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ORIGINAL ARTICLE

The superb microvascular imaging is more sensitive than conventional power Doppler imaging in detection of active synovitis in patients with rheumatoid arthritis

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Abstract

Objectives This study evaluated Superb Microvascular Imaging (SMI) technology for detection of active synovitis in patients with rheumatoid arthritis (RA).

Methods Between June 2015 and October 2016, 56 patients with RA (42 females; mean age, 53.2 years) underwent gray-scale ultrasound (US) imaging, power Doppler imaging (PDI), and SMI for synovitis of both wrists and hands (total 22 joints), scored for each joint from grades 0 to 3. The sum of grades for 22 joints was determined for gray-scale (SYN-sum), PDI (PDI-sum), and SMI (SMI-sum) according to clinical parameters. Follow-up US was performed in 17 patients (mean interval, 251.6 days).

Results The SMI-sum (7.27 ± 4.56) was significantly higher than the PDI-sum (4.38 ± 3.09, $p < 0.001$) and the SYN-sum (4.55 ± 3.72, $p < 0.001$), and was significantly correlated with the erythrocyte sedimentation rate, C-reactive protein (CRP), and Disease Activity Score-28 (DAS28)-CRP ($\gamma = 0.409$, $p = 0.002$; $\gamma = 0.695$, $p < 0.001$; $\gamma = 0.726$, $p < 0.001$, respectively). Moreover, in 28 patients with clinical remission, the SMI-sum (4.32 ± 2.01) was greater than the PDI-sum (2.61 ± 1.60, $p < 0.001$). In 17 patients with follow-up US, the SMI-sum (2.35 ± 1.73) was significantly greater than the PDI-sum (1.24 ± 1.20; $p < 0.001$) and was also significantly correlated with DAS28 ($\gamma = 0.880$).

Conclusion SMI may detect active synovitis with greater sensitivity than PDI in RA patients, even with clinical remission, and is well-correlated with inflammatory parameters during follow-up.

Key points

- *SMI correlated well with PDI and was more sensitive for detection of active synovitis in RA.*
  - *The SMI-sum was not only of greater value but also more strongly correlated than the PDI-sum with clinical inflammatory indicators including ESR, CRP, and DAS28 on initial and follow-up US examinations.*
  - *The SMI-sum was even significantly increased in patients with clinical remission.*

Keywords Doppler · Rheumatoid arthritis · Superb microvascular imaging · Ultrasound · Vascularity

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the synovial lining of the joints. According to European League Against Rheumatism (EULAR) recommendations in 2016 and American College of Rheumatology (ACR) guidelines in 2015 [1, 2], precise evaluation of synovial inflammation and bony deformity is very important for the management of RA, especially for early detection and evaluation of disease activity during follow-up. As a consequence, evaluation using ultrasound (US) or magnetic resonance imaging (MRI) has taken center stage in an "early detection and early treatment" strategy for RA [3]. In addition, there has been debate about whether existing clinical remission criteria are accurate and reproducible for disease activity or the clinical course [4, 5]. In fact, previous studies indicated that residual active synovitis on

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imaging was even observed in patients who met the 2011 ACR/EULAR remission criteria [6, 7]. Therefore, the role of imaging in the precise definition of remission needs to be documented for an RA treatment plan.

Among many imaging modalities, US including Doppler study is popular in the evaluation of RA, because it is noninvasive, rapid, and less expensive, and enables real-time examination [8–10]. Rheumatologists may have difficulty in correctly diagnosing RA with clinical evaluation alone [10]. It was recently reported that US may identify residual synovitis in patients with clinical remission and can predict future radiographic and physical outcomes [11, 12].

Superb Microvascular Imaging (SMI; Toshiba Medical Systems, Tokyo, Japan) was developed to provide vascular information by extracting flow signals from large vessels as well as from smaller microvasculature using advanced clutter suppression without motion artifacts, depicted as a color overlay image (color SMI) or as a grayscale map of flow (monochrome SMI) [13]. Some studies investigated the clinical role of SMI in evaluation of RA and suggested that this technique had greater sensitivity for detection of synovitis [14–17]. However, each study analyzed the results from a different point of view and could not demonstrate changes during follow-up. Our hypothesis was that SMI is not only more sensitive for detection of active synovitis in patients with RA than power Doppler imaging or conventional gray-scale US but is also better correlated with clinical findings during follow-up. Therefore, this study aimed to evaluate the clinical usefulness of SMI technology for detection of active synovitis in patients with RA, compared to that using power Doppler imaging (PDI), and to determine its association with clinical manifestation during follow-up.

Materials and methods

This retrospective study was approved by the institutional review board of our hospital, and the requirement for informed consent was waived.

Patients

Age, sex, medication history, and duration of RA were recorded (Table 1). Between June 2015 and August 2016, a total of 56 consecutive patients with RA (14 males and 42 females; mean age, 53.2 ± 17.6 years) were enrolled in this retrospective study in the outpatient rheumatology clinic of a single tertiary medical center. Patients were diagnosed with RA according to 2010 ACR/EULAR classification criteria [3]. Rheumatoid factor (RF) IgM and anti-cyclic citrullinated peptide antibody (ACPA) were measured. The following disease activity markers were evaluated: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and 28-joint Disease Activity Score (DAS28) [18]. ESR was determined from whole blood using the Westergren method (Afifax, Padua, Italy), and CRP concentration was assessed in serum using a nephelometric method (Beckman Coulter, Fullerton, CA, USA). The number of tender and swollen joints in the DAS28 was determined by the same rheumatologist (with 13 years of clinical experience in rheumatology). Clinical remission was defined as a DAS28 score < 2.6. Seventeen patients (17/56, 30.4%) underwent follow-up US (15 females and 2 males; mean age, 47.2 ± 19.8 years; range, 21–83 years), in which 12 were in clinical remission status. All clinical findings were also measured when follow-up US was performed, without RF and ACPA values.

US examination

Before the start of this study, we tested the SMI device in five healthy volunteers to confirm that signal noise was not present in the absence of synovitis. All patients then underwent ultrasound imaging of both wrists and hands (total 22 joints; wrist joints, metacarpophalangeal joints, and proximal interphalangeal joints). Conventional gray-scale US was performed for the more severely affected dorsal or volar sides of the wrists and hands using a high-resolution ultrasound device with a 14-MHz probe (Aplio TM 500 Ultrasound; Toshiba Medical Systems) and vascular imaging using both conventional Doppler and SMI was acquired at the same probe position as for gray-scale US by one of two musculoskeletal radiologists (with 14 and 12 years of experience, respectively, in musculoskeletal ultrasound). The parameters of PDI were as follows: less than 2.5 cm/s velocity scale, low wall filter, as high gain as possible. The color velocity scale of SMI was adjusted to 1.0 to 2.0 cm/s, the color frequency was adjusted to 14 MHz, a range of 4 to 7 frame average, as high gain as possible, and the vascular information were enhanced by adjusting the time smoothly. During US, the radiologists determined which side would be more appropriate for each patient between dorsal and volar articular surfaces according to the degree of synovitis on gray-scale US and vascularity both on PDI and SMI.

The degree of synovitis was determined semi-quantitatively for each joint on gray-scale US (grade 0, no synovitis; grade 1, mild synovitis; grade 2, moderate synovitis; grade 3, severe synovitis). Lesion vascularity was also measured semi-quantitatively for each joint on PDI or SMI (grade 0, no vascularity; grade 1, single vessel; grade 2, vascular flow less than 50% in field of view; grade 3, equal to 50% or more), as described by Ohrndorf

Table 1 Baseline patient characteristics

	Total RA patients ($n = 56$)	RA patients with remission ($n = 28$)	RA patients without remission ($n = 28$)	p value
Age (years)	53.2 ± 17.6 (range, 21–83)	48.5 ± 18.5 (range, 21–77)	57.9 ± 15.5 (range, 22–83)	0.045*
Sex (female, %)	42 (75.0)	24 (92.3)	18 (69.2)	0.121
Disease duration (months)	48.0 ± 25.4 (range, 1–120)	29.2 ± 25.3 (range, 1–84)	18.8 ± 24.9 (range, 1–120)	0.128
RF positivity (> 20 IU/mL; *n*, %)	73.2% (41/56)	67.9% (19/28)	78.6% (22/28)	0.547
ACPA positivity (> 5 U/mL; *n*, %)	76.9% (43/56)	78.6% (22/28)	75% (21/28)	1.000
ESR (mm/h)	27.13 ± 18.06 (range, 2–67)	18.04 ± 13.14 (range, 2–51)	36.21 ± 17.91 (range, 3–67)	< 0.001*
CRP (mg/L)	6.78 ± 9.14 (range, 0.18–45.3)	1.49 ± 1.99 (range, 0.18–9.6)	12.07 ± 10.40 (range, 0.41–45.3)	< 0.001*
TJC	1.7 ± 1.7 (range, 0–6)	0.4 ± 0.7 (range, 0–2)	2.9 ± 1.4 (range, 1–6)	< 0.001*
SJC	1.4 ± 1.5 (range, 0–5)	0.4 ± 0.6 (range, 0–2)	2.5 ± 1.5 (range, 0–5)	< 0.001*
VAPS	27.9 ± 16.8 (range, 3–70)	16.8 ± 11.7 (range, 3–40)	38.9 ± 13.3 (range, 10–70)	< 0.001*
DAS28-CRP	2.71 ± 1.12 (range, 1.10–4.93)	1.76 ± 0.52 (range, 1.10–2.53)	3.66 ± 0.63 (range, 2.72–4.93)	< 0.001*
Prednisolone dose (mg)	5.2 ± 2.3 (range, 0–15)	2.1 ± 2.4 (range, 0–7.5)	5.3 ± 2.7 (range, 0–15)	< 0.001*
Methotrexate (*n*, %)	40 (71.4)	19 (67.9)	21 (75.0)	0.768
Sulfasalazine (*n*, %)	9 (16.1)	5 (17.9)	4 (14.3)	1.000
Hydroxychloroquine (*n*, %)	10 (17.9)	5 (17.9)	5 (17.9)	1.000
Leflunomide (*n*, %)	15 (28.6)	8 (28.6)	7 (2.5)	1.000
Tacrolimus (*n*, %)	3 (5.4)	1 (3.6)	2 (7.1)	1.000
Azathioprine (*n*, %)	2 (3.6)	1 (3.6)	1 (3.6)	1.000
Adalimumab (*n*, %)	1 (1.8)	1 (3.0)	0 (0)	1.000
Golimumab (*n*, %)	1 (1.8)	0 (0)	1 (3.6)	1.000

Values are presented as mean ± standard deviation

*Statistically significant

et al. [18]. The sum of grading for 22 joints was calculated for synovitis (SYN-sum) using gray-scale and for vascularity using PDI (PDI-sum) and SMI (SMI-sum). Two radiologists, blinded to clinical information, scored about the degree of synovitis and vascularity with the consensus using the US images for each patient. Follow-up US was performed using the same methods, and the average interval between initial and follow-up US was 251.6 ± 176.2 days (range, 39–642 days).

Statistical analysis

To compare the baseline patient characteristics between the patients with remission or without remission, chi-square test for discrete variables and t test for continuous variables were used. SYN-sum, PDI-sum, and SMI-sum in each patient with RA were compared, and clinical remission state was evaluated, using analysis of variance or a t test. The associations between SYN-sum, PDI-sum, and SMI-sum as well as clinical inflammatory parameters including ESR, CRP, and DAS28 were also evaluated using Spearman's coefficient. Statistical analysis was performed with SPSS 20.0 software (IBM Corp., Armonk, NY, USA). A p value < 0.05 was considered significant.

Results

Baseline patient characteristics

Baseline characteristics are summarized in Table 1, listed by the clinical remission state. Mean age only significantly differed between those with or without remission, being younger in the patients with remission (mean, 48.5 years) than without remission (57.9 years; $p = 0.045$). The mean disease duration was 48.0 ± 25.4 months. Among all patients, there were two DMARD-naïve patients in the non-remission group. The mean ESR, CRP, and DAS28 values were 27.13 ± 18.06 mm/h (range, 2–67 mm/h), 6.78 ± 9.14 mg/L (range, 0.18–45.3 mg/L), and 2.71 ± 1.12 (range, 1.10–4.93), respectively. The positive RF (> 20 IU/mL) and ACPA (> 5 U/mL) rates were 73.2% (41/56) and 76.9% (43/56), respectively, and 48 patients were positive for either RF or ACPA (85.7%). As regards the treatment, the dose of prednisolone was significantly different between two groups (mean, 2.1 mg in patients with remission vs. 5.3 mg in patients without remission; $p < 0.001$).

In 17 patients with follow-up US, the mean ESR, CRP, and DAS28 values were 20.35 ± 13.27 mm/h (range, 2–50 mm/h), 1.84 ± 2.04 mg/L (range, 0.10–7.80 mg/L), and 2.16 ± 0.73 (range, 1.10–3.37), respectively.

Correlations between disease activity parameters and US findings

The sum of grades for 22 joints was significantly higher for SMI-sum (7.27 ± 4.56; range, 0–20) compared to PDI-sum (4.38 ± 3.09; range, 0–13; $p < 0.001$) and SYN-sum (4.55 ± 3.72; range, 0–17; $p < 0.001$) (Fig. 1). The SMI-sum was strongly correlated with the PDI-sum ($\gamma = 0.878$, $p < 0.001$) and SYN-sum ($\gamma = 0.448$, $p < 0.001$). The PDI-sum also had a significant correlation with the SYN-sum ($\gamma = 0.316$, $p = 0.018$). As shown in Table 2, the SMI-sum was significantly correlated with all clinical manifestations, including ESR, CRP, visual analog pain scale (VAPS), and DAS28 ($\gamma = 0.409$, $p = 0.002$; $\gamma = 0.695$, $p < 0.001$; $\gamma = 0.672$, $p < 0.001$; $\gamma = 0.726$, $p < 0.001$, respectively). The correlation between the SMI-sum and DAS28 was greater than that of the PDI-sum ($\gamma = 0.646$).

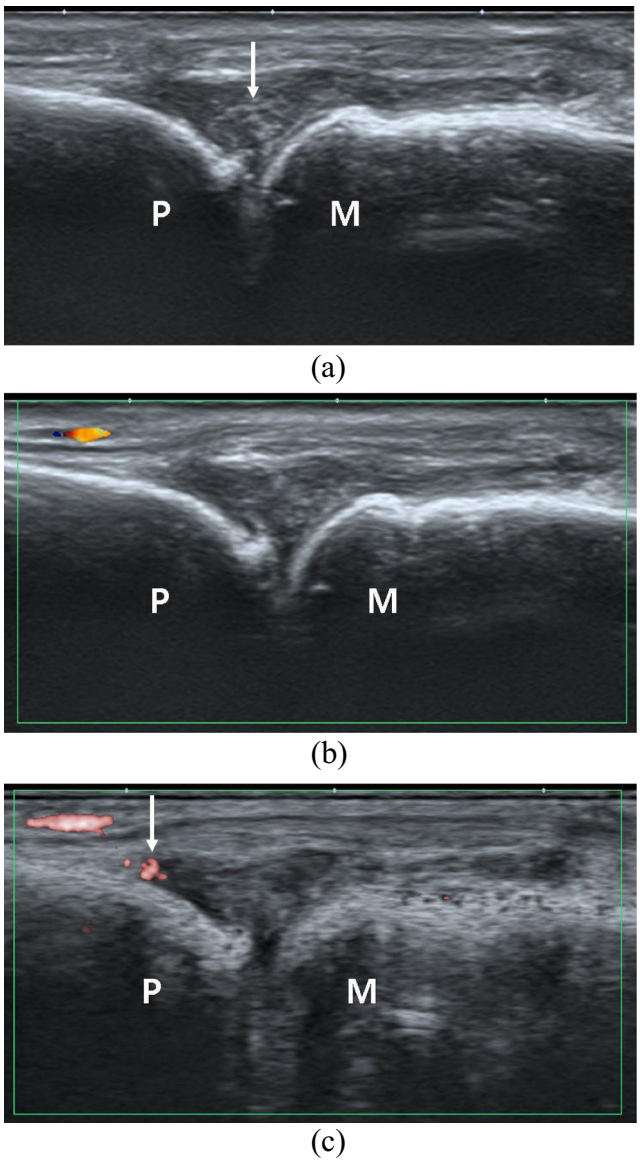

Fig. 1 A 38-year old female with DAS28-CRP score of 3.28 and grade 2 synovitis (arrow) in the dorsal third metacarpophalangeal joint (P, proximal phalanx; M, metacarpal bone) on gray-scale US (**a**). No vascularity is observed on PDI (**b**); grade 1 vascularity (arrow) was found using SMI (**c**)

Table 2 Correlation between clinical features and initial US findings in 56 patients

		Coefficient (γ)	p value
ESR	SYN-sum	0.158	0.244
	PDI-sum	0.458	0.000*
	SMI-sum	0.409	0.002*
CRP	SYN-sum	0.400	0.002*
	PDI-sum	0.646	0.000*
	SMI-sum	0.695	0.000*
VAPS	SYN-sum	0.246	0.067
	PDI-sum	0.534	0.000*
	SMI-sum	0.672	0.000*
DAS28-CRP	SYN-sum	0.348	0.009*
	PDI-sum	0.646	0.000*
	SMI-sum	0.726	0.000*

*Statistically significant

Comparison according to disease activity

A total of 28 (50.0%) patients were in clinical remission (DAS28 score < 2.6). All three sum values, especially the SMI-sum ($p = 0.015$), were significantly different between patients with and without clinical remission (Table 3). In patients with clinical remission, the SMI-sum (4.32 ± 2.01; range, 0–9) was significantly higher than the PDI-sum (2.61 ± 1.60; range, 0–7; $p < 0.001$) (Fig. 2), but there was no significant difference between the SMI-sum and SYN-sum (3.36 ± 2.84; range, 0–14; $p = 0.159$). The PDI-sum was not significantly different from the SYN-sum ($p = 0.245$). All patients with clinical remission showed active synovitis at more than one joint using SMI.

Table 3 US findings in patients with or without clinical remission

	Clinical remission (+) (DAS28 < 2.6; $n = 28$)	Clinical remission (−) (DAS28 ≥ 2.6; $n = 28$)	p value
SYN-sum	3.36 ± 2.84 (2.25, 4.46)	5.75 ± 4.13 (4.15, 7.35)	0.015*
PDI-sum	2.61 ± 1.60 (1.99, 3.23)	6.14 ± 3.23 (4.89, 7.39)	0.000*
SMI-sum	4.32 ± 2.00 (3.55, 5.10)	10.21 ± 4.50 (8.47, 11.96)	0.000*

Values are presented as mean ± standard deviation

*Statistically significant

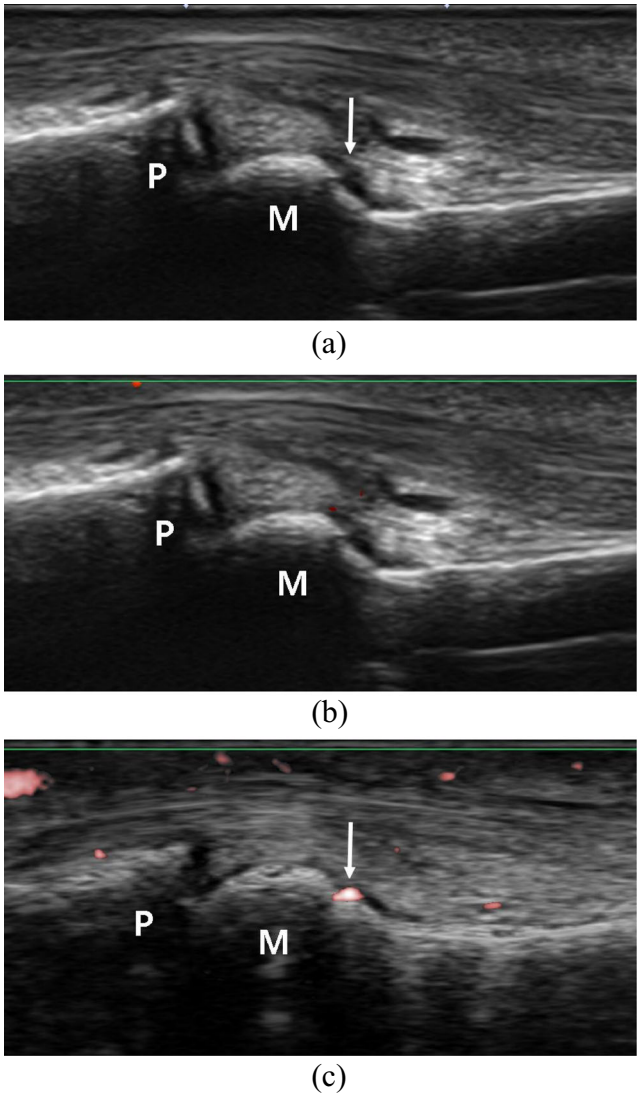

Fig. 2 A 26-year old female in clinical remission (DAS28-CRP = 2.5) showed mild active synovitis (grade 1, arrow) on gray-scale US of the volar third metacarpophalangeal joint (P, proximal phalanx; M, metacarpal bone) (**a**). No vascularity is observed on PDI (**b**); grade 1 vascular flow (arrow) is seen with SMI (**c**)

Follow-up evaluations

In the 17 patients who underwent follow-up US, the SMI-sum (2.35 ± 1.73; range, 0–5) was significantly greater than the PDI-sum (1.24 ± 1.20; range, 0–4; $p < 0.001$), but was not different from the SYN-sum (2.29 ± 1.53; range, 0–5; $p = 0.891$). The SMI-sum was highly correlated with the PDI-sum score ($\gamma = 0.860$, $p < 0.001$), but did not show a significant correlation with the SYN-sum ($\gamma = 0.430$, $p = 0.085$). The PDI-sum did not show a significant correlation with the SYN-sum ($\gamma = 0.334$, $p = 0.190$). All three values were significantly decreased compared to the initial US results ($p < 0.001$), and the mean change in the SYN-sum, PDI-sum, and SMI-sum was 2.71, 4.77, and 7.06, respectively. Similar to prior results, the correlation between the SMI-sum and DAS28-CRP ($\gamma = 0.880$, $p < 0.001$) was significantly greater, as shown in Table 4.

Discussion

This study showed that SMI correlated well with PDI and was more sensitive for detection of active synovitis in RA. The SMI-sum was not only of greater value but was also more strongly correlated than the PDI-sum with clinical inflammatory indicators including ESR, CRP, and DAS28 on initial and follow-up US examinations. In addition, the SMI-sum was even significantly increased in patients with clinical remission.

Early detection of synovial inflammation is very important, as early diagnosis and treatment are necessary for the management of RA. RA is a disease involving multiple joints and accompanied by systemic inflammation, so it is necessary to consider various factors to evaluate disease activity. Therefore, a variety of indices have been developed to assess disease activity, however, each has some limitations. To this end, the use of imaging modalities is increasing, the most important being MRI and US. US is widely used for evaluation of RA because it allows real-time evaluation of active synovitis in an affected joint and has advantages over MRI including relatively low-cost and user-friendly equipment [8–10].

Many previous studies suggested the clinical usefulness of US to investigate synovitis in patients with RA. Classically, gray-scale US has been used for joint evaluation; however, as shown in previous literature [19] and our study, evaluation of active synovitis based on

Table 4 Correlation between clinical features and follow-up US findings in 17 patients

		Coefficient (γ)	p value
ESR	SYN-sum	0.137	0.599
	PDI-sum	0.630	0.007*
	SMI-sum	0.408	0.104
CRP	SYN-sum	0.180	0.491
	PDI-sum	0.628	0.007*
	SMI-sum	0.645	0.005*
VAPS	SYN-sum	0.045	0.865
	PDI-sum	0.676	0.003*
	SMI-sum	0.672	0.003*
DAS28-CRP	SYN-sum	0.228	0.379
	PDI-sum	0.832	0.000*
	SMI-sum	0.880	0.000*

*Statistically significant

gray-scale US alone is inadequate, possibly because coexisting soft tissue degeneration, osteoarthritis, or previous injury around the joint may hinder clear assessment [20]. Therefore, evaluation of joint vascularity in synovitis using Doppler US could provide more reliable information for estimation of activity [21]. However, Doppler examination can be affected by artifacts, such as "bleeding" of color signals due to an inappropriate gain setting or a "branching effect" due to incorrect transducer pressure [22].

SMI technology, primarily developed by Toshiba, can provide more detailed information on vascularity compared to PDI [13]. Previous studies that investigated the clinical role of SMI for thyroid nodules, acute cholecystitis, hepatic artery grafts, etc. indicated superior visualization of fine vascularity in the region of interest [23–27].

Our study showed that SMI can detect synovial inflammation more sensitively in actual clinical practice. In particular, patients with clinical remission were found to have at least one joint with active synovitis when evaluated using SMI. In recent years, as a variety of RA therapeutic agents have been developed, remission has become the primary goal of treatment. However, the currently used remission criteria allow minimal inflammation [5]. Studies have suggested that ongoing inflammation in patients with clinical remission may predict structural progression [28]. Therefore, even when clinical remission criteria are met, more active treatment may be required. Our study shows that active inflammation is present in patients with clinical remission when assessed with SMI, and that SMI is more sensitive than PDI in detecting active inflammation.

Although high sensitivity may be of benefit in early detection of inflammation in patients in the preclinical state, there is also a risk of overdiagnosis and overtreatment caused by false positive results. In some recent studies, MRI or US have identified inflammation in healthy subjects [20, 29].

In our study, it was not clear whether SMI detected true inflammation or was falsely positive for patients not detected with PDI. As higher SMI-sum scores were not correlated with standard references such as pathologic findings on synovial biopsy, their clinical significance in patients with clinical remission was unclear; hence, overestimation of active synovitis using SMI technology was possible. However, our study evaluated five healthy volunteers and confirmed that signal noise was not present in the absence of synovitis to minimize false positive results before US examination was performed in RA patients. This suggests that the higher SMI-sum score in patients with RA can detect active synovitis with greater sensitivity and fewer false positive results, compared with conventional tests. Our findings do not imply that US, including SMI, is absolutely superior to clinical indices such as DAS28. Rather, it suggests that clinical index, US score, and biomarker can be used complementarily to accurately assess the disease activity of RA.

To the best of our knowledge, only four articles have evaluated RA patients using SMI technology on US [14–17]. Li et al. [14] scanned only the second and third digits using SMI, in contrast with our study. The authors showed increased sensitivity for vascularity using SMI compared with that using PDI, even in patients with clinically inactive RA, similar to our results. However, their study did not assess the association between SMI and clinical parameters.

Yu et al. [15] evaluated patients with clinical remission using SMI. As in our study, they concluded that SMI may be more sensitive than PDI for detection of fine vascularity, even in clinical remission. However, there was no consensus on standardized US guidelines for remission in that study, making the results difficult to interpret.

Yokota et al. [16] used SMI summed scores for 26 joints and found that total SMI scores was higher in 27 patients with RA than that of the non-RA group, and good correlation of SMI scores with clinical parameters was observed, as in our study. The wrists and metacarpophalangeal joints were suggested as the most sensitive regions for assessment of synovial inflammation. However, there was no difference in sensitivity for synovitis detection according to joint distribution in our study.

Orlandi et al. [17] assessed patients with early RA and those receiving rituximab using SMI, PDI, and gray-scale US. Since they determined the absence or presence of vascularity signals by arbitrarily selecting the most severely affected joint for analysis, rather than the summation of scores or grades, their results could not be compared with ours. Our results demonstrated a significantly greater correlation between SMI and DAS28 compared to their study. Moreover, we showed that SMI may be more strongly correlated with DAS28 than PDI, contrary to their results.

Some limitations must be noted. First, this study had a retrospective design and a small number of patients from a single medical center. Only five healthy volunteers were tested to confirm that signal noise was not present in the absence of synovitis. Further studies are needed with a larger number of patients. Second, US was performed by one of two musculoskeletal radiologists, and inter- or intra-reader agreement was not determined, because US was not performed twice for each patient. However, previous studies documented good inter-reader agreement for SMI [14, 17]. In addition, comparison between SMI with 14 MHz probe and PD with high-frequency probe (> 18 MHz) was not done. Third, only 17 of the 56 patients (30.4%) underwent follow-up US. However, as previous studies did not report follow-up data, our findings may be useful, despite the small number of patients. Fourth, we evaluated only wrists and hands without about large joints such as knee joints, because of the limitation

of time for US examination. Further studies are needed to evaluate the large joints also.

In conclusion, SMI may detect active synovitis with greater sensitivity than PDI in RA patients, even with clinical remission, and correlated well with clinical inflammatory parameters during follow-up.

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Compliance with ethical standards

Disclosures None.

Ethical standards This retrospective study was approved by the institutional review board of our hospital, and the requirement for informed consent was waived. This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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