

The usefulness of ultrasound in identifying the underlying findings linked to pain in podagra patients

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Abstract

Aim: To explore whether ultrasound (US) can be employed to identify the underlying characteristics associated with pain in patients with podagra by evaluating the relationship between ultrasound findings and clinical pain. **Material and methods:** Patients with podagra were recruited and grouped into a pain group (G1, 82 patients) and a non pain group (G2, 123 patients). US features were collected and compared. US data were analyzed by binary logistic regression analysis and ROC analysis. Interobserver reliability was assessed, too. **Results:** A total of 205 patients (196 male and 9 female) were enrolled in this study. In multivariate analysis, the thickness of the synovium (OR=1.928, CI=1.074-3.463), CD (color Doppler) signal of the synovium (OR=1.458, CI=1.011-2.103), and CD signal of the tophi (OR=1.576, CI=1.142-2.177) were identified as risk factors for clinical pain. Areas under the ROC curves (AUC) were 0.713, 0.686 and 0.641 for the three indicators, respectively. The best cutoff points were 1 mm for the thickness of the synovium, grade 1 for the CD signal of the synovium and grade 2 for the CD signal of the tophi. **Conclusions:** Ultrasound can provide valuable information for determining underlying features associated with pain in patients with podagra.

Keywords: ultrasonography; color Doppler; gout; pain

Background

Gout is a prevalent form of inflammatory arthritis observed in the adult population [1] and is caused by the deposition of monosodium urate (MSU) crystals [2]. The prevalence of gout has been increasing in recent years. Various treatments are recommended based on clinical manifestations, laboratory results and radiological changes, among which clinical pain is one of the most crucial symptoms. The pain usually begins at the first metatarsophalangeal joint [3], which was also called podagra [4].

A typical gout flare usually occurs acutely during night. Patients often report a laceration-like or knife-like, unbearable pain which could last 7 to 14 days before resolution [5]. Undoubtedly, correct assessment and timely treatment of pain plays an important role in clinical practice. However, several factors could interfere with the pain assessment: 1) a precise description of pain may be too complicated for some patients, especially for elderly patients; 2) the pain threshold and perception vary among patients; and 3) in some patients, the duration, peak and extent of the pain was affected by drugs, exercise, or other reasons. Therefore, it is crucial for the doctor to find a reliable and objective tool to identify the underlying characteristics associated with pain.

Although intra-articular aspiration and microscopic observation of urate crystals remain the gold standard for diagnosing gout, ethical considerations preclude routine use in clinical practice. Ultrasound (US) was considered as an optimal diagnostic procedure due to its noninvasive nature, absence of ionizing radiation, high patient compliance, and easy accessibility. After a comprehensive

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literature review, we found that most studies of US and gout focused on the diagnostic efficacy [6,7]: US findings had a high specificity for gout (0.92-0.96) [7]; in gout, the presence of US signs in the symptomatic joint was highly predictive during the diagnosis (PPV = 92%) [8], the sensitivity and specificity of tophi in the first metatarsophalangeal joint and DCS in the ankle joint for early diagnosis of gout were 84% and 81%, respectively [9]. In addition, US showed importance in disease monitoring and ultrasound-guided therapy [10]. The increasing clinical acceptance of US as a tool for gout diagnosis can be attributed to its proven ability to detect MSU crystal deposits in joints through the identification of the double contour sign (DCS) or tophi [9]. In addition to providing two-dimensional imaging, the vascularity of tissues can be assessed by color Doppler (CD) US [11]. Previous studies also proved the clinical value of color Doppler flow imaging (CDFI) in rheumatic disease [12-14]. However, little research has been conducted on the association between CDFI and clinical manifestations in gout.

Hence, we conducted a cross-sectional study to evaluate the feasibility of US in assessing the potential pain-contributing factors in patients with podagra.

Material and methods

Patients

The study received ethical approval from the medical ethics committee of the Affiliated Hospital of Qingdao University (No: QYFY WZLL 27246). All enrolled patients provided fully informed consent prior to data collection. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki [15].

A total of 360 patients presented in the Affiliated Hospital of Qingdao University with suspected podagra were selected between February and August 2022. Among them, 205 patients finally diagnosed with podagra based on clinical symptoms, radiology imaging, and biochemical tests according to the gout classification criteria established by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) in 2015 [16] were enrolled. As depicted in figure 1, a total of 155 patients were excluded.

Medical records

All enrolled patients were asked to complete a clinical information questionnaire designed and stored by MD (Supplementary Material 1). For each patient, the following variables were documented: age (years), sex (male/female), body mass index (BMI) in kg/m², duration of podagra diagnosis (years), frequency of podagra flare (0 times, 1 time per year, or ≥ 2 times per year), se-

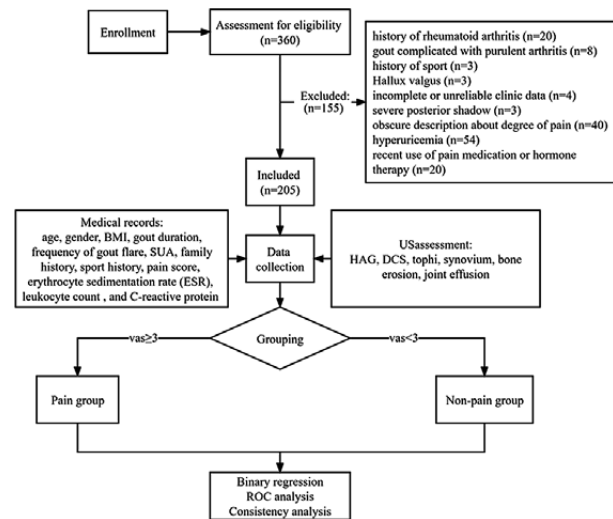


Fig 1. Flow chart of patient enrollment.

rum uric acid (SUA) level ($\mu\text{mol/L}$), family history of podagra (yes/no) and sport history (yes/no).

The visual analog scale (VAS) [17] was used to document the pain feeling. Before the evaluation, the scale was introduced in detail by MD to patients. According to the VAS scores, patients were classified into the pain group (G1, VAS ≥ 3) and the painless group (G2, VAS < 3) [18]. The patient underwent laboratory examination immediately after pain assessment (within 24 hours). A panel of hematological markers, including erythrocyte sedimentation rate (ESR) (mm/60 min), leukocyte count ($10^9/\text{L}$), and C-reactive protein (CRP) levels (mg/L), were obtained from the clinical laboratory.

US examination and graph capture

All US examinations and evaluations were conducted by a radiologist, CN, with more than 10 years of experience in musculoskeletal US. Assessments were performed within 24 hours after clinical pain evaluation. She was blinded to all clinical features during the examination. A HITACHI ARIETTA 70 Advanced Ultrasound machine equipped with a 9-13 MHz linear array transducer was used to examine the affected first metatarsophalangeal (MTP1) joint. US parameters (including frequency, depth, and focusing) were optimized to obtain optimal imaging results for each patient. Machine settings for CDFI were optimized by using a standardized pulse repetition frequency of 400 to 500 Hz and low wall filters, with the gain adjusted just below the disappearance of color signals within the bony cortex. Patients were instructed to sit on the bed with their hips and knees flexed to facilitate a comfortable position for the foot. The MTP1 was scanned dorsally and medially. To scan the medial part of MTP1, the lateral aspect of the foot should be secured to the examination table. At least ten

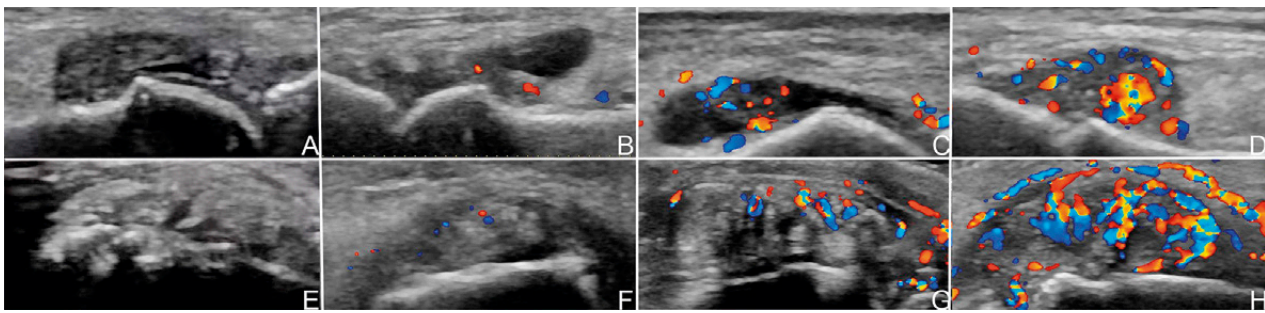


Fig 2. Blood flow signal grading of the synovium. A-D, grade 0-III blood flow. Blood flow signal grading of tophi. E-H, grade 0-III blood flow.

static and four dynamic images were obtained for each patient (Supplementary Material 2).

US evaluation

Ultrasonographic features were assessed and scored according to the Outcome Measures in Rheumatology (OMERACT) criteria [19]: hyperechoic aggregates (HAG) were classified as 0 (absence) or 1 (marked) [6]; double contour sign (DCS): 0 (absent), 1 (possible or definite but minimal), 2 (definite and severe) [20]; bone erosion: 0 (absent), 1 (uneven cortex but no bone defects), 2 (punctured bone defects both in transverse and longitudinal sections); tophi scored to 1 (hypoecho) or 2 (hyperecho). The score range of CD signals of tophi and synovium was from the 0-3 scale [21]: 0 - no color Doppler signal detected within the region of interest (ROI), 1 - up to 3 color Doppler signals detected within the ROI, 2 - blood flow filling within the ROI was less than 50%, and 3 - 50% or more of the ROI was filled with color Doppler signals. Examples of blood flow in synovium and tophi were shown in figure 2. The maximum diameter of tophi, the thickness of the synovium and joint effusion depth were measured quantitatively. Thickest parts of synovium [22] were measured in the vertical synovium direction on the dorsal or medial aspect of MTP1. The deepest part of the joint effusion was measured in the vertical effusion direction of MTP1.

Consistency evaluation

Images and clips for consistency evaluation were randomly selected by MD and re-evaluated by another musculoskeletal US specialist, CJ, with five years of experience. She was blinded to all clinical information. Both were trained at the beginning of the study, and the same standard for image acquisition measurement and judgment were used.

Statistical analysis

All statistical analyses were conducted using SPSS 25. Quantitative variables with a normal distribution were presented as the mean \pm standard deviation and the comparison of means between groups was conducted using t-tests. Quantitative variables with non normal distri-

butions were reported as medians (interquartile ranges) and were analysed using the Mann-Whitney U test. Categorical variables were expressed as numbers (frequencies) and analyzed using the chi-square or Fisher's exact test. Comparison of rank data between two groups using Mann-Whitney U test. Binary regression was employed to examine the factors influencing the binary outcome within each group. Receiver operating characteristic (ROC) analysis was utilized to determine the best cutoff point for independent variables. Statistical significance was defined as $p < 0.05$.

Sample size for the consistency analysis was determined using PASS 2021 software. Interobserver agreement of categorical variables, including CD signal of synovium and tophi, DCS, and bone erosion, was conducted utilizing Kappa statistics. Kappa values ranging from 0 - 0.20 were considered poor; 0.20-0.40, fair; 0.40-0.60, moderate; 0.60-0.80, good; and 0.80-1 indicated excellent agreement [23]. Consistency of synovial thickness was evaluated using ICC and Bland-Altman plots. For ICC values, poor repeatability was indicated by an ICC value less than 0.5, while an ICC greater than 0.75 indicates excellent repeatability of diagnostic tests [24].

Results

General Information and Groups

A total of 205 patients were enrolled in this study. Comparison of the clinical data between Group 1 and Group 2 is presented in Table I. Group 1 comprised 82 patients ($VAS \geq 3$), and Group 2 consisted of 123 patients ($VAS < 3$). Notably, the pain group exhibited significantly higher CRP levels ($p = 0.003$) and a shorter duration of podagra ($p < 0.001$). No statistically significant difference was observed in other clinical parameters between the two groups.

US findings and comparisons between groups

On US, positive findings were observed, including synovial hyperplasia (134 patients), HAG (123 patients),

Table I. Characteristics of study participants

	Total	Group 1	Group 2	t/Z/ χ^2	p	
Number	205	82	123			
Gender, male (n)	196(95.6)	76(92.6)	120(97.5)	2.79	0.10	
Age (years)	47(19)	44(25)	47(16)	0.7	0.48	
BMI (kg/m ²)	27.1(4.3)	27.2(4.5)	27.1(4.1)	0.39	0.70	
Duration (years)	5.0(7.0)	3.0(6.0)	6.0(7.0)	3.69	<0.001	
Family history (n)	54(26.3)	21(25.6)	33(26.8)	0.04	0.85	
Sport history (n)	60(29.2)	25(29.8)	35(28.5)	0.1	0.75	
SUA ($\mu\text{mol/L}$)	490(161)	484(156)	490(176)	0.59	0.56	
Flare frequency (/y)						
	1	97(47.3)	41(50.0)	56(45.5)	0.40	0.53
	≥ 2	108(52.6)	41(50.0)	67(35.4)		
ESR (mm/60 min)	12.5 \pm 1.1	14.9 \pm 1.9	11.0 \pm 1.2	3.94	0.07	
Leukocyte ($10^9/\text{L}$)	7.6 \pm 0.2	7.9 \pm 0.3	7.4 \pm 0.2	6.28	0.07	
CRP (mg/L)	10.5 \pm 2.2	17.7 \pm 4.5	4.9 \pm 1.5	19.82	0.003	

Quantitative variables with a normal distribution are presented as the mean \pm standard deviation. Numerical variables are expressed as the median (IQR). Categorical variables are presented as numbers (frequencies). G1 includes patients with pain, and G2 contains patients without pain. BMI – body mass index, SUA – serum uric acid, ESR – erythrocyte sedimentation rate, CRP-C – reactive protein, n – number.

tophi (149 patients), and DCS (147 patients). Among the 149 tophi detected, 112 were hyperechoic and 37 were hypoechoic compared with the subcutaneous fat. For different echoes of tophi, proportions of positive blood flow detection were 42.0% and 78.4% for hyperechoic and hypoechoic echoes, respectively. In group 1, CD of synovium was observed in more than 61% (50/82) of patients, compared to only 22% (27/123) in group 2. The detection rate of CD in tophi was also higher in G1 (83% VS 71%). US findings comparison between the groups is presented in Table II. G1 exhibited a significantly thicker synovium ($p < 0.001$) and a richer synovium CD signal ($p < 0.001$) compared to G2. The CD signal of tophi in G1 was also higher than that in G2 ($p = 0.002$). Additionally, positive ratios of HAG and DCS were found to be higher in G1 than in G2, and the differences were significant ($p < 0.001$, $p = 0.02$). However, there was no significant difference observed in terms of the number, maximum diameter, and echo of the tophi between the two groups.

Multivariate analysis

All variables with statistical significance ($p < 0.05$) in Table II were taken as candidates for further binary logistic regression analyses. Synovium thickness, CD signal of both synovium and tophi were found to be independent factors ($p < 0.05$) related for pain feeling (fig 3).

ROC analysis

To find the best cutoff point for distinguishing the two groups objectively, a ROC analysis was conducted on variables including the thickness of the synovium, CD signal of synovium and tophi (Table III). Areas under the ROC curve (AUCs) were found to be over 0.5. As depicted in figure 4, patients with a thick synovium (≥ 1

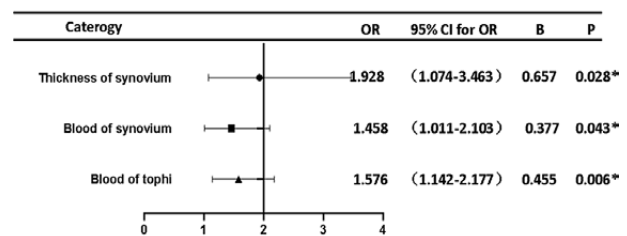


Fig 3. The forest map statistics of three independent impact factors.

mm) and CD signal of both synovium (≥ 1) and tophi (≥ 2) were more likely to experience.

Consistency evaluation

To assess consistency of synovial thickness measurements, 120 patients were randomly selected (Supplementary Material 3) and the ICC method was employed. The

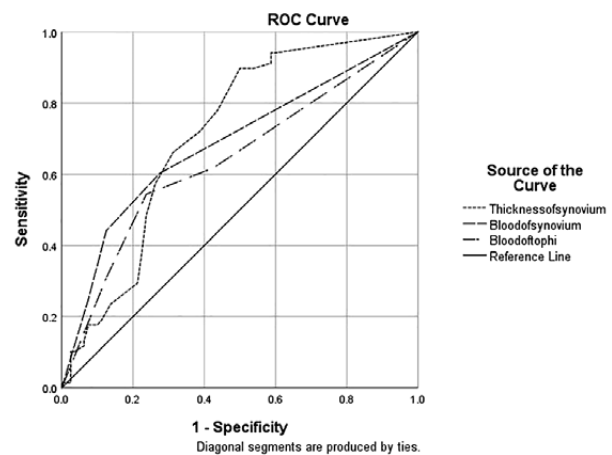


Fig 4. ROC analysis results between G1 and G2.

Table II. Descriptive statistics for US findings in patients

		Group 1	Group 2	Z/ χ^2	p
Number		82	123		
Thickness of synovium (mm)		1.5(0.8)	0.9(0.8)	6.07	<0.001
CD signal of synovium	0	32(39.0)	96(78.0)	6.10	<0.001
	1	12(14.6)	15(12.1)		
	2	16(19.5)	6(4.8)		
	3	22(26.8)	6(4.8)		
HAG		62(75.3)	61(49.5)	13.88	<0.001
Tophi number	0	14(17.0)	42(34.1)	1.42	0.16
	1	56(68.2)	57(34.9)		
	2	5(6.0)	10(5.7)		
	≥3	7(8.5)	14(9.1)		
Maximum diameter of tophi (mm)		8.0(5.0)	10.0(5.0)	1.64	0.10
Tophi echo	hypoechoic	19(27.9)	18(20.7)	0.62	0.43
	hyperechoic	49(72.1)	69(79.3)		
CD signal of tophi	0	26(38.2)	50(57.5)	3.17	0.002
	1	5(7.4)	17(19.5)		
	2	16(23.5)	9(10.3)		
	3	21(30.9)	11(12.6)		
DCS	0	14(17.0)	61(34.9)	2.40	0.02
	1	2(2.4)	1(0.6)		
	2	66(80.4)	113(64.6)		
Bone erosion	0	49(59.7)	121(69.1)	0.05	0.96
	1	2(2.4)	9(5.1)		
	2	31(37.8)	45(25.7)		
Joint effusion (mm)		2.0(1.0)	1.6(1.0)	1.76	0.08

Numerical variables are expressed as the median (interquartile spacing). Categorical variables are presented as numbers (frequencies). HAG – hyperechoic aggregates, DCS – double contour sign, CD – color Doppler

Bland–Altman plot (fig 5) displays the difference among the 120 cases within the 95% confidence interval, ICC analysis yields a coefficient of 0.955, both indicating exceptional consistency.

Kappa values of DCS, bone erosion, and CD of synovium and tophi were 0.525, 0.600, 0.735 and 0.877, respectively. Consistence for blood flow gradients were rather robust. However, the consistency of the DCS was not satisfactory.

Discussion

This is a cross-sectional study aimed at elucidating the relationship between pain and US findings in patients with podagra. Through intergroup comparisons and additional analyses, we identified the synovial thickness, CD signal of synovium and tophi as the three factors that positively correlated with pain, with synovial thickness exhibiting the highest odds ratio. Specifically, synovial thickness ≥ 1 mm, CD signal ≥ 1 of synovium, or CD

Table III. ROC analysis of the predicted risk of pain presence/absence

Test Result Variable(s)	AUC	Cutoff	Se	Sp	Max Youden index
Thickness of synovium	0.713	0.95	0.897	0.500	0.397
Blood of synovium	0.686	0.5	0.603	0.725	0.328
Blood of tophi	0.641	1.5	0.540	0.762	0.302

AUC – area under the curve, Se – sensitivity, Sp – specificity

signal ≥ 2 of tophi were sensitive indicators of pain. We believe that US is an effective and reliable method for identifying underlying factors associated with pain in patients with podagra, especially in patients with atypical pain. The study sheds light on the etiology of acute podagra pain and advances research in pain management and targeted therapeutics.

According to the classification criteria recommended by ACR and EULAR in 2015 [16], pain assessment plays a pivotal role in diagnosing, staging and treatment planning in gout. During episodes of gout flares, anti-inflammatory therapy (colchicine) was usually recommended [25]. In contrast, patients without pain may be given uric acid-lowering therapy which in turn triggers and aggravates gout flares. In clinical practice, we observed that a significant number of patients present with atypical pain. The pain may range from mild to severe, and some can persist for more than 30 days. Current clinical practice employs the semiquantitative VAS score, which is inherently subjective. Clinicians are often confused by patients' ambiguous and uncertain descriptions. In addition, the threshold of pain in patients varies. Thus, it is difficult for clinical doctors to determine whether the cause was exercise-induced, injury-related or gout-related. As an alternative tool to detect pain characteristics, US is more objective than VAS, and is not limited by the patient's pain perception threshold and expression clarity. For patients with atypical or poorly described pain, the synovium, intra-synovial blood flow and intra-tophi blood flow can be assessed in combination with US reports to indicate the current state of the patient, which will be helpful for clinicians to make decisions.

It is widely acknowledged that male sex, obesity, alcohol consumption and a high purine diet are risk factors for gout. The incidence of gout in women, particularly adolescent females, is relatively low. Of the nine female patients included in our study, seven were postmenopausal, and the remaining two had quite high BMIs (31.7 and 40.8, respectively). We also found that patients with a shorter duration were more likely to report pain, possibly due to central sensitization [26], whereas the perception of pain is believed to diminish as the frequency of pain increases. As demonstrated in table I, there exists a notable disparity in CRP levels between the two groups. Therefore, it is reasonable to assume that inflammation was one of the key reasons underlying clinical pain.

In the evaluation of image consistency, our data proved a high level of interobserver agreement regarding bone erosion, synovial thickness, tophi echo, and blood flow of synovium and tophi and we concluded that US examination is a reliable technique for assessing gout arthritis [6]. Interobserver consistency of DCS is only at moderate level as a result of challenge in clinical practice to distinguish DCS from normal cartilage interface, especially in patients in the hyperuricemia stage in which only serum uric acid is increased, and the deposition of uric acid is less.

Previous studies have shown a higher detection rate of US blood flow signals in the synovium [27-30], and

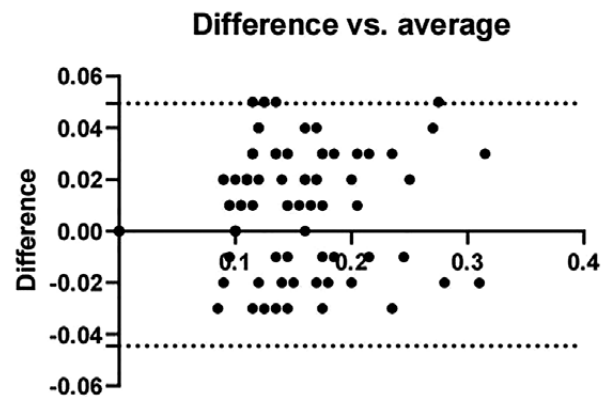


Fig 5. Blant-Altman evaluation of consistency between readers regarding synovial thickness.

some have also revealed the relationship between blood flow signals in synovium and acute pain [31]. In this study, we revealed that both thickness of synovium and blood flow signal in synovium are indicators of pain. A previous animal study demonstrated a positive correlation between the blood flow signal in the synovium and the tissue vascularization measured by CD31 immunohistochemistry [32], suggesting the role of inflammation in mediating high blood flow signals. Similarly, it is reasonable to hypothesize that vasodilation and congestion caused by activation of inflammatory mediators [33] associated with gout flares may lead to the elevation of blood flow, which was further supported by the effectiveness of anti-inflammatory treatments [34].

Most previous experiments focused on the presence [31,35-37] or absence of tophi. Our results further indicated that hypoechoic tophi appeared in a higher number of patients in the pain group (27.9% [19/68]) than in the non pain group (20.7% [18/87]). Additionally, odds of pain-group exposure for those with CD signal of tophi were 1.576 times higher than for those without. Similar to synovial congestion, tophi inflammation-induced vasodilation and hyperemia may cause an increased probability of pain. CRP in G1 was significantly higher than that in G2, providing evidence that supports our hypothesis regarding the influence of inflammation on the correlation between pain and blood flow signals in both the synovium and tophi.

There are several limitations in our study. First, it is a single-center cross-sectional study with a limited sample size. Larger cohort and multicenter studies are needed to validate and refine our findings. Second, our study focused on MTP1, which is the most commonly affected joint in patients with gout [35]. The result may not be generalizable to other joints, such as the ankle and knee. Studies investigating the clinical utility of US in the ankle and knee among patients with gout were planned. Fi-

nally, we classified all the patients into two groups (pain and non pain groups) and no control group was designed. The intensity of pain was not considered due to the limited sample size.

In the future, we will collect more data combined with other imaging data to explore the role of ultrasound in gouty arthritis.

Conclusions

US is a valuable tool for identifying underlying factors associated with pain in patients with podagra. Independent predictors include thickness of the synovium, blood flow in the synovium and tophi in MTP1. Patients usually report pain when the thickness of synovium is ≥ 1 mm or when the blood flow grade exceeds 1 in the synovium or 2 in tophi. Therefore, we suggest that US physicians should report blood flow signal grading clearly in clinical practice.

Conflict of interest: none

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