Original Article

Superb microvascular imaging is as sensitive as contrast-enhanced ultrasound for detecting synovial vascularity in rheumatoid arthritis

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Background: Detection of synovitis is essential for assessing rheumatoid arthritis (RA) activity and predicting prognosis. This study aimed to compare the diagnostic performance of superb microvascular imaging (SMI) with that of contrast-enhanced ultrasound (CEUS) in patients with RA in clinical remission.

Methods: SMI and CEUS were applied to 63 patients with active RA and 48 patients with RA in clinical remission. Differences in positive synovial vascularity (SV) and its semi-quantitative scale were observed, and the correlations of SMI and CEUS results with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) were analyzed.

Results: For the 63 joints with active RA, the detection rates of SV as determined by SMI and CEUS were 90.5% (95% CI: 83.0–97.9%) and 93.7% (95% CI: 87.5–99.8%), respectively, with no significant difference observed between the two modalities (t=–1.137; P=0.260). There was good agreement between the two modalities in detecting positive blood flow (Kappa =0.784) and blood flow signal score (Kappa =0.792). For the 48 joints with clinical remission, the detection rates of SV determined by SMI and CEUS were 79.2% (95% CI: 67.2–91.1%) and 83.3% (95% CI: 72.4–94.3%), respectively, with no significant difference found between the two modalities (t=1.000; P=0.322). There was high consistency between the two modalities in detecting positive blood flow (Kappa =0.727) and blood flow signal score (Kappa =0.661). The vascularity scores of SMI and CEUS were positively correlated with CRP, ESR, and RF in the joints with active RA, but not in those with clinical remission.

Conclusions: SMI is as sensitive as CEUS for detecting vessels in the synovium and displaying local SV in patients with RA who achieve clinical remission.

Keywords: Superb microvascular imaging (SMI); contrast-enhanced ultrasound (CEUS); rheumatoid arthritis (RA); synovial vascularity (SV)

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic and destructive inflammation of the joints which can lead to their permanent destruction and severe disability (1,2). The proliferation of pannus is a crucial event in the pathogenesis of RA. Composed of new microvessels, synovial and inflammatory cells, and cellulose, pannus is the primary cause of joint lesions, deformities, and dysfunction. In patients with RA, synovitis is the most important indicator of aggressive disease. Pannus vascularization in the thickened synovium appears at a very early stage, even before the specific clinical and histological signs of RA (3). The richness of pannus blood flow signals can reflect the severity of RA disease; therefore, it is potentially useful for evaluating the development of RA (4,5).

Remission is achievable for the majority of patients with RA. However, clinical remission does not constitute a full recovery (6), and disease progression and flares may still occur after therapy. Residual inflammation can lead to progressive and irreversible joint damage, and the levels of RA-related biomarkers may not be high; therefore, imaging assessment of disease activity is crucial (7). Ultrasound (US) represents a valuable diagnostic modality for the assessment of synovial thickening and vascularity. Both color and power Doppler ultrasound can assess synovial inflammation by detecting increased blood flow. However, they have limited ability to demonstrate slow flow and flow in the small angiogenic vessels present in synovial proliferation (8,9). Contrast-enhanced ultrasound (CEUS) is an excellent tool for the early diagnosis and therapeutic monitoring of inflammatory arthritis, because it shows the exact vascular patterns of joints (10). The contrast agent circulates through the capillary beds and persists in the blood pool, providing dynamic images with high sensitivity to microvascularization. However, CEUS requires an intravenous contrast agent, which is expensive and poses a challenge to repeated examination. Consequently, its application in the evaluation of joint inflammation is limited (11,12).

Superb microvascular imaging (SMI) is a new high-resolution blood-flow imaging technology developed from grayscale and color Doppler ultrasound imaging. SMI can be used to visualize minute blood vessels with slow velocity without the need to use contrast agents (13). Some researchers have investigated the clinical utility of SMI in the evaluation of RA and have suggested that this technique is more sensitive than power Doppler imaging (PDI) for the detection of active synovial vascularity (SV) in patients (14,15). However, no studies to date have compared the detection of joint SV by SMI and CEUS. Furthermore, the efficacy of SMI for detecting low-grade inflammation in the clinical remission period of RA has been ignored almost completely. In the clinical remission stage of RA, the degree of synovial thickening and blood flow in the synovium are significantly reduced. The detection of SV by imaging modalities in the clinical remission stage indicates that subclinical synovitis is still present (16). Subclinical synovitis is the main reason for the recurrence of inflammation. Some studies have confirmed that both SMI and CEUS are more sensitive than PDI for visualizing the microvessels in joints in clinical remission (17,18); however, no study so far has compared SMI with CEUS. Therefore, the objectives of the present study were to (I) compare the diagnostic performances of SMI and CEUS in the detection of vessels in the synovium during the active period of RA, (II) evaluate the utility of SMI in the detection of synovial inflammation in patients with RA in clinical remission compared with that of CEUS, and (III) compare the correlations of SMI and CEUS signals with laboratory assessment parameters.

We present the following article in accordance with the STARD (Standards for Reporting Diagnostic Accuracy) checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-859/rc).

Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Huadong Hospital, and the need to obtain individual consent for this retrospective analysis was waived.

Between February 2018 and April 2021, a total of 63 consecutive patients with RA (21 males and 42 females; mean age, 48.2±16.4 years) were enrolled in this study. Patients were diagnosed with RA according to the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria (19), as well as the presence of positive manifestations, such as joint swelling and tenderness. The criteria for a diagnosis of definite RA are confirmation of the presence of synovitis in at least one joint, the absence of an alternative diagnosis to better explain the presence of synovitis, and a total score of 6 or more (out of a possible score of 10) from the individual scores in the following four domains: number and site of

involved joints (range: 0–5), serological abnormality (range: 0–3), elevated acute-phase response (range: 0–1), and symptom duration (two levels; range: 0–1). Patients with types of arthritis other than RA, such as Behçet's disease, Sjogren's syndrome, a history of trauma, degenerative joint disease, or obvious joint deformity were excluded.

All patients underwent treatment time ranged from 6 months to 2 years. Treatment drugs included methotrexate, leflunomide, Iguratimod, and biologics. With respect to the RA Clinical Remission Standard (6), patients needed to meet one of these criteria: (I) swelling joint counts, tender joint counts, C-reactive protein (mg/L), and patient global self-assessment all ≤1; and (II) the Simplified Disease Activity Index (SDAI) ≤3.3.

US examination

All US examinations were conducted using a Canon Aplio 700 US machine (Canon Medical Systems Corporation, Tokyo, Japan) with a multifrequency (12–14 MHz) linear transducer. The US scans were performed by a musculoskeletal radiologist with more than 10 years of experience using a high-end US system. For each patient, the knee, wrist, ankle, and metacarpophalangeal (MCP) I to V and proximal interphalangeal (PIP) I to V joints in both hands were evaluated in axial and longitudinal planes. The thickest synovium was observed using two-dimensional (2D) US, and then the richest blood supply to a joint was observed using SMI and CEUS.

SMI

According to the diagnostic criteria of Szkudlarek (20), synovial thickening is graded on a scale of no synovial thickening Grade 0 to obvious synovial thickening Grade 3.

For SMI, the probe was placed lightly on the skin surface to avoid pressure on the vascular structures. The parameters for SMI were velocity scale of <2.0 cm/s, dynamic range of 21 dB, and frame rate of 27–60 frames per second. To ensure the accuracy of SMI scoring, we attempted to eliminate or exclude artifacts. Usually, blood flow on the surface of the bone cortex is not real blood flow. Real blood flow has stable signals, and a regular blood flow spectrum can be acquired using spectral Doppler.

CEUS

The plane with the most abundant blood was selected as the CEUS target section, which was the same plane as that used for SMI. The parameters were fixed in the machine. The scan was performed under a low mechanical index of between 0.06 and 0.10, with a power setting of 36 kPa and a gain of 160. The contrast agent (SonoVue, Bracco, Milan, Italy) was administered through an 18-gauge catheter placed in the antecubital vein. The agent was injected rapidly as a single intravenous bolus (using a 2.4-mL vial), and was followed by 5 mL of saline. Images were recorded with the clip function for 3 minutes. For each patient, the video clips registered were randomly and independently reviewed by two radiologists (with 5 and 10 years of experience in musculoskeletal radiology, respectively), who were blinded to the patients' clinical and laboratory data.

Image analysis

The SMI and CEUS examinations both used the semiquantitative scoring system described by Szkudlarek *et al.* (20), which is as follows: 0 = no synovial flow (that is, normality); 1 = single vessel signals; 2 = confluent vessel signals in less than half of the area of the synovial membrane; 3 = vessel signals in more than half of the area of the synovial membrane.

Laboratory assessment

To assess disease activity in the patients, three RA-related markers were measured: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF). Measurements were performed on the same day of the US examination.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) v 19.0 (SPSS Inc., IL, USA). The chi-square test was used to compare the detection rates, and the 95% confidence intervals (CI) were described. The McNemar-Bowker test was used to examine the difference between SMI and CEUS. The associations of SMI and CEUS results with clinical inflammatory parameters (CRP, ESR, and RF) were evaluated using Spearman's coefficient. Intraobserver reliability was assessed using the Kappa consistency test. The consistency was rated as good with Kappa ≥0.75, medium with Kappa <0.75 and ≥0.4, and poor with Kappa <0.4. A P value <0.05 was considered statistically significant.

Table 1 Demographic and baseline clinical characteristics for patients with RA

Parameter	Total RA patients (n=63)	RA patients with remission (n=48)
Age (years)	48.2±16.4	46.5±18.2
Sex (male/female)	16/47	9/39
Disease duration (months)	48.0±25.4 (range: 1–120)	
Duration of therapy (months)		10.1±3.45 (range: 6–24)
CRP (mg/L)	39.51±16.24 (range: 3–116)	5.58±2.35 (range: 1–9)
ESR (mm/h)	55.36±25.93 (range: 6–147)	17.09±15.42 (range: 3–48)
RF	37.59±22.14 (range: 4–121)	8.26±7.37 (range: 1–16)
ACPA positive, n (%)	50 (79.4)	
SDAI		2.78±0.39 (range: 1.9–3.2)

The values are presented as mean ± standard deviation (SD). CRP <10 mg/L; ESR (male <15 mm/h, female <20 mm/h); RF <10. RA, rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; SDAI, simplified disease activity index.

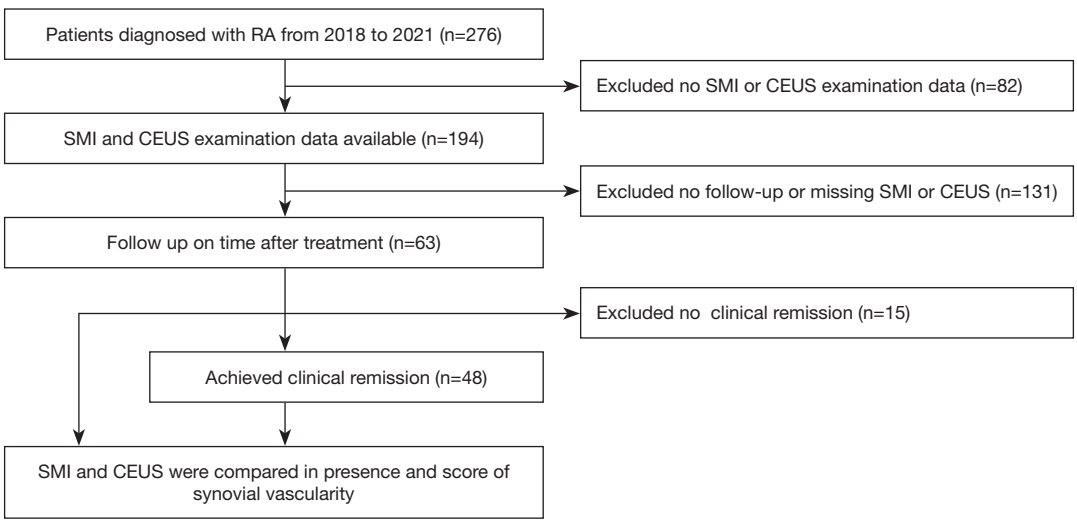

Figure 1 Flowchart showing the selection and grouping of patients with RA. RA, rheumatoid arthritis; SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound.

Results

Patients characteristics

The age, sex, duration of RA, and laboratory data of 63 patients with RA were recorded (*Table 1*; *Figure 1*). Among the 63 patients, there was obvious synovial thickening in 31 wrist joints, 15 MCP joints, 9 knee joints, 4 ankle joints, and 4 PIP joints. No immediate or late adverse events were reported after CEUS.

Comparison of the presence of SV and the score of SV/blood flow by SMI and CEUS in joints with active RA

Before RA treatment, SMI and CEUS detected blood flow signals in 57 joints (90.5%; 95% CI: 83.0–97.9%) and 59 joints (93.7%; 95% CI: 87.5–99.8%) (χ^2=0.704; P=0.402), respectively. There was no significant difference in the detection rates of vascularity between the two US methods (t=–1.137; P=0.260), and strong agreement was observed between them (Kappa =0.784; P=0.000). SMI and CEUS

Table 2 Scoring of SV intensity detected by SMI and CEUS in patients with RA

CEUS	SMI				Total	χ^2	P
	0	1	2	3			
Grade 0	4	0	0	0	4	1.333	0.721
Grade 1	2	17	0	0	19		
Grade 2	0	3	23	1	27		
Grade 3	0	0	3	10	13		
Total	6	20	26	11	63		

SV, synovial vascularity; RA, rheumatoid arthritis; SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound.

also failed to show a statistically significant difference in terms of SV score (P<0.05), and there was strong agreement between them (Kappa =0.792; P=0.000) (*Table 2*; *Figures 2-4*).

Comparison of the presence of SV and the score of SV/blood flow by SMI and CEUS in joints with RA in clinical remission

After an average treatment duration of 10.1 months, 48 patients out of 63 patients achieved clinical remission. Blood flow signals were detected in 38 joints (79.2%; 38/48) by SMI (95% CI: 67.2–91.1%) and in 40 joints (83.3%; 40/48) by CEUS (95% CI: 72.4–94.3%), with values of χ^2=0.552 and P=0.458, respectively. The RA remission rate as assessed by SMI and CEUS was far lower than the clinically assessed remission rate. No significant difference was observed in the synovial blood flow score between SMI and CEUS (t=1.000; P=0.322). A high level of consistency was observed between the evaluation results of the two methods (Kappa =0.727). In patients with RA in clinical remission, although CEUS slightly up-regulated the degree of blood-flow classification, the consistency between SMI and CEUS was good (kappa =0.661), with no significant difference found between the two methods with respect to blood flow score (P<0.05) (*Table 3*; *Figures 2-4*). In the US analysis, there was good interobserver agreement between the two expert radiologists (Kappa =0.82).

Correlations of SMI and CEUS with CRP, ESR, and RF

In joints with active RA, the vascularity scores of SMI and CEUS were positively correlated with CRP, ESR, and RF. However, neither US method showed a correlation with CRP, ESR, or RF in patients with clinical remission (*Table 4*).

Discussion

Synovitis is an early pathological change in RA, which is mainly characterized by synovial edema and thickening, and pannus formation. Pannus is a crucial event in the pathogenesis of RA, and it can be seen before clinical evidence of joint destruction and deformity. Pannus vascularization may be key to the invasive and destructive behavior of RA, with the degree of pannus vascularization directly reflecting the extent of synovial proliferation and inflammatory activity of RA (21). Therefore, early detection of synovial thickening SV may provide a basis for the diagnosis and evaluation of RA activation.

The goal of RA therapy is to control the inflammation to alleviate joint injury and dysfunction. However, many patients do not attain an adequate response to therapy, and sustained remission is rarely achieved. Cohen *et al.* (22) reported that 16.7% of patients with RA in clinical remission experience the progression of radiographic structural damage, which, as preliminary data have suggested, may be due to subclinical synovitis. Subclinical synovitis has been found to be prevalent detected in patients with clinical remission. Many studies have confirmed subclinical ultrasonographic SV positivity to be an independent risk factor for flares in patients with RA in clinical remission (23,24). As a result, achieving both clinical and ultrasonographic remission is becoming a new target in the treatment of RA (25). Therefore, the detection of vascularization in synovial proliferation is crucial for the early diagnosis of inflamed joints and for monitoring the efficacy of anti-inflammatory treatment.

CEUS is an imaging technique that can be used to detect low-velocity blood flow in the microcirculation. However, CEUS is subject to certain restrictions regarding the use of contrast agent, and it adds to the financial burden on

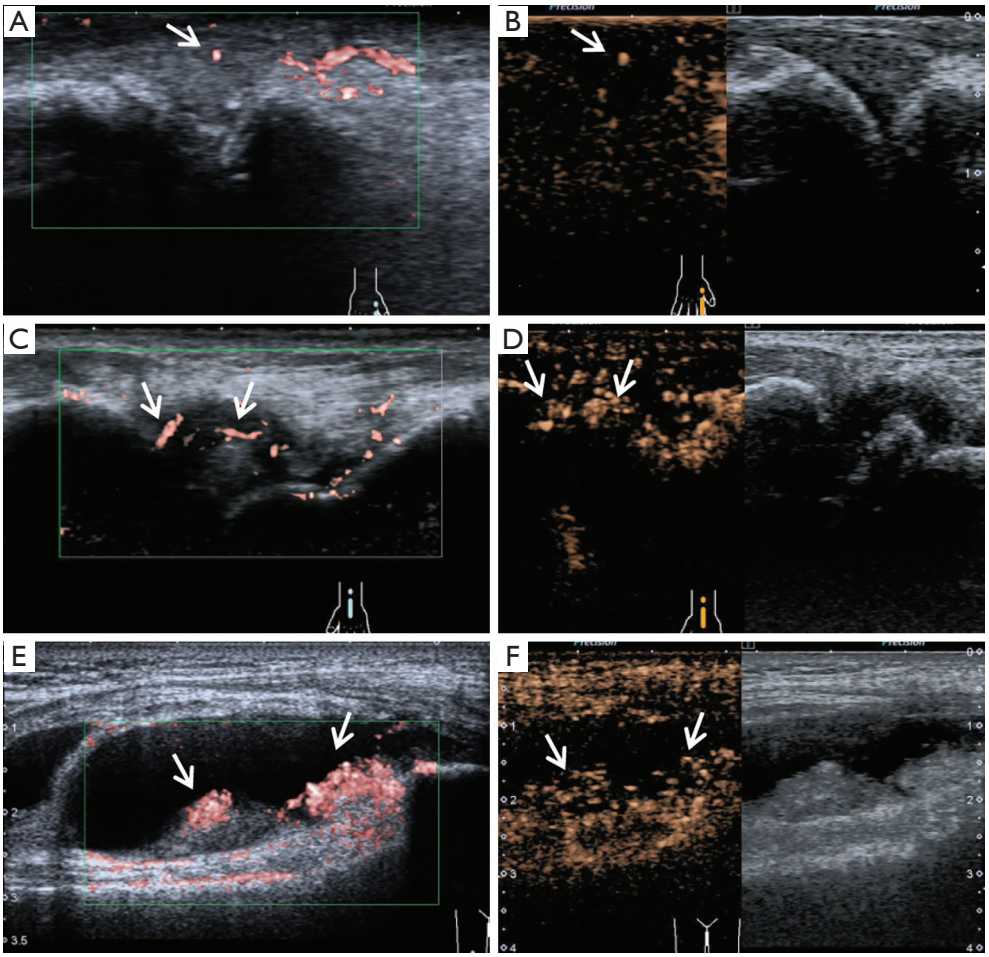

Figure 2 Representative SMI and CEUS images of SV. (A,B) Wrist: a single SMI signal in the synovium, and CEUS showing tiny echogenic spots (Grade 1). (C,D) Wrist: confluent SMI signals in less than half the area of the synovium (Grade 2), and slow-flow vessel enhancement (arrows) detected on CEUS (Grade 2). (E,F) Knee: SMI signals and CEUS enhancement in more than half the area of the synovium (Grade 3). Arrow point to the vessels. SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound; SV, synovium vascularity.

the patient. SMI, another imaging technique, can display low-speed blood flow signals and vessel distribution in detail. However, unlike CEUS, it does not require the use of intravenous contrast agents, which is a significant advantage for patients who are fearful of injections or for whom injection may be difficult due to their swollen hands. However, it had remained unclear whether the sensitivity of SMI is comparable to that of CEUS in the detection of inflammatory blood flow in patients with RA, especially those with clinical remission. Therefore, in the present study, we compared the performances of SMI and CEUS in the evaluation of joint SV scores in patients with active RA and those with clinical remission, and also compared the correlation of these scores with laboratory assessment parameters.

Our results showed that the detection rates of positive SV using SMI and CEUS were 90.5% (95% CI: 83.0–97.9%) and 93.7% (95% CI: 87.5–99.8%), respectively. In terms of SV scoring, there was no statistically significant difference between the two US methods ($P<0.05$), and there was strong agreement between them. The serum levels of CRP, ESR, and RF were significantly correlated with the SV scores on SMI and CEUS. CRP and ESR can provide information about disease activity, while RF is correlated with a risk of developing RA, and can predict bone erosion and severe disease progression. However, these biomarkers alone do not have sufficient predictive ability for the purposes of treatment decision-making (26).

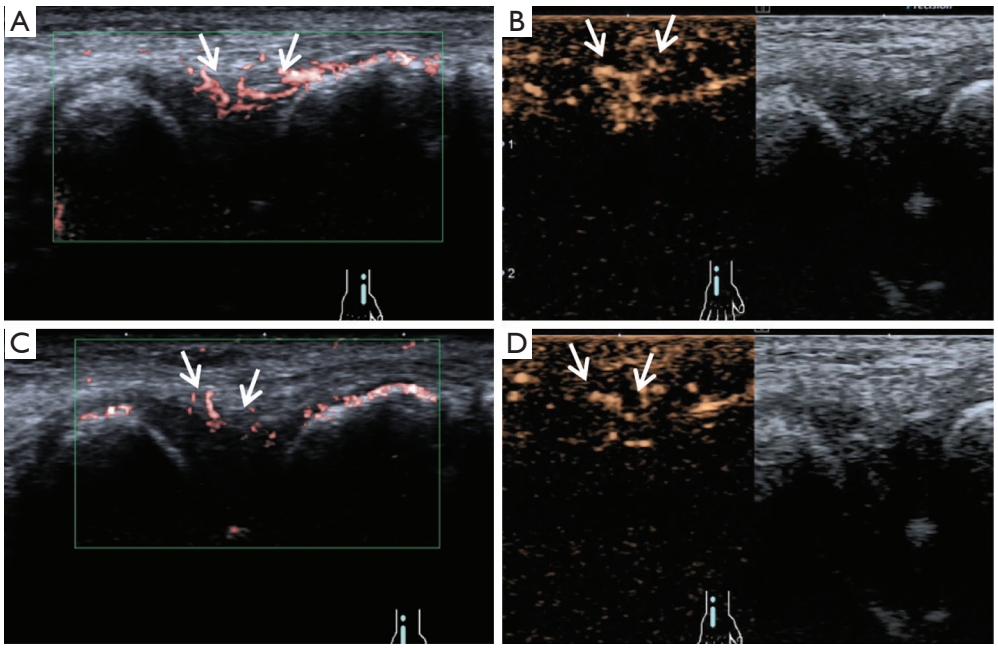

Figure 3 Longitudinal dorsal ultrasound of the wrist joint. (A,B) In the active period of RA, SMI and CEUS show the vessel signals in less than half the area of the synovium (Grade 2). (C,D) In RA in the clinical remission period, strip and dot blood flow detected by SMI and CEUS (Grade 1). Arrow point to the vessels. RA, rheumatoid arthritis; SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound.

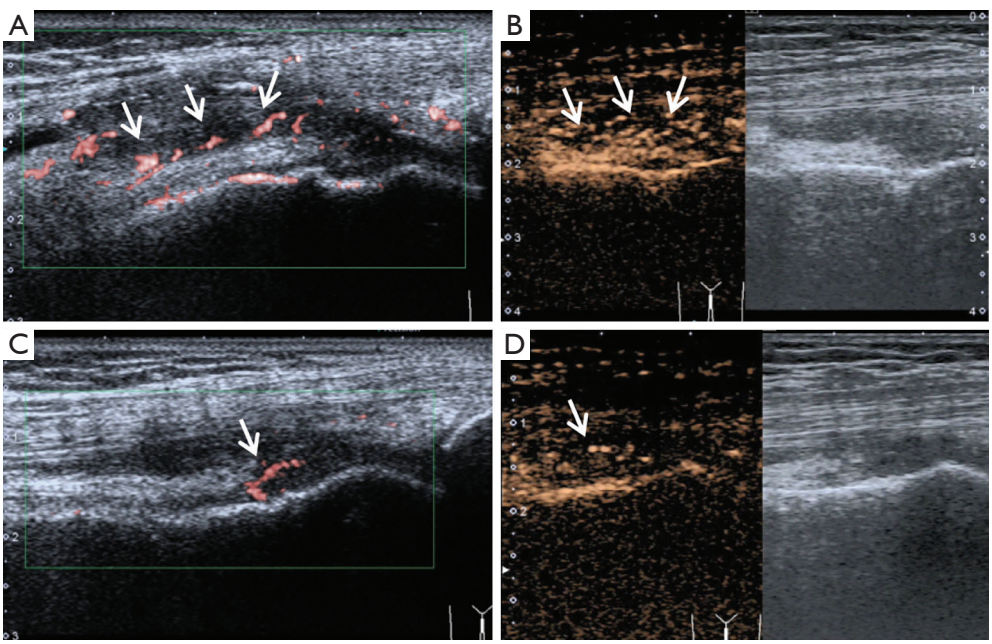

Figure 4 Longitudinal dorsal ultrasound of the knee joint. (A,B) In the active period of RA, SMI shows a small amount of color signal in the hypertrophic synovium (Grade 2), and CEUS exhibits intensive enhancement (Grade 3). (C,D) In RA in the clinical remission period, strip blood flows are still visible on both SMI and CEUS (Grade 1). Arrow point to the vessels. RA, rheumatoid arthritis; SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound.

Table 3 Scoring of SV intensity detected by SMI and CEUS in patients with RA in clinical remission

CEUS	SMI				Total	χ^2	P
	0	1	2	3			
Grade 0	7	1	0	0	8	6.000	0.112
Grade 1	3	19	2	0	24		
Grade 2	0	2	7	1	10		
Grade 3	0	0	2	4	6		
Total	10	22	11	5	48		

SV, synovial vascularity; SMI, superb microvascular imaging; RA, rheumatoid arthritis; CEUS, contrast-enhanced ultrasound.

Table 4 Correlations of SMI and CEUS with CRP, ESR, and RF in patients with RA

Parameter	Examination method	RA coefficient (γ)	Remission RA coefficient (γ)
ESR	SMI	0.782	0.179
	CEUS	0.794	0.183
CRP	SMI	0.829	0.192
	CEUS	0.844	0.168
RF	SMI	0.746	0.175
	CEUS	0.770	0.163

SMI, superb microvascular imaging; CEUS, contrast-enhanced ultrasound; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; RA, rheumatoid arthritis.

This study has shown that SMI has sufficient sensitivity to detect vascularization of the synovial membrane in patients with RA. It could therefore be a potentially useful imaging modality for accurately diagnosing and monitoring the disease activity of RA, in addition to the above-discussed biomarkers. Among the 48 joints that achieved clinical remission, the rates of synovitis displayed by SMI and CEUS were 79.2% (95% CI: 67.2–91.1%) and 83.3% (95% CI: 72.4–94.3%), respectively. Both imaging methods determined that more than half of the patients still had subclinical synovitis and that very few patients had achieved ultrasonic remission. This observation indicates that clinical remission may not accurately reflect the inflammatory activity level of RA. SMI proved to be as sensitive as CEUS in detecting neovascularization in the synovium (Kappa =0.727). Among the joints with RA in clinical remission, one joint displayed short-strip blood flow by SMI but not by CEUS; the reason for this may be that SMI is sensitive to the degree of intraarticular vascularization, and may result in false positives. For example, noise expression on bone surfaces was judged as abnormal blood flow. In another three joints, blood flow was detected by CEUS but not by SMI; the reason for this may be that microvessels with very low-velocity blood flow are difficult to detect using SMI. Contrast microbubbles measure 2.5–5 μm in diameter, meaning they can reach all small blood vessels. However, displaying all microvessels using SMI is difficult because of its limited penetration, especially for deep vessels in swollen hands. In terms of blood-flow signal score, there was no significant difference between SMI and CEUS (P=0.322). Both US methods were sensitive for detecting the degree of pannus inflammatory activity, although the imaging modes differed. In CEUS, the contrast agent circulates through capillary beds and persists in the blood pool, generating high-intensity signals that can be detected by the transducer, which show as diffuse or lumpy enhancement patterns. In contrast, SMI is designed to improve the visualization of blood flow by maintaining very high frame rates; therefore, it can better depict the vessel branching details and microvascular structures. The difference in the imaging features led to a slight difference in blood flow signal scores.

Correlation analysis showed that SMI and CEUS had no correlation with CRP, ESR, or RF in patients with RA

in clinical remission. The expression of CRP and ESR, which are used as indicators of inflammation and disease activity, was lower in patients with clinical remission, which indicates that it is difficult to detect subclinical synovitis based on clinical assessment alone, especially in patients with only slight synovial thickening. Such patients usually do not experience discomfort such as swelling, stiffness, and pain, and they rarely go to hospital for further follow-up, which leads to a lack of detection of subclinical synovitis and recurrence of inflammation. The detection of synovial microvessels using SMI can directly reflect the existence of inflammation; hence, this imaging technique could be used as an objective evaluation method for patients with RA who have local inflammation and low CRP and ESR levels. SMI is as sensitive as CEUS for assessing the extent of synovitis and identifying true remission of RA. Furthermore, compared with CEUS, it has the advantage of enabling the visualization of joints from any angle and random section without the imposition of time limitations or contrast agent injection. However, there is also another point to consider: although SMI and CEUS can lead to the early detection of inflammation, they might also lead to over-diagnosis or over-treatment, with previous studies showing that MRI and US have identified inflammation in healthy individuals (27,28).

The present study has several limitations. First, the study included only a small number of patients; in future, a larger number of patients and long-term follow-up are needed to accurately determine the clinical utility and applicability of SMI. Second, the quantitative relationship between SMI and the levels of CRP and ESR needs further research, as does the issue of how to effectively combine ultrasonic examination with clinical evaluation.

In conclusion, SMI can visualize low-velocity blood flow in the microvessels of patients with RA. Therefore, this imaging technique has the potential to play a more important role in the assessment of inflammatory activity in patients with RA.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-859/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-859/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Huadong Hospital, and individual consent for this retrospective analysis was waived.

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