Impact of disease duration and gender on the sensitivity and specificity of 2015 ACR/EULAR classification criteria for gout. Cross-sectional results from an Italian multicentric study on the management of crystal-induced arthritis (ATTACk)

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Abstract

Objective

We aimed to assess the performance of the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) gout classification criteria in an Italian cohort of patients with crystal-induced arthritis stratified by disease duration and gender in a real-life setting.

Methods

Consecutive patients referred to Rheumatology Units for suspected acute crystal-induced arthritis were enrolled in a multicentre cohort study by the Italian Society of Rheumatology which was designed to improve the management of crystal-induced arthritis (ATTACk). To test the performance of the criteria (sensitivity and specificity), the presence of monosodium urate (MSU) crystals in synovial fluid (SF) was used as gold standard. Subgroup analyses by gender and disease duration were performed.

Results

Two hundred and seventy-seven patients were enrolled. SF analysis was available in 137 (49%) patients. Complete SF analysis and ACR/EULAR scores were obtained in 44% of patients. MSU crystals were found in 66% of patients. The sensitivity and the specificity of all criteria sets were 78% (95%CI, 67–86) and 98% (95%CI, 87–100), respectively; only clinical criteria yielded 70% (95%CI, 59–80) sensitivity and 93% (95%CI, 80-98) specificity, respectively. In early-stage disease (<2 years), the sensitivity dropped to 58% (95%CI, 39-75), while the specificity was 100% (95%CI, 85–100).

Conclusion

The ACR/EULAR criteria showed good performance in patients presenting with acute arthritis; changes were observed when a subset of criteria were used, especially in early-stage disease.

Key words

gout, disease duration, gender, classification, diagnosis

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Introduction

Gout is the most frequent chronic inflammatory arthritis: its pathophysiology is largely known as deposition of monosodium urate (MSU) crystals in synovial fluid (SF) and other tissues, and effective treatment is available (1-3). Its incidence and prevalence are gradually increasing in many countries in parallel with the spread of a westernised lifestyle, medical care, more comorbidities and increased longevity (4, 5). The gout estimated incidence in these countries is around 0.6–2.1 per 1,000 per year, with a prevalence of 3–7.5 per 1,000 per year (6-10). The increased longevity of the population in industrialised countries may contribute to a higher prevalence of gout through the disorder's association with age-related diseases such as hypertension and cardiovascular diseases (11-13). Optimal management of gouty patients starts from the correct diagnosis during the first episode of acute arthritis: classification criteria support the clinicians in focusing their attention on the accurate and early diagnosis (14, 15). Early disease may be underdiagnosed, especially with incomplete or atypical clinical presentations (*e.g.* in females). Differential diagnoses usually include other crystal arthropathies, such as acute calcium pyrophosphate crystal arthritis disease (CPPD) (16-20). SF analysis or tophi aspiration for MSU crystals under a polarising microscope are the recommended gold standard (21, 22). In absence of SF analysis, a clinical diagnosis of gout is supported by suggestive features such as: the first metatarsophalangeal joint (1st MTPJ) or ankle joint involvement, previous similar acute arthritis episodes, rapid onset of severe pain, swelling and erythema which are listed in the main classification criteria. Since the publication of the Rome criteria in 1963, several sets of gout classification criteria have been developed, including the New York criteria, the 1977 American Rheumatology Association (ARA) preliminary classification criteria, followed by Mexico and the Netherlands criteria (23-27). However, none of these scoring systems have become widely adopted in clinical practice due to limited sensitivity and specificity (28). The 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria were published and proved to be highly sensitive and specific (29) when comparing gout patients to other rheumatic diseases in rheumatology centres and general practice settings. These newest criteria were validated on a sample of 983 patients with arthritis (MSU-positive 509, MSU-negative 474) who were included in the Study for Updated Gout Classification Criteria (SUGAR) and underwent SF analysis for MSU crystals identification (30, 31). However, performance was observed to be decreased in early-stage disease *versus* established disease, whereas performance in atypical clinical patterns, (*i.e.* female patients), remains undefined (32, 33). In 2015, on behalf of the Italian Society of Rheumatology (SIR), the multicentric observational study on Achieving improvemenT in the managemenT of crystAl-induCed arthritis (ATTACk) was started, with the aim of testing the 2015 ACR/EULAR classification criteria performance, applied as full (all domains) and clinical-only set excluding imaging and SF analysis, according to gout duration and gender differences as well. We hypothesised that criteria may perform differently in early-stage disease and in female patients *versus* established disease and males.

Materials and methods

Study design and subject recruitment

This is the cross-sectional analysis of a multicentric cohort study involving Rheumatology centres nationwide and promoted by SIR. Participants considered eligible for the recruitment were consecutive adult (>18 years old) with acute (within one week from onset) mono- or oligo- or poly-arthritis referred to a Rheumatology Unit between 2015 and 2019, and those who were suspected of crystal-induced joint disease by the attending physician. The study protocol was approved by the local ethics committees of the 11 participating centres (approval no. 3488/AO/15). The study was conducted in compliance with the principles of the Declaration of Helsinki. Each patient provided written informed consent for

their participation in the study and sensitive personal data management.

Clinical assessment and measurement of the variables

All enrolled patients initially underwent full clinical evaluation, including ACR/EULAR score as the index test and SF analysis as reference standard. General health and disease-specific variables were recorded by using structured electronic web-based case report forms. Data collection and index/reference tests occurred simultaneously. Clinical data included the patients' demographics, comorbidities, medications, alcohol consumption, duration of disease, and current and past characteristics of arthritis episodes. Serum uric acid (SUA) was measured within 2 weeks from onset of the current arthritis episode. The highest SUA level also was recorded from medical records, if available. Conventional radiograph and/or ultrasonography of the symptomatic joints were reviewed and recorded, if performed. The disease duration was measured as the time between the first episode of acute arthritis and enrolment visit. Early-stage disease and established disease were defined as disease duration <2 years or ≥2 years since the first arthritis episode, respectively, as previously reported (33). Mono-articular, oligo-articular, and poly-articular involvement were defined as the presence of arthritis in 1, 2–4, and more than 4 joints, respectively. The three characteristics of symptomatic episode in the ACR/EULAR classification criteria were: 1) redness of the skin overlying the affected joint, as reported by the patient or observed by the physician, 2) inability to bear touch or pressure in the affected joint, and 3) great difficulty in walking or inability to use the affected joints. Typical episode was defined by the presence of at least two out of three characteristics: maximal pain within 24 h, resolution of symptoms within 14 days, and complete resolution to baseline level between each symptomatic episode. Time course of the arthritis episodes were distinguished in single or recurrent typical episodes. Evidence of joint damage from radiographs was defined as the presence of cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints. Ultrasonographic evidence of urate deposition was defined as the presence of hyperechoic line over the surface of the hyaline cartilage, known as double-contour sign. The ACR/EULAR score comprises 8 items (31). The entry criterion for these classification criteria requires at least one episode of peripheral joint/bursa swelling, pain, or tenderness. The presence of MSU crystals in SF samples or in tophi aspirations is a sufficient criterion for classification of the subject as having gout, and does not require further scoring (29). The new classification criteria include many domains: clinical (pattern of joint/bursa involvement, characteristics and time course of symptomatic episodes); laboratory (serum urate, MSU-negative synovial fluid aspirate); and imaging (double-contour sign on ultrasound or urate on dual-energy computed tomography (DECT), radiographic gout-related erosion). The gout diagnosis is established with a score ≥8. The performance of criteria was also tested using only clinical set, *i.e.* without MSU results, scored as 0 (unknown/not done) and without imaging (*i.e.* x-ray, ultrasound or DECT) results, scored as 0; the latter scoring was in keeping with similar weighting given to imaging studies that were negative *versus* not performed in the discrete-choice experiments. The ACR/EULAR criteria were therefore applied as full (all domains) and only clinical set excluding imaging and SF analysis. To classify a patient as having clinical gout, the sufficient criterion (MSU-positive SF) was ignored and cut-off score ≥8 was used. The analysis of the SF from symptomatic joint or bursa or tophus was considered as the gold standard to classify patients as having gout (presence of MSU crystals) or CPPD (presence of CPP crystals) according to the 2015 ACR/EULAR gout classification criteria (29) and the 2011 EULAR CPPD recommendations (34). The examination by microscope with a polarising filter to detect crystals was performed by an experienced rheumatologist in each participating centre. Other SF analysis including cultures, special staining, and white blood cell counts were performed according to the treating physician. We only considered patients with suspected crystal-induced arthritis and whose diagnosis was subsequently confirmed at time of enrolment via SF analysis. Patients were excluded if they did not undergo arthrocentesis, were positive for both MSU and CPP crystals, or were negative for both MSU and CPP crystals. Finally, patients whose SF analysis was negative for MSU were classified as MSU-negative and pooled with patients with CPP detected in the SF.

To avoid information bias and improve the accuracy of data collection and clinical measurements, instructions on standard definitions and operating procedures were provided to all rheumatologists. Data were checked by a centralised monitoring for missing values or inconsistencies, and subjected to standardised retrieval and cleaning procedures during their collection.

Statistical methods

Categorical variables were described as frequency and percentage, and continuous variables as mean ± standard deviation (SD) or median where appropriate. Comparison between patients with SF analysis and those without SF analysis and between MSU-positive and MSU-negative patients was performed using the χ^2 or Fisher's exact test for categorical variables and Wilcoxon test for continuous variables. The performance of classification criteria in overall patients was assessed via sensitivity, specificity, positive predictive value and negative predictive value. Sensitivity and specificity of the ACR/EULAR classification criteria were tested against the gold standard of MSU crystal identification, and positive and negative likelihood ratios were calculated. Additional subgroup analyses were performed: i) male and female patients; ii) patients with early-stage disease or established disease. Statistical analyses were performed using R statistical software v. 3.3 (Foundation for Statistical Computing, Vienna, Austria). $p<0.05$ was considered statistically significant.

Results

A number of 277 patients with acute arthritis suspected for crystal-induced disease were enrolled from 11 Italian

Rheumatology Centres. Of these 46.3% had early-stage disease, 19.7% were non-tophaceous. Sociodemographic data, general health and disease-related variables of the enrolled patients are summarised in Table I. The flowchart of the ATTACk study (cross-sectional) is reported in Figure 1. SF analysis was available in 49.4% patients from the following joints: knee in 56.9%; 1st MTFJ in 24.1%; ankle in 17.5%; wrist in 13.1%; hand in 8.7%; shoulder in 7.3%; in other joints in 13.9%. Out of these 137 patients, MSU crystals were identified in SF in 59.1%, CCP crystals in 29.9% and both MSU and CPP crystals in 2.2%. Twelve patients whose SF not highlighted presence of crystals were excluded from this study. Both complete SF analysis and ACR/EULAR score were obtained in 43.7% patients, which were confirmed eligible and included in the second phase of study. Out of all these eligible patients, MSU crystals were detected in 66.1% and were not detectable in 33.9%. The median (interquartile range) ACR/EULAR score was 10.0 (8.0–14.0) and 2.0 (1.0–4.0) in MSU-positive and MSU-negative patients, respectively. The differences between patients who had both SF analyses and complete ACR/EULAR score and who did not relate to demographics and clinical features, pattern of joint involvement, comorbidities and medications, functional and disease activity indexes are shown in Table II. We observed in patients who performed SF analysis a higher frequency of smokers (p=0.001), a higher frequency of hyperuricaemia (p=0.023), a higher intake of NSAIDs (p<0.001), of corticosteroids (p<0.001) and low-dose aspirin (p=0.002), a more frequent involvement of knee (p<0.001) and shoulder (p=0.005); while patients without SF analysis showed a higher BMI (p<0.001), a higher prevalence of swollen joints (p=0.029), a higher HAQ score (p<0.001), a more frequent involvement of 1stMTFJ (p=0.035) and hand (p=0.04). Mono-arthritis and oligo-arthritis shared the same pattern frequency of articular involvement in those who performed or not performed SF analysis, although poly-arthritis was present only in patients without SF analysis. No significant differences were observed between these subgroups regarding sex, age of onset and disease duration. The performance of the full and only clinical set of classification criteria against the gold standard as well subgroup analyses by disease duration and gender are shown in Table III and a receiver operating characteristic plot (Fig. 2). Overall, the full ACR/EULAR classification criteria showed a sensitivity and specificity of 78% and 98%, respectively. The sensitivity and specificity dropped to 70% and 93%, respectively, when applying only clinical parameters. The sensitivity of the only clinical criteria was lower in the early-stage disease subgroup *versus* the

Table I. Baseline demographics and clinical characteristics of patients with acute arthritis patients.

	Total (n=277)
Demographics	
Female, n (%)	68/273 (24.9)
Age (years), mean (± SD)	64.3 (±12.4)
Caucasian, n (%)	265/275 (96.4)
BMI, mean (± SD)	26.9 (±4.0)
Clinical characteristics	
Current smokers, n (%)	62/269 (23)
Duration since first arthritis (years), mean (± SD)	5.9 (±8.3)
Early-stage disease (<2 years), n (%)	124/268 (46.3)
Pattern of current joint involvement, n (%)	262/277 (94.6)
Monoarticular (1 joint)	187
Oligoarticular (2 to 4 joints)	74
Polyarticular (>4 joints)	1
Swollen joints (0 to 66), median (range)	1 (1-2)
Tender joints (0 to 68), median (range)	1 (1-3)
Presence of tophi, n (%)	52/264 (19.7)
Current SUA level (mg/dl), mean (± SD)	6.9 (±2.2)
Highest SUA level (mg/dl), mean (± SD)	8.1 (±2.2)
UMS crystals positive, n (%)	82/137 (59.9)
Double contour or tofus (articular ecography inspection), n (%)	86/200 (43)
VAS pain, mean (± SD)	66.2 (±25.7)
HAQ, mean (± SD)	0.9 (±0.7)
ACR/EULAR score, mean (± SD)	8.44 (±5.30)
Concurrent therapies	
Urate-lowering agent, n (%)	89/234 (38)
NSAIDs or colchicine, n (%)	155/262 (59.2)
Corticosteroids, n (%)	46/216 (21.3)
Diuretics, n (%)	71/227 (31.3)
Low-dose aspirin, n (%)	49/229 (21.4)
Comorbidities	
Hypertension, n (%)	165/268 (61.6)
Ischaemic heart disease, n (%)	40/261 (15.3)
Kidney failure/nephropathy, n (%)	45/259 (17.4)
COPD, n (%)	22/257 (8.6)
Hyperuricaemia, n (%)	191/267 (71.5)
DM type II, n (%)	25/258 (9.7)
Dyslipidaemia, n (%)	99/262 (37.8)
Metabolic syndrome, n (%)	48/258 (18.6)
Psoriasis, n (%)	19/260 (7.3)
Lymphoproliferative disorders, n (%)	3/258 (1.2)
Haemolytic process, n (%)	1/256 (0.4)
Hyperparathyroidism, n (%)	7/258 (2.7)
Hypothyroidism, n (%)	20/256 (7.8)
Haemochromatosis, n (%)	1/258 (0.4)
Inflammatory arthropathy, n (%)	19/269 (7.1)
Arthrosis, n (%)	143/277 (51.6)
Fibromyalgia, n (%)	7/249 (2.8)
Other comorbidities, n (%)	72/252 (28.6)

Data shown as mean ± standard deviation (SD) or median and interquartile range or number (%).
BMI: Body Mass Index; SUA: serum uric acid; COPD: chronic obstructive pulmonary disease; DM diabetes mellitus; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; NSAIDs: non-steroidal anti-inflammatory drugs; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; SD: standard deviation.

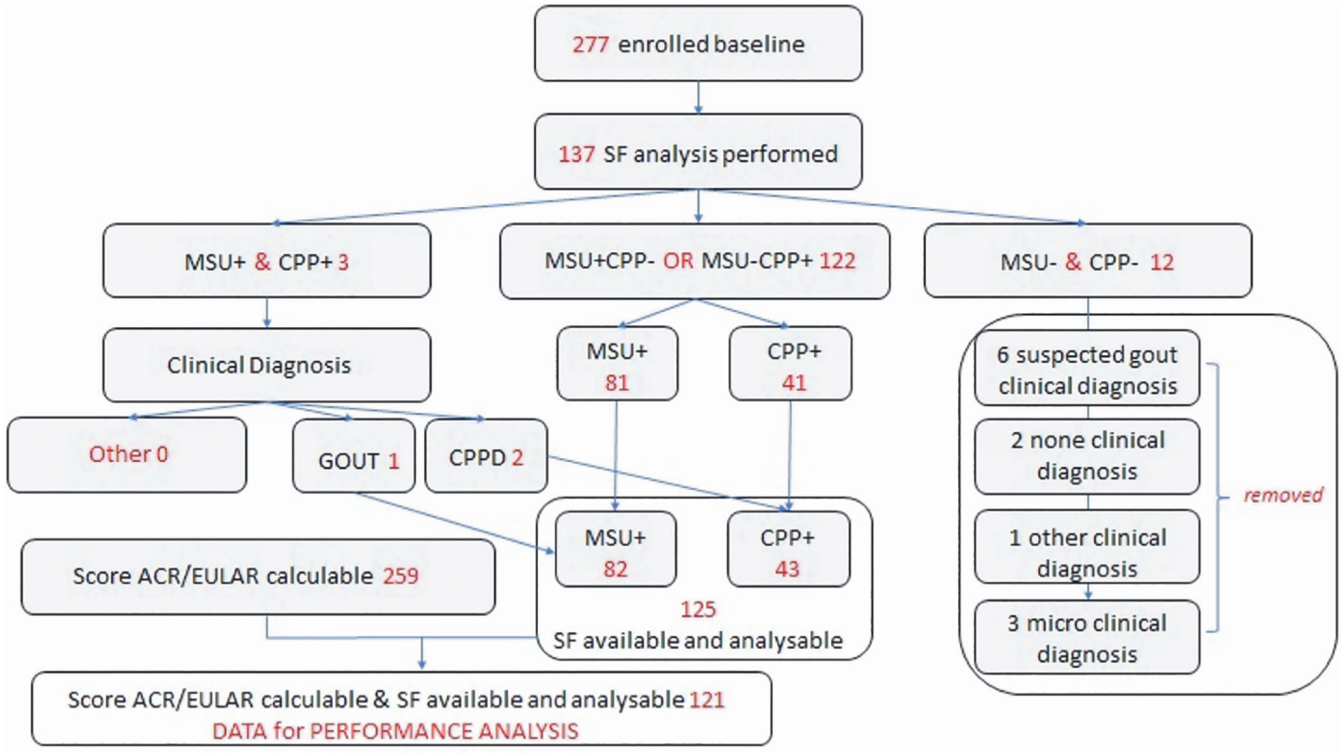

Fig. 1. Patient inclusion flow-chart of the ATTACk study (cross-sectional).

whole study population (45% *vs*. 70%) and higher in the established disease subgroup *versus* the whole study population (86% *vs*. 70%). The specificity in the early-stage disease subgroup (100% *vs*. 93%) and in the established disease subgroup (100% *vs*. 83%) was higher than in the whole study population. The sensitivity of full and only clinical criteria was higher in male patients *versus* females (80–73% *vs*. 50–33%), whereas the specificity of both criteria was lower in the former (93–87% *vs*. 100–96%) (Table III, Supplementary Table S1). The total ACR/EULAR scores and the subtotal per items are listed in Table IV. MSU-positive patients more frequently showed acute arthritis of lower limbs (ankle-midfoot, $p<0.001$; 1stMTFJ, $p<0.001$) and more one a typical arthritis ($p<0.001$) with multiple characteristics (two characteristics $p<0.001$; three characteristics, $p<0.001$) than MSU-negative patients. Clinical tophi were found in in 28.8% of MSU-positive patients. Mean SUA level was significantly higher in MSU-positive patients than MSU-negative patients (75/80 *vs*. 9/41 patients, $p<0.001$). Radiographic damage structural lesions (*i.e*. erosions, over-hanging edge lesions) were seen in 8.8% MSU-positive patients, but only in 4.9% MSU-negative. US signs of urate deposition were found in 30% MSU-positive patients, while were found in only 9.8% MSU-negative. Also, patients with established disease presented more characteristics of symptomatic episodes ($p=0.001$) and recurrent typical episodes ($p=0.001$) than those with early-stage disease. Tophi were found more in the first subgroup than the latter ($p=0.003$). Male patients had more frequently involvement of 1st-MTFJ ($p=0.007$), more three characteristics of symptomatic episode ($p=0.027$) and recurrent episodes ($p=0.043$). Females presented a higher, albeit not significant, prevalence of tophi (33.3% *vs*. 28.4%). We observed no differences in laboratory and imaging data across subgroups with early-stage *versus* established disease and males *versus* females. The sociodemographic, general health and disease-related variables of our study population are reported in Supplementary Tables S2-3. Female patients had a lower BMI ($p=0.02$), a lower mean SUA level ($p=0.03$), more comorbidities such as inflammatory arthropathies ($p=0.008$), and predominant upper extremity joint involvement (*i.e*. hand, wrist). Patients with early-stage disease the 1st MTFJ was the most frequently involved joint in patients with early-stage disease ($p=0.004$) *versus* slightly higher SUA levels in patients with established disease.

Discussion

This study evaluated the performance of the 2015 ACR/EULAR classification criteria for gout. Overall, as compared to the original SUGAR validation data set, our population yielded good performance as well as high specificity and sensitivity for full and only clinical criteria (30). The relatively lower sensitivity in our sample might be due to reduced availability of imaging items (scored 0 for all cases to indicate not done), as MSU deposition was detected by US or DECT (score 4) in few cases (false negative according to the criteria). Our results were in line with previous studies in clinical setting (35). In fact, Neogi *et al*. (29) and by Louthrenoo *et al*. (36) reported a higher sensitivity (85% and 79.8%, respectively *vs*. 70%) and lower specificity (78% and 87.8%, respectively *vs*. 93%) for the only clinical criteria. The choice of controls is critical to performance tests. Bearing in

Table II. Baseline characteristics and clinical, laboratory and imaging features in patients who underwent synovial fluid analysis and in those who did not.

	Synovial fluid (n=137)	No synovial fluid (n=140)	*p*-value
Demographics			
Female, n (%)	37/136 (27.2)	31/137 (22.6)	0.463
Age (years), mean (±SD)	64.1 (±11.1)	64.4 (±13.6)	0.505
Caucasian, n (%)	133/137 (97.1)	132/138 (95.7)	0.175
BMI, mean (±SD)	25.9 (±3.8)	27.9 (±4)	**<0.001**
Clinical characteristics			
Current smokers, n (%)	43/136 (31.6)	19/133 (14.3)	**0.001**
Duration since first arthritis (years), mean (±SD)	6.1 (±8.6)	5.8 (±8)	0.211
Early-stage disease (<2 years), n (%)	62/137 (45.3)	62/131 (47.3)	0.828
Pattern of current joint involvement, n (%)	134/137 (97.8)	128/140 (91.4)	0.941
Monoarticular (1 joint)	95	92	
Oligoarticular (2 to 4 joints)	39	35	
Polyarticular (>4 joints)	0	1	
Swollen joints (0 to 66), median (range)	1 (1-2)	1 (1-2)	**0.029**
Tender joints (0 to 68), median (range)	1 (1-3)	1 (1-3)	0.811
Joint involvement:			
first metatarsophalangeal, n (%)	33/137 (24.09)	51 (36.4)	**0.035**
other metatarsophalangeal, n (%)	2/137 (1.46)	8 (5.7)	0.103
tarsal, n (%)	7/137 (5.11)	7 (5)	1
ankle, n (%)	24/137 (17.52)	33 (23.6)	0.273
knee, n (%)	78/137 (56.93)	25 (17.9)	**<0.001**
hand, n (%)	12/137 (8.76)	25 (17.9)	**0.04**
wrist, n (%)	18/137 (13.14)	23 (16.4)	0.547
elbow, n (%)	3/137 (2.19)	5 (3.6)	0.723
shoulder, n (%)	10/137 (7.3)	1 (0.7)	**0.005**
tendons, n (%)	2/137 (1.46)	3 (2.1)	1
bursa, n (%)	5/137 (3.65)	3 (2.1)	0.497
Presence of tophi, n (%)	30/134 (22.4)	22/130 (16.9)	0.336
Current SUA level (mg/dl), mean (±SD)	6.8 (±2.3)	7 (±2)	0.338
Highest SUA level (mg/dl), mean (±SD)	7.8 (±2.4)	8.5 (±1.8)	**0.031**
Double contour or tofus (articular ecography inspection), n (%)	41/101 (40.6)	45/99 (45.5)	0.581
VAS pain, mean (±SD)	68.7 (±22.9)	63.6 (±28.2)	0.296
HAQ, mean (±SD)	1 (±0.6)	0.7 (±0.7)	**<0.001**
Concurrent therapies			
Urate-lowering agent, n (%)	42/117 (35.9)	47/117 (40.2)	0.59
NSAIDs or colchicine, n (%)	98/136 (72.1)	57/126 (45.2)	**<0.001**
Corticosteroids, n (%)	34/116 (29.3)	9/117 (7.7)	**<0.001**
Diuretics, n (%)	34/121 (28.1)	37/106 (34.9)	0.337
Low-dose aspirin, n (%)	15/117 (12.8)	34/112 (30.4)	**0.002**
Comorbidities			
Hypertension, n (%)	74/133 (55.6)	91/135 (67.4)	0.064
Ischaemic heart disease, n (%)	25/131 (19.1)	15/130 (11.5)	0.128
Kidney failure/nephropathy, n (%)	19/128 (14.8)	26/131 (19.8)	0.369
COPD, n (%)	17/127 (13.4)	5/130 (3.8)	**0.007**
Hyperuricaemia, n (%)	87/134 (64.9)	104/133 (78.2)	**0.023**
DM type II, n (%)	13/128 (10.2)	12/130 (9.2)	0.967
Dyslipidaemia, n (%)	48/130 (36.9)	51/132 (38.6)	0.874
Metabolic syndrome, n (%)	21/128 (16.4)	27/130 (20.8)	0.459
Psoriasis, n (%)	11/130 (8.5)	8/130 (6.2)	0.634
Lymphoproliferative disorders, n (%)	1/128 (0.8)	2/130 (1.5)	1
Haemolytic process, n (%)	0/127 (0)	1/129 (0.8)	1
Hyperparathyroidism, n (%)	6/128 (4.7)	1/130 (0.8)	0.065
Hypothyroidism, n (%)	10/127 (7.9)	10/129 (7.8)	1
Haemochromatosis, n (%)	1/128 (0.8)	0/130 (0)	0.496
Other comorbidities, n (%)	41/128 (32)	31/124 (25)	0.273
Inflammatory arthropathy, n (%)	11/135 (8.1)	8/134 (6)	0.646
Arthrosis, n (%)	78/137 (56.9)	65/140 (46.4)	0.103
Fibromyalgia, n (%)	5/122 (4.1)	2/127 (1.6)	0.274

Data shown as mean ± standard deviation (SD) or median and interquartile range or number (%). Significant *p*-values are indicated in bold.
BMI: Body Mass Index; SUA: serum uric acid; COPD: chronic obstructive pulmonary disease; DM diabetes mellitus; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; NSAIDs: non-steroidal anti-inflammatory drugs; ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; SD: standard deviation.

mind that the main differential diagnosis for gout is CPPD, we were able to confirm that the performance of ACR/EULAR criteria remains high irrespective of overlapping clinical features (16-20). Regarding disease duration, early-stage disease criteria showed high specificity but low sensitivity, whereas sensitivity was higher in longstanding gout. We observed a decreased sensitivity of full, and specifically, only clinical criteria in early-stage disease, as most patients presented only first-time arthritis (58.1%); thus, we hypothesised that the presence of recurrent arthritis may be an important criterion in the clinical diagnosis of gout and SF microscopy is warranted. This finding is corroborated by Choi *et al*. who previously reported sensitivity for full and only clinical EULAR/ACR criteria of around 50% (37), and by Taylor *et al*. with a reported sensitivity of 66.3% (33). As corroborated by previous studies, the specificity in our study was lower – and the sensitivity higher – in the established disease subgroup *versus* early-stage disease (33, 36), probably due to more recurrent episodes of acute crystal arthritis (*i.e*. CPPD) similar to that observed in MSU-positive patients. GOSPEL and other studies demonstrated that patients with gout onset before 40 years of age often had poly-articular flares, a family history, longer urate-lowering treatment, higher SUA levels, and metabolic syndrome (38-40); likewise, gout onset before 20 years of age was associated with a family history and obesity (41). However, in our study population we observed no differences related to the presence of comorbidities or hyperuricaemia levels between patients with early-stage and established disease. Nevertheless, patients with established disease presented more characteristics of symptomatic and recurrent typical episodes and more tophi than those with early-stage disease. The most involved joint in patients with early-stage disease was the 1st MTPJ. The identification of typical clinical features and assessing the performance of the 2015 classification criteria in the early onset of gout are vital, in light of the natural history of gout, from the preclinical state with asymptomatic MSU crystal deposi-

Table III. The performance of ACR/EULAR 2015 Gout classification criteria (full and only clinical) in all patients and stratified by subgroups of interest (early-stage disease *vs*. established disease and male *vs*. female).

	Sensitivity % (95% CI)		Specificity % (95% CI)		Prevalence	LR+		LR-	
	Full	Clinical	Full	Clinical	MSU+	Full	Clinical	Full	Clinical
Overall n=121	78 (67-86)	70 (59-80)	98 (87-100)	93 (80-98)	66%	>10	10	0.2	0.3
Disease duration									
<2yrs n=54	58 (39-75)	45 (27-64)	100 (85-100)	100 (85-100)	57%	>10	>10	0.4	0.6
≥2yrs n=67	90 (78-98)	86 (73-94)	94 (73-100)	83 (59-96)	73%	>10	5	0.1	0.2
Gender									
Male n=89	80 (69-88)	73 (61-83)	93 (68-100)	87 (60-98)	83%	>10	6	0.2	0.3
Female n=32	50 (12-88)	33 (4-78)	100 (87-100)	96 (80-100)	19%	>10	8	0.5	0.7

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; MSU: monosodium urate; <2 yrs: less than two years or early-stage disease; ≥2 yrs: greater than or equal to two years or established disease; LR: likelihood ratio; + positive; - negative.

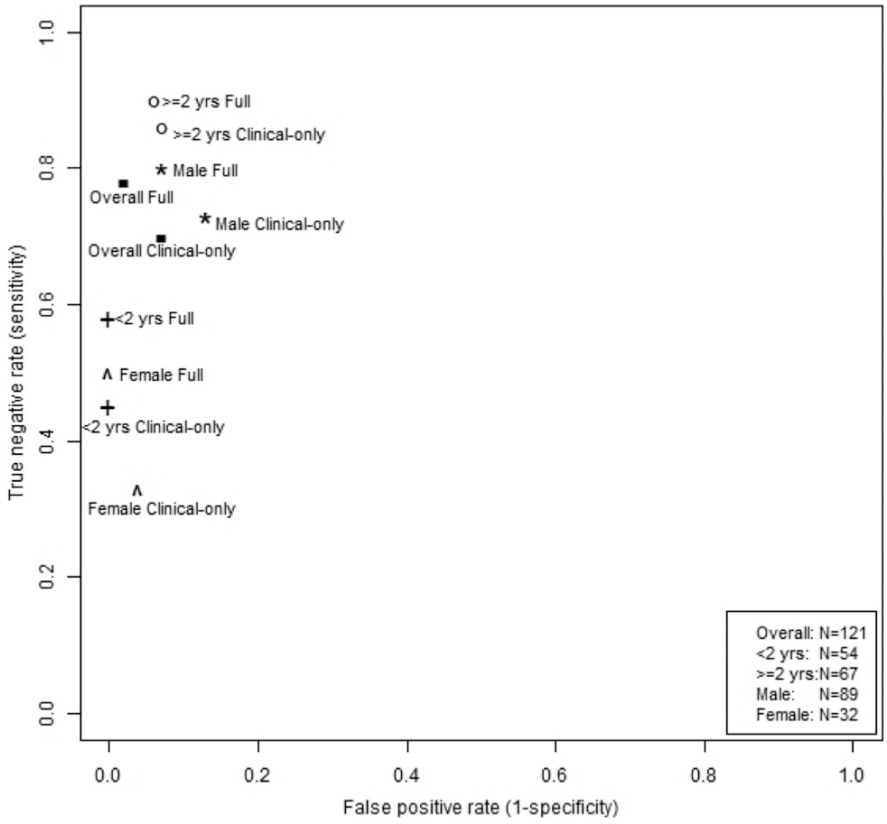

Fig. 2. Performance of ACR/EULAR 2015 Gout classification criteria (full and clinical-only) in overall patients and across the subgroups (early-stage disease, *i.e*. <2 years, *vs*. established disease, *i.e*. ≥2 years, and male *vs*. female). Receiver operating characteristics plots.

tion to the first gout flare (31). Gout is generally considered a predominantly male disease, affecting around 1% of adult men in Western countries, usually over 45 years of age – in females, gout may occur in post-menopause (2, 3, 5, 10-14). Therefore, we aimed to assess differences in clinical features of gout arthritis and the performance of the 2015 ACR/EULAR classification criteria for gout between male and female patients. Specificity and sensitivity were low when applying only clinical criteria to both groups, which may stem from the small sample size of our female population (n=6 *vs*. n=74). In our cohort, male patients more frequently had an involvement of the 1st MTPJ, >3 characteristics of symptomatic episode and recurrent episodes than females, as previously reported (42-46). Previous studies reported that female patients more often had multiple joints involvement, such as ankle, fingers, and upper limbs and a poly-articular pattern (44, 47). Similarly, we observed that women in our study population were more likely to have predominant upper extremity joint involvement (*i.e*. hand, wrist), although we did not find any prevalent poly-articular involvement. Therefore, gout should be strongly considered as a differential diagnosis in elderly women with an acute mono- or oligo-arthritis, especially in the upper joints. The unfamiliarity of clinicians with the atypical presentation of gout in women may lead to a delay in the diagnosis or misdiagnosis with other forms of arthritis. We also found a higher, albeit not statistically significant, prevalence of tophi in females *versus* males. These findings are corroborated by Puig *et al*. who found significantly more tophi that may be misdiagnosed with rheumatoid nodules in female gout (42). However, it bears noting that several other studies have reported varying percentages of tophi in males and females (44, 45, 47, 48). Although our female subgroup had more comorbidities such as inflammatory arthropathies, the frequency of cardiovascular diseases, diabetes and obesity was similar in both males and females. This finding is in contradiction with the current literature, where women with gout more often present renal insufficiency and hypertension, dyslipidaemia, chronic heart disease, diabetes and a more frequent use of diuretics

Table IV. Univariate association of each clinical, laboratory and imaging item of the 2015 ACR/EULAR gout classification criteria in MSU-positive and MSU-negative patients; and in MSU-positive subgroups (early-stage disease *vs*. established disease and male *vs*. female).

Features	Categories	Values	n=121			MSU + n=80					
			MSU+ n=80	MSU- n=41	*p*-value	< 2 years n=31	≥ 2 years n=49	*p*-value	Male n=74	Female n=6	*p*-value
Clinical											
Pattern of joint/bursa involvement during symptomatic episode(s) ever	-	0	9 (11.3 %)	31 (75.6 %)	<0.001	5 (16.1 %)	4 (8.2 %)	0.283	6 (8.1 %)	3 (50 %)	0.007
	Ankle or mid-foot	1	22 (27.5 %)	9 (22 %)		6 (19.4 %)	16 (32.6 %)		20 (27 %)	2 (33.3 %)	
	Involvement of the first metatarsophalangeal joint	2	49 (61.3 %)	1 (2.4 %)		20 (64.5 %)	29 (59.2 %)		48 (64.9 %)	1 (16.7 %)	
Characteristics of symptomatic episode(s) ever	-	0	1 (1.3 %)	14 (34.2 %)	<0.001	0 (0 %)	1 (2.0 %)	0.001	1 (1.4 %)	0 (0 %)	0.027
	One characteristic	1	14 (17.5 %)	14 (34.2 %)		11 (35.5 %)	3 (6.1 %)		11 (14.9 %)	3 (50 %)	
	Two characteristics	2	28 (35 %)	5 (12.2 %)		12 (38.7 %)	16 (32.7 %)		25 (33.8%)	3 (50 %)	
	Three characteristics	3	37 (46.3 %)	8 (19.5 %)		8 (25.8 %)	29 (59.2 %)		37 (50 %)	0 (0 %)	
Time course of episode(s) ever	-	0	1 (1.3 %)	21 (52.5 %)	<0.001	0 (0 %)	1 (2.0 %)	0.001	1 (1.4 %)	0 (0 %)	0.043
	One typical episode	1	28 (35 %)	9 (22.5 %)		18 (58.1 %)	10 (20.4 %)		23 (31.1 %)	5 (83.3 %)	
	Recurrent typical episodes	2	51 (63.8 %)	10 (25 %)		13 (41.9%)	38 (77.6 %)		50 (67.6 %)	1 (16.7 %)	
Clinical evidence of tophus	-	0	57 (71.3 %)	41 (100 %)	<0.001	28 (90.3 %)	29 (59.2 %)	0.003	53 (71.6 %)	4 (66.7 %)	1
	Present	4	23 (28.8 %)	0 (0 %)		3 (9.7 %)	20 (40.8 %)		21 (28.4 %)	2 (33.3 %)	
Laboratory											
Serum urate	<4 mg/dL (<0.24 mmol/L)	-4	1 (1.3 %)	2 (5.6 %)	<0.001	0 (0 %)	1 (2.1 %)	0.459	1 (1.4 %)	0 (0 %)	0.669
	4-<6 mg/dL (0.24-<0.36 mmol/L)	0	3 (3.8 %)	25 (69.4 %)		2 (6.5 %)	1 (2.1 %)		2 (2.7 %)	1 (20 %)	
	6-<8 mg/dL (0.36-<0.48 mmol/L)	2	16 (20.3 %)	6 (16.7 %)		8 (25.8 %)	8 (16.8 %)		15 (20.3 %)	1 (20 %)	
	8-<10 mg/dL (0.48-<0.60 mmol/L)	3	40 (50.6 %)	1 (2.8 %)		16 (51.6 %)	24 (50 %)		37 (50 %)	3 (60 %)	
	≥10 mg/dL (≥0.60 mmol/L)	4	19 (24.1 %)	2 (5.6 %)		5 (16.1 %)	14 (29.2 %)		19 (25.7 %)	0 (0 %)	
Synovial fluid analysis of simptomatic (ever)	MSU negative	-2	0 (0 %)	41 (100 %)	<0.001	0 (0 %)	0 (0 %)	1	0 (0 %)	0 (0 %)	1
	MSU positive	0	80 (100 %)	0 (0 %)		31 (100 %)	49 (100 %)		74 (100 %)	6 (100 %)	
Imaging											
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa	-	0	56 (70 %)	37 (90.2 %)	0.013	22 (71 %)	34 (69.4 %)	1	51 (68.9 %)	5 (83.3 %)	0.663
	Present (either modality)	4	24 (30 %)	4 (9.8 %)		9 (29 %)	15 (30.6 %)		23 (31.1 %)	1 (16.7 %)	
Imaging evidence of gout-related joint damage	-	0	73 (91.3 %)	39 (95.1 %)	0.716	29 (93.6 %)	44 (89.8 %)	0.7	68 (91.9 %)	5 (83.3 %)	0.434
	Present	4	7 (8.8 %)	2 (4.9 %)		2 (6.5 %)	5 (10.2 %)		6 (8.1 %)	1 (16.7 %)	

Data shown as number (%). $p<0.05$. MSU: monosodium urate crystals; <2 yrs: less than two years or early-stage disease; ≥2 yrs: greater than or equal to two years or established disease; + positive; - negative.

(46, 47, 49). This may be attributable, at least in part, to the older age of gout onset in females and higher risk of age-related comorbidities (*i.e.* cardiovascular and renal diseases). Therefore, the delayed diagnosis of gout in females may also stem from the severity of other comorbidities which may mask gout symptoms and manifestations. A better understanding of gender differences in gout patient profiles may provide indications for tailored treatment recommendations in the future (50-52).

The strengths of this study are: all patients were clinically diagnosed (gout *vs*. non-gout arthritis) by experienced rheumatologists supported by SF analysis, the wide-ranging and comprehensive data collection that allowed classification by multiple criteria sets. Some of the limitations of our study include the paucity of DECT data, as the routine use of these advanced imaging tools in primary care facilities may be impractical. Furthermore, this study was performed at rheumatology clinics affiliated with University Hospitals, meaning that our study population was limited to patients with more severe patterns of gout than is usually the case in primary care facilities. Finally, there may have been a preferential selection of patients with large joint disease for SF sample collection by arthrocentesis.

In conclusion, the 2015 ACR/EULAR classification criteria for gout yielded an overall good performance in patients presenting with acute arthritis. The proven sensitivity and specificity of only clinical criteria might help discern gout from non-gout patients when microscopy analysis of SF and advanced imaging tools are not available. Considering only clinical criteria, subgroup analysis in patients with early-stage disease showed high specificity and moderate-low sensitivity. The typical 1st MTPJ involvement, multiple characteristics of symptomatic episodes and recurrent acute arthritis occurred more frequently in males. Our study represents the first external validation of the 2015 ACR/EULAR classification criteria for gout in the Italian population, using a cross-sectional multicentre cohort covering various types of gout, as well as in early and established form. Future studies with a larger female population may provide a better understanding of the impact of gender on the 2015 ACR/EULAR classification criteria.

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