMENTS

We thank Dr. Yoon-Woo Lee in 'Withus clinic' and Dr. Chan-Hee Lee in Ilsan Hospital in Korea for their valuable advices on this work.

DISCLOSURE

The authors have no commercial associations that might pose a conflict of interest in connection with this article.

AUTHOR CONTRIBUTION

Conception and design of the work: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. Acquisition of data: Lee KH, Lee SK. Analysis of data: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. Drafting the work or revising the content of manuscript: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. Wrote the paper: Lee KH. Final approval of the manuscript to be published: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY. ICMJE criteria for authorship read and met: Lee KH, Choi ST, Lee SK, Lee JH, Yoon BY.

ORCID

Kwang-Hoon Lee *http://orcid.org/*0000-0002-9506-9072
Sang-Tae Choi *http://orcid.org/*0000-0002-2074-1733
Soo-Kyung Lee *http://orcid.org/*0000-0002-3979-4560
Joo-Hyun Lee *http://orcid.org/*0000-0003-4549-6284
Bo-Young Yoon *http://orcid.org/*0000-0002-9635-4799

REFERENCES

1. Siva C, Velazquez C, Mody A, Brasington R. *Diagnosing acute monoarthritis in adults: a practical approach for the family physician. Am Fam Physician 2003; 68: 83-90.*
2. Janssens HJ, Fransen J, van de Lisdonk EH, van Riel PL, van Weel C, Janssen M. *A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Arch Intern Med 2010; 170: 1120-6.*
3. Sack K. *Monarthritis: differential diagnosis. Am J Med 1997; 102: 30s-4s.*
4. Margaretten ME, Kohlwes J, Moore D, Bent S. *Does this adult patient have septic arthritis? JAMA 2007; 297: 1478-88.*
5. Mathews CJ, Coakley G. *Septic arthritis: current diagnostic and therapeutic algorithm. Curr Opin Rheumatol 2008; 20: 457-62.*
6. Dalbeth N, Fransen J, Jansen TL, Neogi T, Schumacher HR, Taylor WJ. *New classification criteria for gout: a framework for progress. Rheumatology (Oxford) 2013; 52: 1748-53.*
7. 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: 895-900.*
8. 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: 22-4.*
9. 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. Ann Rheum Dis 2010; 69: 1255-6.*
10. Peláez-Ballestas I, Hernández Cuevas C, Burgos-Vargas R, Hernández Roque L, Terán L, Espinoza J, Esquivel-Valerio JA, Goycochea-Robles MV, Aceves FJ, Bernard AG, et al. *Diagnosis of chronic gout: evaluating the American College of Rheumatology proposal, European League against rheumatism recommendations, and clinical judgment. J Rheumatol 2010; 37: 1743-8.*
11. Kienhorst LB, Janssens HJ, Fransen J, Janssen M. *The validation of a diagnostic rule for gout without joint fluid analysis: a prospective study. Rheumatology (Oxford) 2015; 54: 609-14.*

http://dx.doi.org/10.3346/jkms.2015.30.6.700