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ORIGINAL ARTICLE

Diagnostic values of different musculoskeletal ultrasound signs, serum uric acid, and their combined detection for gouty arthritis

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ABSTRACT

Objectives: The study aimed to investigate the diagnostic values of different musculoskeletal ultrasound (MSUS) signs, serum uric acid (SUA), and their combined detection for gouty arthritis (GA).

Patients and methods: In this retrospective study, 70 patients (62 males, 8 females; mean age: 46.1±14.1 years; range, 25 to 86 years) diagnosed with GA (the GA group) between August 2022 and March 2023 and 70 patients (54 females, 16 males; mean age: 49.0±14.1 years; range, 21 to 75 years) diagnosed with rheumatoid arthritis and osteoarthritis during the same period (the non-GA group) were included. The positive rate of MSUS signs and SUA in both groups was recorded to compare the differences. The correlations of MSUS signs and SUA with GA were analyzed using Spearman's rank correlation analysis. The diagnostic values of different MSUS signs, SUA, and their combined detection for GA were analyzed using a receiver operating characteristic, the area under the curve (AUC), sensitivity, specificity, and the Youden index.

Results: The positive rate of the double contour (DC) sign (chi-squared [χ^2]=102.935, p<0.001), hyperechoic spots (χ^2=56.395, p<0.001), bone erosions (χ^2=10.080, p<0.001), and SUA (χ^2=41.117, p<0.001) were higher in the GA group than in the non-GA group. The positive rate of the DC sign (rs=0.829, p=0.001), hyperechoic spots (rs=0.631, p<0.001), bone erosion (rs=0.268, p=0.001), and SUA (rs=0.542, p<0.001) were positively correlated with GA. Among the single-indicator measures, the DC sign exhibited the highest diagnostic value (AUC=0.907, sensitivity=81.4%, specificity=100%, p<0.001). Among the combined-indicator measures, the DC sign combined with SUA exhibited the highest diagnostic value (AUC=0.929, sensitivity=91.4%, specificity=94.3%, p<0.001), higher than DC sign detection alone.

Conclusion: The DC sign combined with SUA yielded a high diagnostic value and can thus provide a reliable basis for effectively and efficiently diagnosing GA.

Keywords: Diagnostic value, gouty arthritis, musculoskeletal ultrasound, serum uric acid.

Gouty arthritis (GA) is one of the most common forms of inflammatory arthritis, and its prevalence is rapidly increasing worldwide.[1] Therefore, the global burden of GA is substantial.[2,3] GA is caused by the chronic elevation of serum uric acid (SUA) above the saturation point for monosodium urate (MSU) crystal formation.[4] The deposition of MSU crystals in the joints and surrounding tissues causes inflammation and tissue damage. GA often affects multiple joints, resulting in inconvenience and even disability, reducing the patients' quality of life. GA is associated with many conditions that affect longevity and well-being,[5] such as metabolic syndrome,[6] diabetes,[7] myocardial infarction,[8-10] and premature death.[9,11] Early detection and diagnosis of GA can prevent disability and reduce the risk of comorbidities (e.g., cardiovascular and renal diseases);[12,13] in addition, it can relieve the economic burden on patients and aid in optimizing the allocation of healthcare resources. Therefore, it is vital to diagnose GA as early as possible and reduce misdiagnosis and underdiagnosis.

The current gold standard for the diagnosis of GA is the microscopic identification of MSU crystals in synovial fluid or tophi.[14,15] However, the examination is invasive, complex, and requires microscopic analysis techniques, making it difficult to be widely implemented as a routine diagnostic tool. In addition, the gout classification criteria published by American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) in 2015[16] diagnose GA by summing up the scores based on clinical symptoms, laboratory tests, and imaging. However, the implementation process of the classification is cumbersome, and there are difficulties in the practical application of the criteria in primary healthcare institutions. Clinically, diagnosis of suspected GA is based on typical clinical symptoms (e.g., swelling and pain) and laboratory tests (e.g., SUA and C-reactive protein).[17,18] However, SUA is easily affected by many factors (e.g., diet and medication), detection of the SUA level over a short period of time does not fully reflect the patient's actual condition, and changes in the SUA level are not fully representative of changes in the joints. Conventional imaging can assist in observing changes in the joints. Radiographs can reveal structural lesions in the joints,[19] but they are radioactive and are not sensitive enough to detect arthritis in the early stages.[20] In addition, radiographs are poor at differentiating GA from other types of arthritis. Dual-energy computed tomography exhibits high sensitivity and specificity for the detection of GA and can visualize MSU crystals and bone destruction in the joints.[21,22] However, it is radioactive and expensive and is not widely available in primary healthcare institutions. Magnetic resonance imaging can reflect subtle changes in articular cartilage[23] and is often used to detect arthritis; however, it is relatively expensive,[24] and the examination time is long, making it unsuitable as a routine diagnostic tool for GA.

More convenient indicators with high diagnostic values can assist in the efficient clinical diagnosis of GA and reduce misdiagnosis and underdiagnosis. Ultrasound has gradually come into prominence due to its advantages of being noninvasive, relatively cheap, easily accessible, and capable of real-time detection.[25] Furthermore, musculoskeletal ultrasound (MSUS) can scan the joints from multiple angles and show lesions in small joints (e.g., metatarsophalangeal joints and finger joints) and is widely available in primary healthcare institutions. The sensitivity and specificity of ultrasound in the diagnosis of GA are approximately 85% and require further improvement. The combination of MSUS and laboratory tests can be considered for the diagnosis of GA; however, there are few studies on the diagnostic values of such indicators, and further studies are required.

This retrospective study aimed to explore the diagnostic values of different MSUS signs, SUA, and their combined use for efficient diagnosis of GA and to provide a reference for the early detection and diagnosis of GA, contributing to delaying or avoiding disease deterioration, improving patients' quality of life, and optimizing the allocation of healthcare resources.

PATIENTS AND METHODS

In this retrospective study, 70 patients (62 males, 8 females; mean age: 46.1±14.1 years; range, 25 to 86 years) with GA who presented to the The Fourth Afliated Hospital, Zhejiang University School of Medicine between August 2022 and March 2023 were included (the GA group), and 70 patients (54 females, 16 males; mean age: 49.0±14.1 years; range, 21 to 75 years) with rheumatoid arthritis (RA) and osteoarthritis (OA) were included as the control group (the non-GA group). The inclusion criteria were as follows: *(i)* age >18 years; *(ii)* no symptomatic treatment for the associated arthritis within the last six months. The patients with GA satisfied the 2015 ACR/EULAR gout classification criteria.[16] The patients with RA and OA satisfied the 2010 ACR/EULAR RA classification criteria[26] and the Chinese guideline for the diagnosis and treatment of OA (2021 edition).[27] The exclusion criteria were as follows: *(i)* previous trauma to the examined joint; *(ii)* combination of other arthritis or malignant diseases; *(iii)* pregnancy or breastfeeding.

The historical ultrasound data used in this study were obtained from standardized scans of the involved joints of all subjects by an experienced and highly qualified

ultrasonographer. MSUS examinations were performed using an Aplio i800 (Canon, Medical Systems Corporation, Otawara, Tochigi, Japan) machine and i18XL5 (Canon, Medical Systems Corporation, Otawara, Tochigi, Japan) linear array transducer (10-18 MHz) under the musculoskeletal mode. In this study, MSUS signs (double contour [DC] sign, hyperechoic spots, joint effusion, bone erosions, synovial thickening, and vessel signals) were qualitatively graded as positive or negative.

The DC sign are crystals deposited in the most superficial layer of the hyaline articular cartilage and appear as an irregular hyperechoic line over the anechoic cartilage, together with another underlying hyperechoic line caused by the subchondral bone (Figure 1a). Hyperechoic spots are crystals deposited in synovial membranes or joint cavity effusions forming punctate hyperechogenicity (Figure 1b). Joint effusion is a compressible anechoic intracapsular area (Figure 1c). Synovial thickening is the thickening of incompressible hypoechoic areas within the joint cavity (Figure 1d). Bone erosion is the change in the surface of the bone near the joint (Figure 1e). Vessel signals in the synovium are displayed as colored signals under superb microvascular imaging mode (Figure 1f).

We collected 5 mL of fasting venous blood of the patient, centrifugated the serum, detected the SUA level of the subjects by using the uricase peroxidase method, and marked it as positive or negative (an SUA level >420 μmol/L was considered positive in males; an SUA level >360 μmol/L was considered positive in females).

Statistical analysis

The statistical analysis was performed using IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers (percentages). The chi-square test and independent samples t-test were used for comparing the demographic data, MSUS signs, and SUA. The correlation analysis of MSUS signs and SUA with GA was performed using Spearman's rank correlation analysis. Correlation coefficients were interpreted as weak ($rs \leq 0.3$), moderate ($0.3 < rs < 0.7$), or strong ($rs \geq 0.7$).[28] The diagnostic value analysis was performed using receiver operating characteristic (ROC) curves, the area under the curve (AUC), sensitivity, specificity, and the Youden index. The level of statistical significance was set at $p < 0.05$.

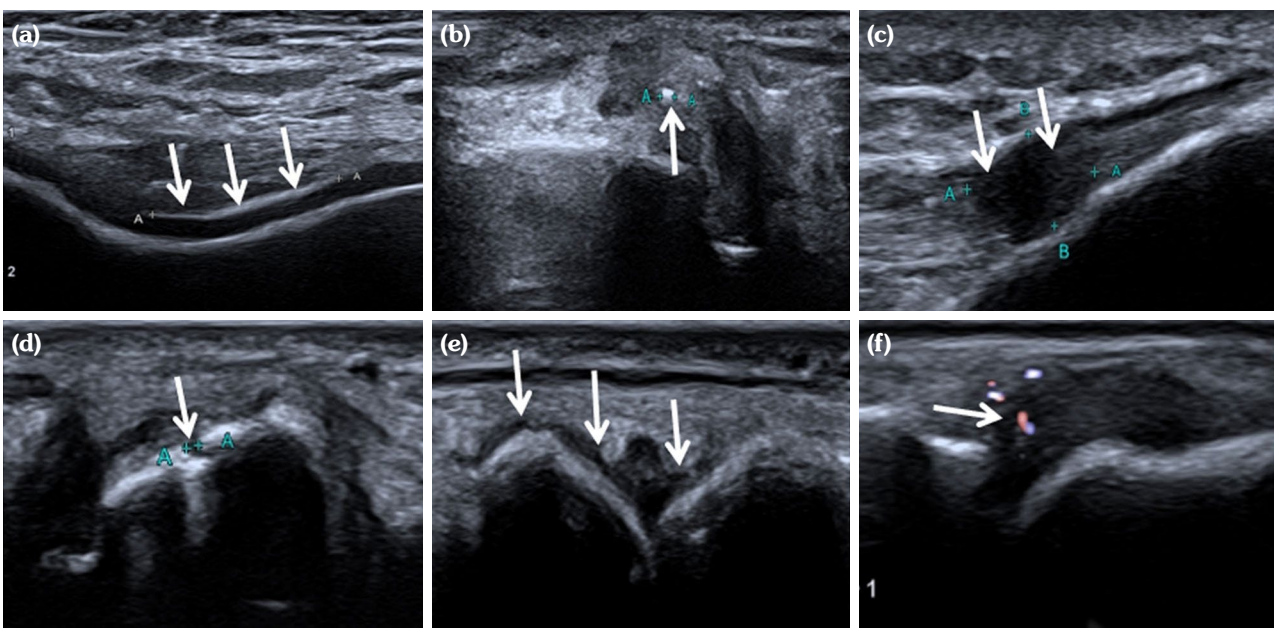

Figure 1. Musculoskeletal ultrasound signs: **(a)** double contour sign; **(b)** hyperechoic spots; **(c)** joint effusion; **(d)** bone erosion; **(e)** synovial thickening; **(f)** vessel signals.

Table 1. Demographic data, MSUS signs, and SUA levels of the GA group and the non-GA group

	Non-GA group (n=70)			GA group (n=70)				
Variables	n	%	Mean±SD	n	%	Mean±SD	t/χ^2	*p*
Age (year)			49.0 ±14.1			46.1 ±14.1	1.231	0.220
Sex Males	16	22.86		62	88.57		61.257	0.000*
DC sign Positive Negative	0 70	0 100		57 13	81.43 18.57		96.145	0.000*
Hyperechoic spots Positive Negative	16 54	22.86 77.14		60 10	85.71 14.29		55.724	0.000*
Joint effusion Positive Negative	13 57	18.57 81.43		23 47	32.86 67.14		3.739	0.053
Bone erosion Positive Negative	16 54	22.86 77.14		34 36	48.57 51.43		10.080	0.001*
Synovial thickening Positive Negative	70 0	100 0		70 0	100 0		-	-
Vessel signals Positive Negative	60 10	85.71 14.29		61 9	87.14 12.86		0.061	0.805
SUA Positive Negative	4 66	5.71 94.29		39 31	55.71 44.29		41.117	0.000*

MSUS: Musculoskeletal ultrasound; SUA: Serum uric acid; GA: Gouty arthritis; SD: standard deviation; DC: Double contour; * p<0.05.

RESULTS

There were statistically significant differences in sex distribution between the groups, whereas there was no statistically significant difference in age between the two groups. The positive rate of DC sign (chi-squared [χ^2]=96.145, p<0.001), hyperechoic spots (χ^2=55.724, p<0.001), bone erosion (χ^2=10.080, p=0.001), and SUA (χ^2=41.117, p<0.001) were higher in the GA group than in the non-GA group. However, no significant difference was observed in joint effusion (χ^2=3.739, p=0.053), synovial thickening, and vessel signals (χ^2=0.061, p=0.805). The results of the independent sample t-tests and chi-square tests comparing the demographic characteristics, MSUS signs, and SUA of the two groups are presented in Table 1.

Spearman's rank correlation coefficient showed that the positive rate of the DC sign, hyperechoic spots, bone erosion, and SUA were positively correlated with SUA. The DC sign (rs=0.829, p<0.001) was strongly correlated with GA, the hyperechoic spots

Table 2. Correlation of MSUS signs and SUA with GA

Indicators	DC sign	Hyperechoic spots	Joint effusion	Bone erosions	Synovial thickening	Vessel signals	SUA
r_s	0.829	0.631	0.163	0.268	-	0.021	0.542
P value	<0.001*	<0.001*	0.054	0.001*	>0.999	0.807	<0.001*

MSUS: Musculoskeletal ultrasound; SUA: Serum uric acid; GA: Gouty arthritis; DC: Double contour; r_s: Correlation coefficient of Spearman's rank correlation; * p<0.05.

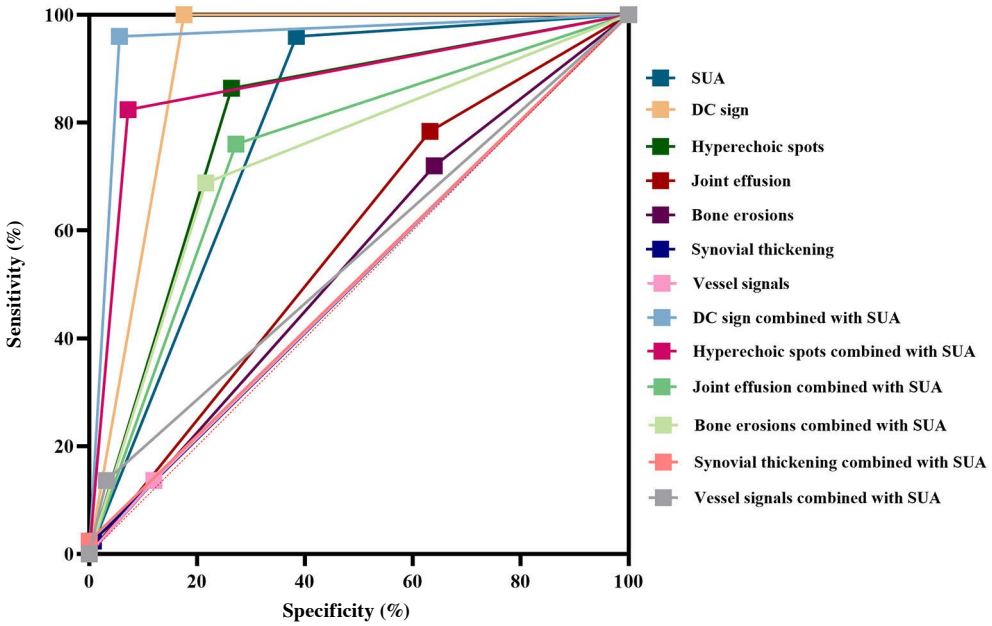

Figure 2. ROC curves for diagnosis of GA by MSUS signs detection alone, SUA detection alone, and combined detection.

ROC: Receiver operating characteristic; GA: Gouty arthritis; MSUS: Musculoskeletal ultrasound; SUA: Serum uric acid.

(rs=0.631, p<0.001) and SUA (rs=0.542, p<0.001) were moderately correlated with GA, and bone erosion (rs=0.268, p=0.001) was weakly correlated with GA. However, the correlations of joint effusion (rs=0.163, p=0.054), synovial thickening (p>0.999), and vessel signals (rs=0.021, p=0.807) with GA were not statistically significant. The correlation coefficients of MSUS signs and SUA with GA are listed in Table 2.

Table 3. Diagnostic values of MSUS signs detected alone, SUA detected alone, and combined detection for GA

Diagnostic indicators	AUC	95% CI	*p*	Sensitivity (%)	Specificity (%)	Youden index
DC sign	0.907	0.851~0.963	<0.001*	81.4	100	0.814
Hyperechoic spots	0.814	0.740~0.889	<0.001*	85.7	77.1	0.628
Joint effusion	0.571	0.447~0.662	0.145	32.9	81.4	0.143
Bone erosion	0.629	0.536~0.721	0.009*	48.6	77.1	0.257
Synovial thickening	0.500	0.404~0.596	>0.999	-	-	-
Vessel signals	0.507	0.411~0.603	0.884	87.1	14.3	0.014
SUA	0.750	0.667~0.833	<0.001*	55.7	94.3	0.5
DC sign combined with SUA	0.929	0.879~0.978	<0.001*	91.4	94.3	0.857
Hyperechoic spots combined with SUA	0.829	0.756~0.901	<0.001*	94.3	71.4	0.657
Joint effusion combined with SUA	0.707	0.620~0.794	<0.001*	65.7	75.7	0.414
Bone erosion combined with SUA	0.757	0.675~0.839	<0.001*	80	71.4	0.514
Synovial thickening combined with SUA	0.500	0.404~0.596	>0.999	-	-	-
Vessel signals combined with SUA	0.529	0.433~0.624	0.560	92.9	12.9	0.058

MSUS: Musculoskeletal ultrasound; SUA: Serum uric acid; GA: Gouty arthritis; AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; DC: Double contour; * p<0.05.

The AUC is commonly used to assess the discriminative ability of prediction models.[29] The results of the diagnostic value analysis (Figure 2 and Table 3) revealed that the AUCs for the DC sign, hyperechoic spots, bone erosion, and SUA were statistically significant among the single-indicator measures, with the highest to lowest diagnostic values being the DC sign, hyperechoic spots, SUA, and bone erosion. Among the combined-indicator measures, the AUCs for the DC sign combined with SUA, hyperechoic spots combined with SUA, joint effusion combined with SUA, and bone erosion combined with SUA were statistically significant, with the highest to lowest diagnostic value being the DC sign combined with SUA, hyperechoic spots combined with SUA, bone erosion combined with SUA, and joint effusion combined with SUA. Of all the indicators in this study, the DC sign combined with SUA exhibited the highest diagnostic value, followed by the DC sign detection alone.

DISCUSSION

In this study, we investigated the diagnostic values of different MSUS signs, SUA, and their combined detection for GA diagnosis. The DC sign exhibited the highest diagnostic value among single-indicator measures, and the DC sign combined with SUA exhibited the highest diagnostic value among combined-indicator measures, higher than the DC sign detection alone. In addition, the positive rate of DC sign, hyperechoic spots, bone erosion, and SUA were higher in the GA group than in the non-GA group. Moreover, the DC sign was strongly correlated with GA, the hyperechoic spots and SUA were moderately correlated with GA, and bone erosion was weakly correlated with GA. However, joint effusion, synovial thickening, and vessel signals are not associated with GA.

Musculoskeletal ultrasound signs of the GA and non-GA groups were compared, and the positive rates of DC sign, hyperechoic spots, and bone erosion were significantly higher in the GA group than in the non-GA group. In addition, the correlation analysis revealed that the DC sign was strongly correlated with GA, the hyperechoic spots and SUA were moderately correlated with GA, and bone erosion was weakly correlated with GA, indicating the potential diagnostic values of these three types of MSUS signs for GA. Nevertheless, joint effusion, synovial thickening, and vessel signals may not be used for gout diagnosis. In recent years, smaller, higher-frequency probes have been used in MSUS, conferring the advantages of high resolution and definition[30] and allowing clear imaging of cartilage, muscle ligaments, and other tissue structures.[31] The presence of bone erosion and synovial thickening can be directly observed in the grayscale mode, MSU deposition can be detected through the DC sign and hyperechoic spots, and the presence of vessel signals in the synovial can be observed in the power Doppler mode to assess whether inflammation is active or inactive. Ogdie et al.[32] performed a systematic literature review and meta-analysis to analyze the usefulness of different imaging modalities in GA, with the aim of developing new classification criteria, including imaging modalities. They included 11 studies (seven on ultrasound) that investigated the sensitivity and specificity of imaging modalities compared to the detection of MSU crystals. They concluded that imaging techniques, particularly ultrasound, may have a promising role in the diagnosis of GA and the classification of patients with symptomatic disease. SUA levels and the DC sign are included as part of the GA classification criteria in the 2015 ACR/EULAR gout classification criteria.[16] The results of this study, the features of MSUS, and previous studies suggest that MSUS can aid in detecting GA.

The pathology of GA is a disturbance in purine metabolism or a decrease in uric acid excretion, which results in high concentrations of uric acid in the blood and deposition of MSU in joints and tissues, causing inflammation or tissue damage.[33] Duskin-Bitan et al.[34] found that people with hyperuricemia had a 32-fold increased risk of developing GA compared to those with normal SUA. Shiozawa et al.[35] also showed that the higher the SUA level, the higher the incidence and recurrence rate of GA. Dalbeth et al.[36] found that the three-year cumulative incidence of GA in those with an SUA <6 mg/dL was 0.21%, whereas the three-year cumulative incidence of GA in those with an SUA level ≥10 mg/dL was up to 10%. The results of the independent samples

t-test showed that the positive rate of SUA was significantly higher in the GA group than in the non-GA group, and the correlation analysis further showed a moderate positive correlation between SUA and GA. This is consistent with the pathology of GA and previous studies.[34-36] The results of the current study and previous studies demonstrate the importance of SUA in the diagnosis of GA.

The results of the diagnostic value analysis showed that in the single-indicator measures, the DC sign exhibited the highest diagnostic value of GA, with an AUC, sensitivity, and specificity of 0.907, 81.4%, and 100%, respectively, followed by the hyperechoic spots, with an AUC, sensitivity, and specificity of 0.814, 85.7%, and 77.1%, respectively; as such, further improvement is required. Further analysis of the diagnostic values of the combined indicators detections in this study revealed that the DC sign combined with SUA exhibited the highest diagnostic value of GA, with an AUC, sensitivity, and specificity of 0.929, 91.4%, and 94.3%, respectively, thus indicating that combined detections have a high diagnostic value of GA. The diagnostic value of ultrasound signs in GA has been studied extensively. For example, in a retrospective case-control study, Naredo et al.[14] found that the sensitivity and specificity of the abnormal ultrasound signs for GA were 84.6% and 83.3%, respectively. A controlled multijoint study by Norkuviene et al.[37] found that gout nodules in the first metatarsophalangeal joint and the DC sign in the ankle were significant in the diagnosis of GA, with a sensitivity and specificity of 84% and 81%, respectively. Compared to these studies, the current study not only validates the sensitivity and specificity of the MSUS signs for the diagnosis of GA but also combines the MSUS signs and SUA for the diagnosis of GA, in which the DC sign combined with SUA has a high diagnostic value. This can help reduce the misdiagnosis and underdiagnosis of GA in a convenient and efficient manner, thus delaying or avoiding disease progression, preventing irreversible damage, such as movement disorders and joint deformities, and reducing the occurrence of complications.

This study has some limitations. First, height, weight, and duration of disease were not included in the analysis; as such, more indicators need to be included in future studies. Second, the DC sign, hyperechoic spots, joint effusion, bone erosion, synovial thickening, and vessel signals were not analyzed quantitatively, and subsequent studies should consider quantifying these MSUS signs. Finally, this study is a single-center study, and multicenter studies can be conducted in the future.

In conclusion, the DC sign was strongly correlated with GA, the hyperechoic spots and SUA were moderately correlated with GA, and bone erosion was weakly correlated with GA. Moreover, among the single-indicator measures, the DC sign exhibited the highest diagnostic value. Among the combined detections, the DC sign combined with SUA exhibited the highest diagnostic value, higher than DC sign detection alone. Due to the noninvasive and portable features of MSUS, the DC sign combined with SUA can conveniently and efficiently reduce underdiagnosis and misdiagnosis of GA, thus preventing recurrent pain, discomfort, and even disability due to the deterioration of GA and reducing the economic burden on patients and the country.

Ethics Committee Approval: The study protocol was approved by the Zhejiang University School of Medicine Ethics Committee (date: 21.02.2023, no: K2023011). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Contributed to conceptualization, data collection, data analysis, investigation, and manuscript writing: W.J.Y.; Contributed to conceptualization and ultrasound assessment: Y.J.L.; Contributed to conceptualization and clinical evaluation: C.J.; Contributed to data collection and data analysis: L.C.; Contributed to ultrasound assessment and manuscript revision: X.B.; Contributed to investigation and manuscript revision: L.S.N.; Contributed to conceptualization, manuscript revision, funding acquisition, and supervision: Z.X.J.; Contributed to conceptualization, manuscript revision, funding acquisition, and supervision: Z.Q.L.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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