Application of vascular index based on superb microvascular imaging technique for assessing disease activity in rheumatoid arthritis patients with signal-positive joints

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Abstract

Objective

To explore the value of the vascular index (VI) based on superb microvascular imaging (SMI) technique in assessing rheumatoid arthritis (RA) disease activity.

Methods

The study involved 119 RA patients who underwent SMI examinations of 28 joints. Observers obtained the VI values by manually drawing the area of interest and calculating the sum of the VI values for each patient to obtain the VIsum, and then dividing the VIsum by the number of signal-positive joints to obtain the VIstand. Data of patients' 28-joint Disease Activity Score (DAS28) and laboratory tests were also collected. The relationship between VI parameters and clinical indexes as well as the differences of VI parameters among groups with different disease activity were investigated. Moreover, the cut-off values of VI parameters to identify RA patients with DAS28 <2.6/DAS28 ≤3.2 were calculated using the receiver operating characteristic (ROC) curves.

Results

VIsum, VIstand correlated with clinical and laboratory indicators, especially with DAS28 (r=0.740, 0.659, respectively, p<0.05). The differences of VIsum and VIstand among the 4 groups of patients were statistically significant (p<0.05). VIsum had higher diagnostic efficacy than VIstand for identifying patients in remission or in low and below activity. With a VIsum cut-off value of 35.5/47.8, the area under the ROC curve for identifying DAS28 <2.6/DAS28 ≤3.2 was 0.872/0.846.

Conclusion

As a quantitative indicator to assess synovitis activity of RA patients, SMI-based VI was helpful in assessing RA disease activity.

Key words

rheumatoid arthritis, vascular index, superb microvascular imaging, synovial blood flow

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterised by joint damage, which typically affects small and medium-sized joints symmetrically (1). Synovitis constitutes the primary lesion and is the hallmark of the disease (2). If patients are not treated timely, disease progression can lead to joint damage or even disability. Therefore, the key to the clinical management of patients with RA is to find a validated index to predict the progression of disease activity so that appropriate treatment measures can be taken.

Intrasynovial vascularisation is closely related to RA disease activity. Superb microvascular imaging (SMI; Toshiba Medical Systems, Tustin, CA), a technology that can sensitively detect low-speed blood flow, and is widely used in superficial, musculoskeletal and other fields to evaluate the degree of synovitis of rheumatoid arthritis, so as to help clinicians to diagnose RA earlier and evaluate disease activity and treatment effect. Although it is now more common to use a semi-quantitative scoring system for blood flow signals in the SMI model, the scale is still not precise enough. Recently, SMI algorithm provides a novel quantification as vascular index (VI) corresponding the blood flow per tissue within the selected region by calculating the ratio of colour pixels to the total pixels (3). However, the application of VI in the assessment of synovitis in rheumatoid arthritis remains rare. In this study, we proposed to quantitatively analyse the synovitis activity of RA patients using the VI parameters by the SMI model, aiming to provide a more objective and convenient ultrasonic indicator for the clinical evaluation of RA disease activity, so as to provide a new idea for the assessment of the clinical condition of RA patients and the prevention of adverse events.

Materials and methods

Research design

This was a cross-sectional study in Henan Provincial People's Hospital between June 2023 and May 2024, which involved 119 patients with RA. Below are the inclusion and exclusion criteria.

Inclusion criteria: age ≥18 years; confirmed diagnosis of rheumatoid arthritis verified according to the ACR/EULAR 2010 criteria before the experiment (4); at least one joint with SMI signal-positive of each patient; informed consent to participate in the experiment.

Exclusion criteria: significant joint deformities hindering adequate ultrasound examination; hand injuries and surgeries; presence of another established autoimmune disease; infectious diseases and tuberculosis in the active stage; severe hepatic and renal insufficiency; pregnant women and nursing patient.

All participants were divided into 4 groups. Group 1 (Rem group) consisted of RA patients (n=29) in remission (DAS28<2.6). Group 2 (LDA group) consisted of RA patients (n=29) with low disease activity (2.6 ≤DAS28 ≤3.2). Group 3 (MDA group) consisted of RA patients (n=33) with moderate disease activity (3.2<DAS28 ≤5.1). Group 4 (HDA group) consisted of RA patients (n=28) with high disease activity (DAS28 >5.1). At the beginning of the study, all patients underwent a series of evaluations at the same day, including clinical assessment of the joints, ultrasonography, and laboratory tests.

Patients

The median age of the patients was 48.0 years with a range of 22 to 72 years. There were more female patients (n=97, 82%) than male patients (n=22, 18%). All patients provided written informed consent, and ethical approvals for participation in the study were obtained from the Medical Ethics Committee of Henan Provincial People's Hospital (no. 2020138).

Clinical assessment

Clinical assessments included the 28-joint tender (TJC) and swollen counts (SJC) and the patient's general health (GH) assessment of disease activity. Demographic data, duration of RA since diagnosis, and laboratory exams such as anticyclic citrullinated peptide antibody (Anti-CCP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

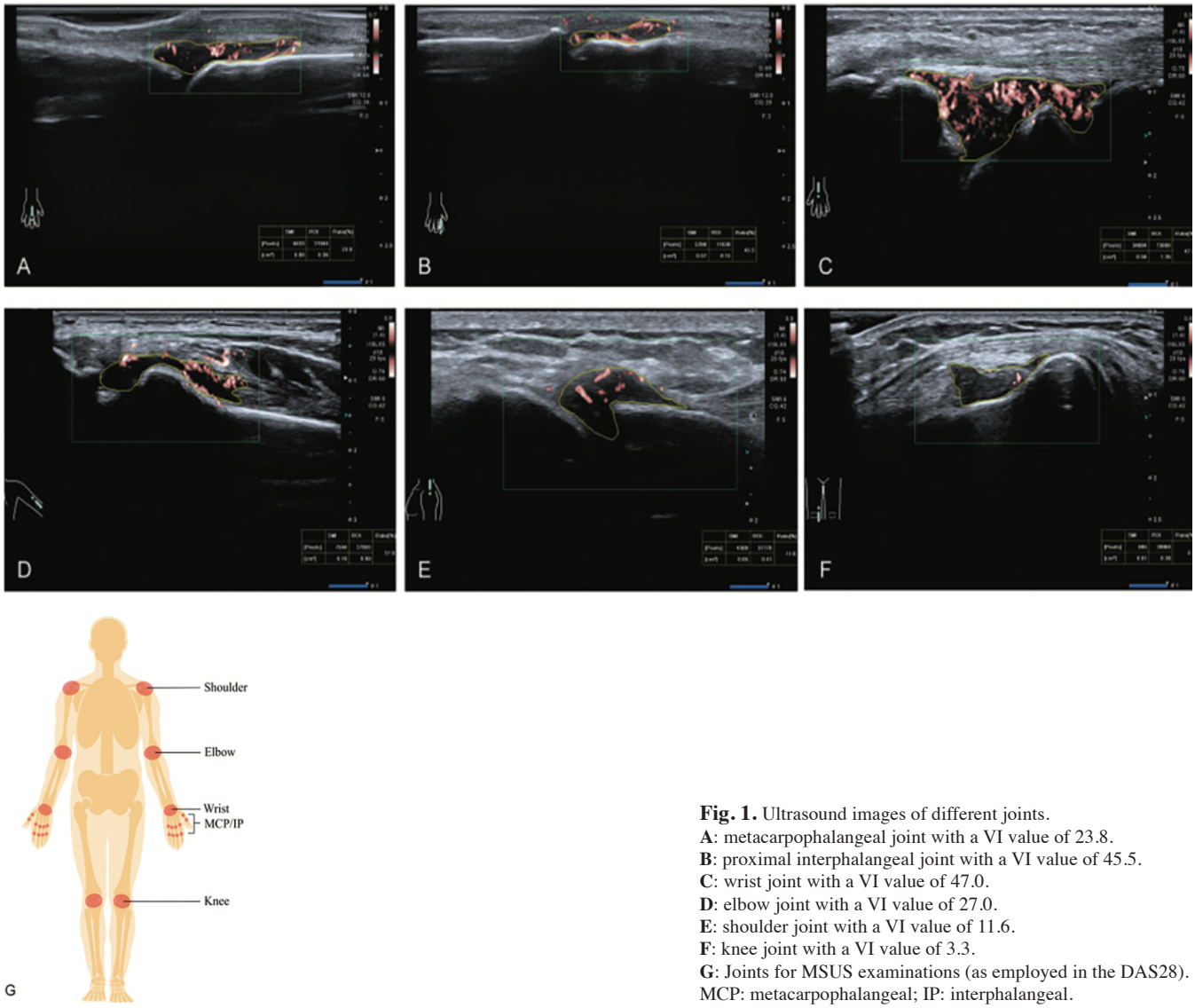

Fig. 1. Ultrasound images of different joints.
A: metacarpophalangeal joint with a VI value of 23.8.
B: proximal interphalangeal joint with a VI value of 45.5.
C: wrist joint with a VI value of 47.0.
D: elbow joint with a VI value of 27.0.
E: shoulder joint with a VI value of 11.6.
F: knee joint with a VI value of 3.3.
G: Joints for MSUS examinations (as employed in the DAS28).
MCP: metacarpophalangeal; IP: interphalangeal.

were collected from the electronic medical record.

Disease activity was assessed with the Disease Activity Score in 28 joints (DAS28), and patients were categorised as either in remission (DAS28 <2.6) or low (2.6 ≤ DAS28 ≤3.2) or moderate (3.2 < DAS28 ≤5.1) or high (DAS28 >5.1) disease activity. DAS28 was calculated using the following formulas, as previously described (5): $DAS28 = [0.56 \times \sqrt{TJC}] + [0.28 \times \sqrt{SJC}] + 0.70 \times \ln[ESR] + 0.014 \times GH$.

Ultrasound assessment

The musculoskeletal ultrasound (MSUS) examinations were conducted by two trained experienced sonographers (5~7 years) and who were blinded to the clinical and laboratory data (joint count, patient's global health assessment, Anti-CCP, RF, ESR, CRP, DAS28). The exam was performed using Aplio i900 (Canon Medical Systems Corporation, Tokyo, Japan) with a 24 MHz linear probe (PLI-2004BX) and a 18 MHz linear probe (PLI-1205BX).

The ultrasound investigation of 28 joints in SMI mode was performed to detect synovial hypervascularisation. Bilateral joints including metacarpophalangeal (MCP), interphalangeal, proximal interphalangeal (PIP), wrist, elbow, shoulder and knee, were examined as shown in Fig. 1. When sweeping in SMI mode, patients were instructed to relax and remain still to avoid motion artifacts. At the same time, gently place the probe on the skin to avoid affecting the display of microblood flow due to compression. For the joints with SMI signal-positive, the view with the richest blood flow signal and the largest area of synovial hyperplasia was selected, and SMI images were acquired here to map the synovial thickening region of interest (ROI), to further obtain the VI value (represented as a percentage), which defined as the ratio of colored pixels to total pixels in the selected ROI. The summary vascular index (VIsum) was defined as the sum of the VI values for each of the 28 joints. The standardised vascular index (VIstand) was obtained by dividing VIsum by the number of joints with SMI signal-positive among the 28 joints (6). The VI values of all joints with SMI signal-positive were measured three times and averaged.

Table I. Characteristics of patients with rheumatoid arthritis.

Parameters	Total RA patients (n=119)
Gender (F/M)	97 / 22
Age (years)	48.0 (20.0)
Disease duration (years)	1.0 (2.8)
Anti-CCP (U/mL)	98.4 (161.9)
RF (IU/mL)	51.5 (103.7)
ESR (mm/h)	31.0 (47.0)
CRP (mg/L)	6.8 (14.0)
TJC	2.0 (3.0)
SJC	1.0 (3.0)
GH	30.0 (50.0)
DAS28	3.5 (2.4)
VIsum (%)	56.3 (91.4)
VIstand (%)	10.6 (8.7)

anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count of 28 joints; SJC: swollen joint count of 28 joints; GH: general health; DAS28: Disease Activity Score in 28 joints; VIsum: summary vascular index; VIstand: standardised vascular index.

Table II. Correlation analysis of VI parameters and clinical and laboratory indicators in RA patients.

	VIsum		VIstand	
	r-value	*p*-value	*r*-value	*p*-value
Anti-CCP (U/mL)	0.436	<0.001	0.393	<0.001
RF (IU/mL)	0.408	<0.001	0.293	0.001
ESR (mm/h)	0.463	<0.001	0.432	<0.001
CRP (mg/L)	0.440	<0.001	0.535	<0.001
TJC	0.725	<0.001	0.585	<0.001
SJC	0.764	<0.001	0.576	<0.001
GH	0.588	<0.001	0.618	<0.001
DAS28	0.740	<0.001	0.659	<0.001

anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count of 28 joints; SJC: swollen joint count of 28 joints; GH: general health; DAS28: Disease Activity Score in 28 joints; VIsum: summary vascular index; VIstand: standardised vascular index.

Statistical analysis

Data were presented as mean and SD or median and IQR for continuous variables and frequency for categorical variables. Chi-square (χ^2) test or Kruskal-Wallis H-test was used for the comparisons among the groups where appropriate, and further pairwise comparisons were using the Bonferroni correction method. The relationships between different indices were captured by Spearman correlation. The *r* value <0.30 were considered poor, 0.30–0.59 fair, 0.60–0.79 moderate, and ≥0.80 strong (7). The receiver operating characteristic (ROC) curve was used to select the cut-off values of VI value for diagnosing signal-positive score and of VI parameters for determining disease activity at different levels. Intra- and inter-observer repeatability tests were expressed as intragclass correlation coefficients. All statistical analyses were conducted using IBM SPSS Statistics v. 25 (IBM, Armonk, NY). A *p*-value <0.05 was considered statistically significant.

Results

Characteristics of the RA patients

Among the 119 patients with RA, 97 were female and 22 were male, with a median age of 48.0 years and a median disease duration of 1.0 years. The characteristics of the patients are shown in Table I.

VI parameters and clinical and laboratory parameters

- Correlation analysis in all patients

VI parameters (VIsum, VIstand) of the joints were found to correlate with the clinical and laboratory parameters. In all patients of RA, VIsum and VIstand were both moderately correlated with DAS28 (r=0.740, p<0.001; r=0.659, p<0.001, Table II). VIsum and VIstand also showed a fair relationship with Anti-CCP, ESR, CRP (r=0.393-0.535, p<0.001, Table II). Besides, VIsum has a fair relationship with RF (r=0.408, p<0.001, Table II), while VIstand has a poor relationship with RF (r=0.293, p<0.001, Table II).

- Comparison of characteristics between 4 groups

Table III shows the comparison of the

Table III. Comparison of the parameters between the groups.

Data	Rem group (n=29)	LDA group (n=29)	MDA group (n=33)	HDA group (n=28)	χ^2 / *H*	*p*-value
Gender (F/M)	24 / 5	22/ 7	27 / 6	24 / 4	0.974	0.807
Age (years)	42.1 ± 11.2	48.0 (24.0)	45.3 ± 11.4	51.3 ± 14.1	7.252	0.064
Disease duration (years)	1.0 (4.3)	1.0 (1.5)	2.0 (2.1)	1.0 (6.8)	1.850	0.604
Anti-CCP (U/mL)	65.1 (54.8)	51.3 (135.2)	123.4 (182.8)	253.1 (127.7)[abc]	36.900	<0.001
RF (IU/mL)	41.5 (37.9)	25.7 (64.3)	51.5 (94.5)	137.7 (153.4)[ab]	29.217	<0.001
ESR (mm/h)	8.0 (14.0)	11.0 (16.0)	42.8 ± 19.5[ab]	76.0 ± 23.9[abc]	76.901	<0.001
CRP (mg/L)	2.1 (5.6)	3.5 (5.5)	6.0 (11.8)[a]	30.3 (65.8)[abc]	44.046	<0.001
TJC	1.0 (1.0)	1.0 (1.0)	3.0 (3.0)[a]	7.5 (7.0)[abc]	65.964	<0.001
SJC	0.0 (0.0)	0.0 (1.0)	1.0 (2.0)[ab]	6.0 ± 3.6[abc]	69.581	<0.001
GH	10.0 (13.0)	20.0 (40.0)	40.0 (40.0)[a]	65.0 (30.0)[abc]	59.492	<0.001
DAS28	2.0 ± 0.4	3.0 (0.3)[a]	4.4 ± 0.5[ab]	5.8 (1.1)[abc]	110.543	<0.001
VIsum (%)	14.4 (24.5)	38.9 (62.3)[a]	67.6 (65.1)[a]	222.3 ± 127.1[abc]	62.088	<0.001
VIstand (%)	5.6 (3.8)	9.1 (3.9)	11.4 (6.8)[a]	19.0 ± 5.0[abc]	56.484	<0.001

anti-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count of 28 joints; SJC: swollen joint count of 28 joints; GH: general health; DAS28: Disease Activity Score in 28 joints; VIsum: summary vascular index; VIstand: standardised vascular index.

[a] p<0.05 *vs*. Rem group; [b] p<0.05 *vs*. LDA group; [c] p<0.05 *vs*. MDA group.

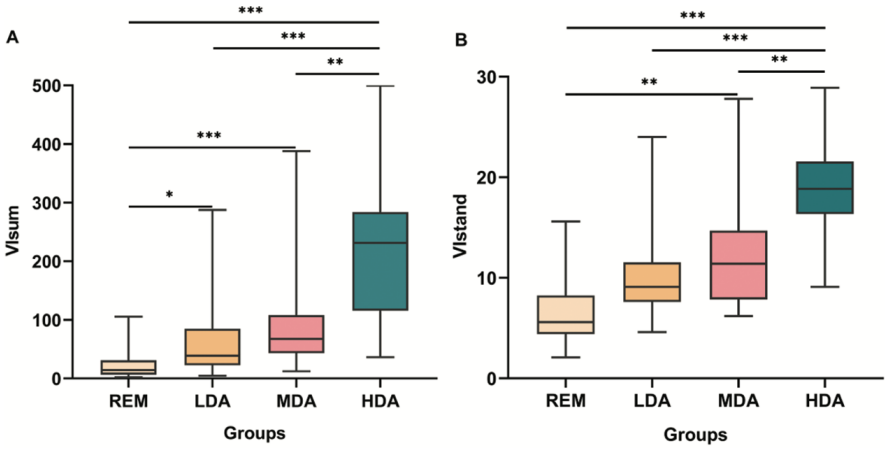

Fig. 2. The box plots illustrate the differences in VIsum (**A**) and VIstand (**B**) between these groups. *p<0.05, * p<0.01, ***p<0.001.

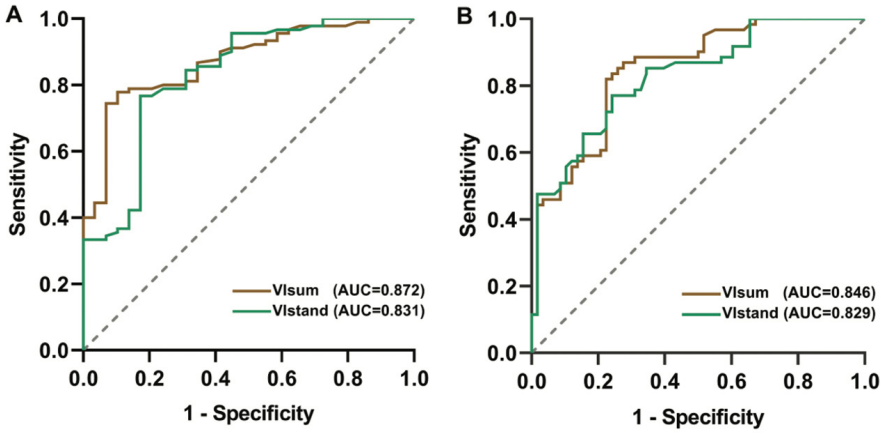

Fig. 3. ROC curves of VIsum and VIstand for diagnosing DAS28 < 2.6 (**A**) and DAS28 ≤ 3.2 (**B**). To identify DAS28<2.6 (A), the optimal cut-off values for VIsum and VIstand were 35.5 and 8.8, respectively. To identify DAS28 ≤3.2 (B), the best cut-off values were 47.8 and 10.5 for VIsum and VIstand, respectively.

Table IV. Diagnostic performance of VI parameters.

DAS28	Index	AUC	p-value	95%CI	Sensitivity	Specificity	Cut-off value
<2.6	VIsum	0.872	<0.001	0.804–0.940	0.778	0.897	35.5
	VIstand	0.831	<0.001	0.741–0.922	0.767	0.828	8.8
≤3.2	VIsum	0.846	<0.001	0.777–0.915	0.820	0.776	47.8
	VIstand	0.829	<0.001	0.757–0.901	0.770	0.759	10.5

DAS28: Disease Activity Score in 28 joints, VIsum: summary vascular index, VIstand: standardised vascular index.

Table V. Intra- and inter-observer repeatability tests.

Index	Intra-observer reliability		Inter-observer reliability	
	ICC	95% CI	ICC	95% CI
VIsum	0.986	0.974–0.993	0.989	0.979–0.994
VIstand	0.923	0.855–0.959	0.955	0.916–0.976

VIsum: summary vascular index, VIstand: standardised vascular index.

parameters between the groups. Comparison of gender, age and disease duration between the 4 groups showed no statistically significant differences; There were statistically significant differences in TJ, SJ, GH, Anti-CCP, RF, ESR, CRP, DAS28, VIsum, VIstand between the 4 groups (all p<0.001) (Fig. 2).

- Diagnostic performance of VI parameters

The ROC curves showed that the cut-off values of VIsum and VIstand had high diagnostic efficacy for DAS28 <2.6 (AUC=0.872, 0.831, respectively)/DAS28 ≤3.2 (AU=0.846, 0.829, respectively) (Table IV, Fig. 3).

Repeatability evaluation of VI measurements

Ten patients were randomly selected from each group to test the reproducibility of their VI parameters. Repeated measurements were taken at intervals of no more than 24 hours and no treatment was received during this period. The results in Table V showed excellent intra- and inter-observer agreement.

Discussion

Generally, rheumatoid arthritis first affects the synovial tissue of joints, and the main pathological changes include infiltration of synovitis cells in affected joints, proliferation of new blood vessels in synovial tissue, and the destruction of cartilage followed by subchondral bone destruction (8), resulting in joint damage and dysfunction. If not diagnosed and treated promptly, the disease progression may lead to joint destruction and deformity, significantly impairing the individual's quality of life (9). The active stage is a marker of the progression of RA (10). Therefore, timely and accurate assessment and monitoring of disease activity is of greater clinical significance for taking measures to control the progression of disease and reduce the disability rate of RA patients.

In the pathogenesis of RA, microvascular proliferation can occur early in the course of synovitis which is considered an important cause of the formation and maintenance of synovitis in RA, and the degree of microvascular proliferation can directly reflect the degree of synovitis activity in the affected joints (11).

At present, there are many imaging methods applied to the assessment of rheumatoid diseases. X-ray can indirectly evaluate the lesions according to the changes of joint space and bone joint

surface. Magnetic resonance imaging (MRI) can accurately display structures such as synovitis, tendons, ligaments and cartilage, especially enhanced magnetic resonance imaging can detect synovitis lesions early and conduct quantitative evaluation. However, although enhanced MRI can better display synovitis and improve the diagnosis rate of synovitis, there are still some defects such as high cost, risk of enhancer allergy, poor repeatability and so on.

In recent years, ultrasound has gained increasing attention for its value in the diagnosis, differential diagnosis, and assessment of the efficacy of rheumatoid arthritis due to its real-time, portable, cost-effective, and non-invasive features. The European League Against Rheumatism has also recommended musculoskeletal ultrasound to assess the activity of rheumatoid arthritis, monitor the response to treatment and predict the progression of the disease (12). Currently, the main modalities of high-frequency ultrasound for the visualisation of blood flow in hyperplastic synovium are colour Doppler ultrasound (CDFI), power Doppler ultrasound (PDUS), and contrast-enhanced ultrasonography (CEUS).

Traditional ultrasound detection of synovial blood flow mainly uses CDFI and PDUS. However, because CDFI will be limited by the angle and direction of the sound velocity and PDUS will produce certain artifacts due to the interference of the tissue movement, so that both of them have certain limitations in the display of microvessels (13, 14). By injecting agent, contrast-enhanced ultrasound can qualitatively show the enhancement characteristics of hyperplastic synovial vessels and the degree of blood perfusion, and visually and accurately reflect the degree of synovial inflammatory activity. Therefore, CEUS is currently recognised as the most sensitive ultrasound technique for detecting blood perfusion (15, 16). However, the shortcomings of CEUS examination are that it requires contrast injection and only one joint can be observed in one injection, which is not favourable to the comprehensive evaluation of RA patients with multiple joints. Superb Microvascular Imaging is a novel Doppler technology introduced by Toshiba in 2015. Through intelligent adaptive algorithms and unique filtering technology, it can more effectively suppress tissue movement and reduce motion artifacts while truly detecting blood flow, allowing for more sensitive detection of small and slow-flowing blood without the use of contrast media, as well as easy, non-invasive sweeps of multiple joints (17). Jin *et al*. (18) applied CDFI, PDUS, and SMI techniques, respectively, to grade and compare the blood flow signals in the suprapatellar crypt of the knee joints of 41 patients with RA, and the results showed that the synovial flow signals detected by SMI were significantly elevated in patients with RA compared with CDFI and PDUS, indicating that SMI detects slow blood flow in inflamed synovial tissue with a higher sensitivity than conventional Doppler techniques. Besides, Diao *et al*. (11) found a high concordance between SMI and CEUS in detecting positive flow and assessing flow signal scores in both active and clinically remission RA patients, suggesting that the accuracy of SMI was comparable to that of CEUS in detecting neovascularisation within the proliferative synovium. It also indicated that the non-invasive SMI technology, which does not require the use of contrast agents, may be an ideal alternative to CEUS. Moreover, Matsuo *et al*. (19) found SMI could identify subclinical synovitis in a study of RA patients with remission.

The semi-quantitative scale, originally proposed by Szkudlarek for the PDUS technique and later also applied to the SMI technique (20), is now a widely accepted and validated means of evaluating the active degree of synovitis (21). However, the semi-quantitative scoring method is not precise sufficiently. In contrast, the SMI-based VI is an index that can quantitatively evaluate blood flow signals within the region of interest. Through applying VI, Alis *et al*. (22) found that SMI was superior to PDUS in describing blood flow in hypertrophic synovial tissue of the knee in patients with juvenile idiopathic arthritis. Duan *et al*. (6) attempted to apply VI to the assessment of synovitis in RA and concluded that VI parameters could objectively assess the degree of synovitis activity in patients with RA and had high diagnostic efficacy for moderate to high disease activity.

Currently, DAS28 is one of the most widely used clinical methods for assessing disease activity in RA patients (23). In addition, auto-antibody (anti-CCP, RF) and inflammation indicators (ESR, CRP) can also reflect the disease activity of RA patients to some extent (19). In this study, we found that the VI parameters showed a good positive correlation with DAS28 and a weak to moderate correlation with inflammatory indicators, suggesting that the VI parameters may reflect to some extent the activity of synovitis as well as disease activity in RA patients.

In addition, to further explore the value of VI in assessing rheumatoid arthritis disease activity, RA patients with positive SMI signals were classified into four groups: remission, low activity, moderate activity, and high activity according to DAS28. VIsum and VIstand showed statistically significant differences among the four groups, but further pairwise comparisons revealed that the differences of both VIsum and VIstand were not statistically significant between the LDA group and the MDA group, and that the difference of VIstand was also not statistically significant between the REM group and the LDA group. Currently, the main goal of RA treatment is to achieve remission (DAS28 <2.6) or low and below activity (DAS28 ≤3.2) (23), thus, accurate identification of disease activity is clinically significant in evaluating the efficacy of treatment and selecting subsequent treatment options. Therefore, we further investigated the diagnostic efficacy of VI parameters using DAS28 <2.6 and DAS28 ≤3.2 as criteria, respectively. The results showed that VI parameters had high diagnostic efficacy for identifying patients in remission or in low and below activity, where VIsum was higher than VIstand. Based on a VIstand cut-off value of <35.5, the area under the ROC curve (AUC) for diagnosing DAS28 <2.6 was 0.872 (sensitivity: 0.778, specificity: 0.897). And based on a VIsum cut-off value of ≤47.8, the AUC for diagnosing DAS28 ≤3.2 was

0.846 (sensitivity: 0.820, specificity: 0.776). This revealed that VI parameters may be beneficial in identifying disease activity of RA. Moreover, we noted that the diagnostic efficacy of the VIsum was higher, which differed from the finding of Duan *et al*. (6), and the reason may be related to the number, distribution, and activity of affected joints in the patients in both studies.

This study has several limitations. In order to be consistent with the DAS28, 28 joints were still used in this study, but there is still no accepted standard for the minimum number of joints that need to be included in the MSUS assessment for patients with RA (24). These differences may prevent the use of summed scores to determine the overall level of disease activity in RA patients. On the other hand, 28 joints may be somewhat time consuming. Moreover, further studies are needed to validate the cut-off value of VI parameters for diagnosing disease activity.

In conclusion, our study affirms the value of VI based on SMI technology in quantitatively evaluating the activity of intra-articular synovitis with SMI signal-positive. Moreover, the VI parameters can reflect the disease activity of rheumatoid arthritis patients to a certain extent, thus providing a more accurate ultrasound reference indicator for the evaluation of disease activity, efficacy, and prognosis in patients with rheumatoid arthritis. In addition, the detection technology is simple and convenient, which is expected to be widely popularised and applied in the clinic in the future.

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