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IMAGING

Quantitative power Doppler signal assessment in the subchondral bone region of the metacarpophalangeal joint is an effective predictor of radiographic progression in the hand of rheumatoid arthritis: a pilot study

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Abstract

Ultrasonography is useful for assessment of synovitis in the hand of rheumatoid arthritis (RA) patients. The aim of this study was to investigate the predictive value of the quantitative power Doppler (PD) signal assessment in the subchondral bone region of the metacarpophalangeal (MCP) joint in patients with RA showing radiographic progression of the hand by comparing with those of previously reported scoring systems. Twenty-two patients (20 women) with RA who underwent power Doppler ultrasonography (PDUS) of the bilateral one to five MCP joints at baseline were included in the study. Radiography of both hands was performed at baseline and at 1 year. PDUS of the synovial space was evaluated according to semi-quantitative scoring (0–3) and quantitative measurement (0–100%). The PD signal in the subchondral bone region was qualitatively (0, 1) and quantitatively (mm^2) assessed. The performance of PDUS assessment was compared using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve and the risk ratio (RR). As a predictor for radiographic progression, the quantitative PD signal assessment in the subchondral bone region (AUC = 0.842, $p < 0.01$) was equivalent to quantitative vascularity (AUC = 0.817, $p < 0.05$) and semi-quantitative scoring (AUC = 0.754, $p < 0.05$). As for the RR of the PD signal in the subchondral bone region for radiographic progression, the quantitative PD signal assessment was 5.40 ($p < 0.01$), whereas the qualitative PD signal assessment was 1.60 ($p = 0.204$). Quantitative PD signal assessment in the subchondral bone region can predict radiographic progression in the hand of RA patients.

Keywords Arthritis · Ultrasonography · Hand · Bone · Synovitis · Radiography

Introduction

Inflammatory synovitis is considered to be an active lesion of rheumatoid arthritis (RA) that causes joint destruction [1]. The detection and evaluation of synovitis play important roles in deciding the treatment plan [2]. Imaging modalities like ultrasonography (US) and magnetic resonance imaging (MRI) are useful for detection of synovial inflammation that predicts subsequent joint damage [3–6]. In particular, US is widely accepted for assessment of synovitis due to its short examination duration time and low cost [7, 8].

The power Doppler (PD) signal for synovitis has been clinically evaluated according to the semi-quantitative scoring which has a predictive value in disease activity as well as radiographic outcome during 1 year of follow-up [5, 9]. However, the scoring consists of only four steps, which are not able to assess subtle changes with sufficient sensitivity, requiring extensive experience for observers [9–11]. Some researchers have indicated that the quantitative value of the PD signal enables objective assessment and is more predictive of structural damage progression than semi-quantitative scoring [12–14]. A recent study suggests that PD signals in contact with/or penetrating bone as well as conventional PD grading scale are qualitatively associated with radiographic progression in RA patients in remission [15].

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We hypothesize that patients with more PD signal in the subchondral bone region are more prone to radiographic progression. The objective of our study was to analyze the predictive value of quantified PD signal in the subchondral bone region of the MCP joint in terms of future joint destruction of the hand in RA patients by comparing with those of previously reported scoring systems.

Materials and methods

Patients

We retrospectively reviewed 22 patients (20 women and 2 men) with RA on disease-modifying antirheumatic drugs (DMARDs) (Table 1). All patients underwent power Doppler ultrasonography (PDUS) of the bilateral one to five metacarpophalangeal (MCP) joints at baseline. Radiography of both hands was performed at baseline and at 1 year (median 13 months). All patients met the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA [16]. They were managed in a dedicated rheumatology department in a university hospital and were assessed for continuation/cessation of biological treatment or for switching to an alternative biological agent. Consecutive patients evaluated at the university hospital were eligible to participate. Out of 22 patients, 21 already had received DMARDs for RA at baseline at the time of this study. One patient without medication at baseline underwent DMARDs thereafter. Four patients who received methotrexate monotherapy at baseline temporarily received combination therapy during follow-up. This study was approved by the local ethics committee of our institution and was performed in accordance with the Declaration of Helsinki. Informed consent was waivered because of the retrospective study design.

Ultrasonography

The grayscale and PD mode in ultrasonography were performed at baseline using an Avius (Hitachi, Ltd, Tokyo, Japan) or LOGIQ E9 (GE Healthcare, Piscataway, NJ, USA) by one of multiple ultrasonographers specialized in musculoskeletal ultrasonography. For Avius, using a linear probe 6–14 MHz, pulse repetition frequency (PRF) 800 Hz at preset was adjusted: FINGER; depth, 1.75 cm; color focus, 1 cm; Doppler gain, 40; color flow mapping filter, M; transmit power, 1.0; frame rate, 8–10. For LOGIQ E9, using a linear probe, ML6-15, PRF 500 Hz at preset was adjusted: MSK superficial; depth, 2.75 cm; color focus, 1.5 cm; Doppler gain, 15; transmit power, 0.4; frame rate, 10. For both models, the level of wall filter was automatically determined according to PRF settings by linked controls. The transmit frequencies were 7.5 MHz for Avius and 15 MHz for LOGIQ E9. The probe was placed longitudinally across the first to fifth MCP joints of both hands. The basic scanning

Table 1 Clinical and laboratory characteristics of patients with RA at baseline

Characteristic	Value
Total no. of subjects included	22
Age, median (range) years	64 (34–75)
Sex, female/male	20/2
Rheumatoid factor positive, yes/no	19/3
Duration of symptoms, median (IQR) years, $n=22$	2.5 (1.3–6.8)
Swollen joint count, median (IQR), $n=22$	4 (1–9)
Tender joint count, median (IQR), $n=22$	6 (1–11)
Visual analog scale, median (IQR), $n=22$	42 (17–62)
Erythrocyte sedimentation rate, median (IQR) mm/h, $n=22$	18 (9–51)
C-reactive protein, median (IQR) mg/dl, $n=22$	0.28 (0.03–0.98)
DAS28-erythrocyte sedimentation rate, median (SD), $n=21$	4.5 (3.0–5.6)
DAS28-C-reactive protein, median (SD), $n=20$	3.7 (2.4–5.2)
Health assessment questionnaire, median (IQR), $n=21$	5 (1–8)
Prior use of DMARDs, yes/no	21/1
DMARDs, no.	
None	1
Methotrexate	9
Tocilizumab	1
Combine therapy	11

IQR interquartile range, *SD* standard deviation, *DAS28* disease activity score with 28 joints, *DMARDs* disease-modifying antirheumatic drugs

technique followed the 2001 European League Against Rheumatism guidelines [17]. The synovial vascular area with the most pronounced PD activity in each MCP joint was identified from the cine loop and stored.

Semi-quantitative scoring was used to assess synovitis in the joint (grade 0, absence of signal; 1, single vessel dots; 2, vessel dots over less than half of the synovium; and grade 3, vessel dots over more than half of the synovium) [18]. Here, this scoring is referred to as "conventional semi-quantitative scoring."

To quantify MCP joint synovial vascularity, we set the region of interest (ROI) according to a previous study [14].

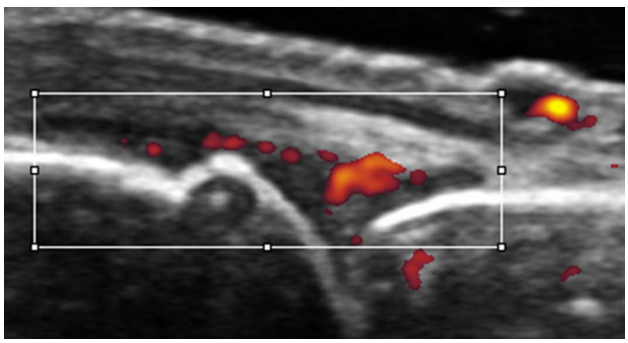

Fig. 1 Representative PD image for quantitative ROI method in the MCP joint. The ROI was a rectangle 5 × 15 mm, located to contain as many vascular flow pixels as possible. The percentage of vascular flow pixels in the ROI was calculated automatically (6.5%). *PD* power Doppler, *MCP* metacarpophalangeal, *ROI* region of interest

The ROI was a rectangle 5 × 15 mm, located to contain as many of the vascular flow pixels as possible. The percentage of vascular flow pixels in the ROI was calculated automatically by an in-house developed software application (Fig. 1). This method is referred to as "quantitative ROI method" in this study.

The PD signal in the subchondral bone region was qualitatively and quantitatively assessed. Qualitative assessment for the PD signal was performed according to a previous study [15]: capsular or within synovial tissue without bone contact (negative) and with bone contact or penetrating bone cortex (positive) (Fig. 2). Each patient who had PD signal with bone contact or penetrating bone cortex in at least one joint was defined as a patient with positive PD signal in the subchondral bone region. This assessment is referred to as "qualitative subchondral bone signal assessment" in this study.

For quantitative assessment, the subchondral bone region was manually defined. We drew lines between cartilage and subchondral bone at the proximal and distal MCP joint using ImageJ while referring to the grayscale image. The ROI was automatically segmented with width 0.5 mm in parallel with the line in direction at the subchondral bone by an in-house developed software application so that the subchondral bone could be placed inside the ROI. The positive PD area inside the ROI was then calculated (Fig. 3). This is referred to as "quantitative subchondral bone signal assessment" in this study.

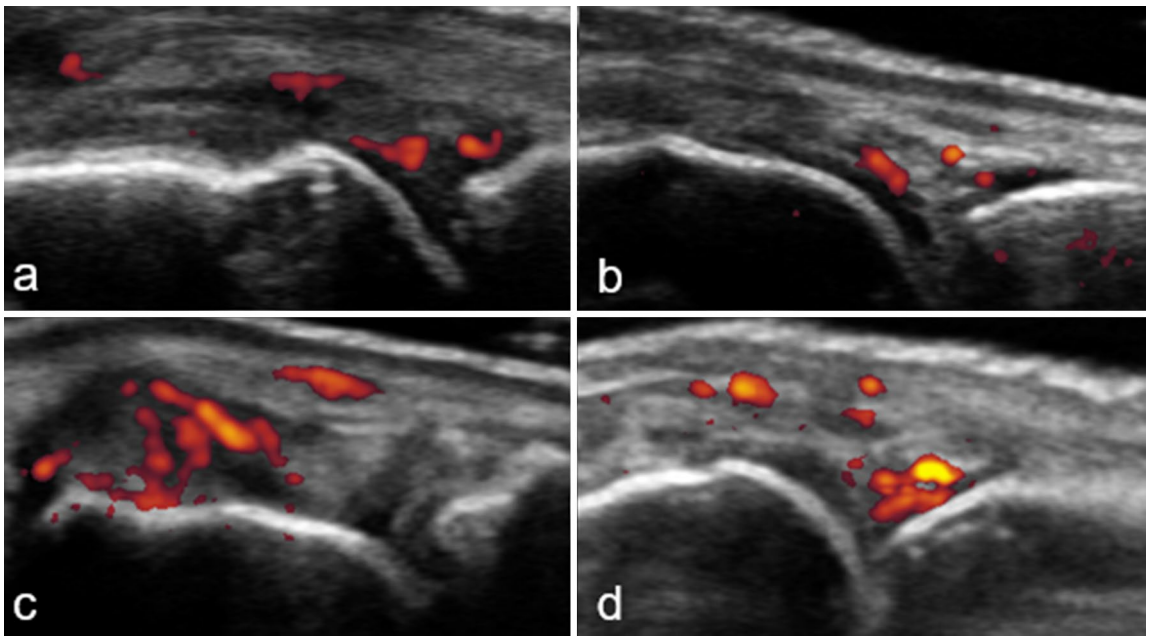

Fig. 2 Qualitative subchondral bone signal assessment at the MCP joints. **a**, **b** Negative vascularity adjacent to the subchondral bones. **c**, **d**: Positive vascularity with contact to the subchondral bones of the metacarpal head (**c**) and basal phalanx (**d**). *MCP* metacarpophalangeal

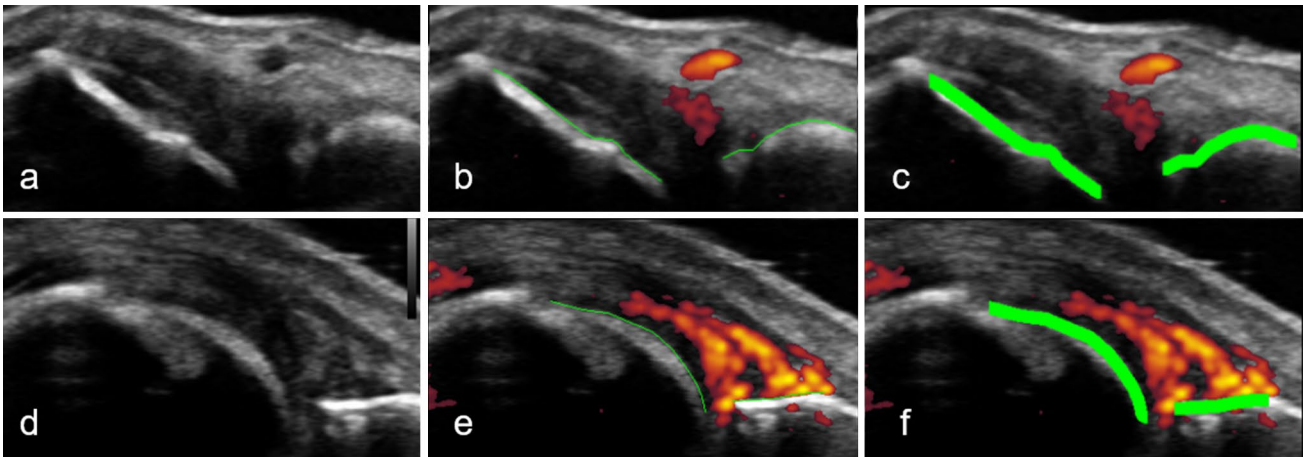

Fig. 3 Quantitative subchondral bone signal assessment at the MCP joints. Top (**a**–**c**) is negative and bottom (**d**–**f**) is positive for subchondral bone PD signals. **b**, **e** We drew lines between cartilage and subchondral bone at the proximal and distal MCP joint using ImageJ while referring to the grayscale images (**a**, **d**). **c**, **f** The ROI was automatically segmented with width 0.5 mm in parallel with the line in direction at the subchondral bone by an in-house developed software application so that the subchondral bone could be placed inside the ROI. The positive PD area inside the ROI was then calculated. *MCP* metacarpophalangeal, *PD* power Doppler, *ROI*, region of interest

Conventional semi-quantitative scoring and qualitative subchondral bone signal assessment using visual assessment for all static images were independently carried out by two sonographers (AN, MH) both with 18 years of experience in musculoskeletal ultrasonography who were blinded to other clinical information. The quantitative ROI method and the quantitative subchondral bone signal assessment using the software for all static images were independently carried out by two radiological technologists (MF, YT) with 2 and 1 years of experience. They were blinded to other clinical information. For calculation of intraobserver repeatability, the second quantitative ROI method and the quantitative subchondral bone signal assessment using the software for all static images were performed by one radiological technologist (MF) with more than 1 month interval to avoid memory bias.

Radiography

Plain radiographs of both hands of the posteroanterior view were obtained at baseline and at 1 year using digital X-ray equipment (BENEO DR-XD 100, Fujifilm Corporation, Tokyo, Japan and DHF-155H, Hitachi, Ltd, Tokyo, Japan) under standardized conditions. One radiologist with 20 years of experience (TK), who was blinded to other clinical information, scored joint space narrowing (JSN) and bone erosion according to the Sharp/van der Heijde (SvdH) scoring system [19]. JSN and bone erosions were assessed by scores of 0–4 and 0–5 at the 15 and 16 joints for each hand. The maximal score of SvdH for the left and right hands was thus 280. Each patient who had a progression in SvdH score (e.g., score 0 at baseline to score 1 at follow-up) in at least one joint was defined as a patient with radiographic progression according to a previous study [15]. Repeatability of scoring is described elsewhere [20].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 24.0 for Windows (IBM Corp., New York, NY, USA) and Excel (Microsoft Corp., Redmond, WA, USA) was used for the statistical analysis. Non-parametric statistics were used to compare continuous parameters.

For semi-quantitative and quantitative assessment, interobserver and intraobserver agreement were calculated using intraclass correlation coefficients (ICCs) employing a two-way mixed effects model using consistency definition for interobserver agreement and a one-way random effects model for intraobserver agreement. For qualitative assessment, interobserver reliability was estimated using Cohen's κ. The relationship between the PDUS assessments and radiographic progression was evaluated using a receiver operating characteristics (ROC) curve and risk ratio (RR). ROC curve analysis was done to determine a cutoff value for each PDUS assessment. Optimal cutoff values were obtained by the maximum value of sensitivity plus '1-specificity'. Comparative analysis was undertaken between area under the curve (AUC) of two different methods using the Mann–Whitney test. RR of radiographic progression was assessed using Fisher's exact test. Any p value less than 0.05 was considered statistically significant.

Results

Imaging analysis

The descriptive analytical statistics for PDUS and radiographic assessments are shown in Table 2. Out of 22 patients, one joint of one patient and two joints of one patient were excluded from PDUS analysis because these images did not include the proximal or distal MCP joint. In the qualitative subchondral bone signal assessment, 14/22 (64%) patients had positive PD signal in the subchondral bone region, with bone contact or penetrating bone cortex, in at least one joint. Radiographic progression was observed in 10/22 (45%) patients.

Intra- and interobserver reliability for ultrasonography

Interobserver ICC for conventional semi-quantitative scoring (0-3) was 0.982 (95% confidence interval [95% CI] 0.957–0.992). Intra- and interobserver ICC for quantitative ROI method was 0.992 (95% CI 0.981–0.997) and 0.982 (95% CI 0.958–0.993), respectively.

The obtained interobserver Cohen's κ for qualitative subchondral bone signal assessment was 0.680. Intra- and interobserver ICC for quantitative subchondral bone signal assessment was 0.928 (95% CI 0.837–0.969) and 0.875 (95% CI 0.690–0.949), respectively.

Prediction of radiographic progression

The accuracy, sensitivity and specificity of laboratory, PDUS and radiographic assessment at baseline for radiographic progression based on the ROC curve are shown in Table 3. ROC curves of each PDUS assessment for radiographic progression are shown in Fig. 4. The AUC was 0.754 (95% CI 0.539–0.969, $p < 0.05$) and 0.817 (95% CI 0.627–1.000, $p < 0.05$) for conventional semi-quantitative scoring and quantitative ROI method, respectively. Quantitative subchondral bone signal assessment revealed favorable AUC values for the prediction of radiographic progression (AUC = 0.842, 95% CI 0.660–1.000, $p < 0.01$), and the sensitivity and specificity was 90.0 and 83.3%, respectively. Nevertheless, there were no significant differences in AUCs between two different methods: the quantitative PD signal assessment in the subchondral bone region vs quantitative vascularity, $p = 0.625$ and the quantitative PD signal assessment in the subchondral bone region vs semi-quantitative scoring, $p = 0.138$, respectively.

Table 4 shows the RR of radiographic progression by the measure of disease activity, PDUS and radiographic assessment at baseline. RR of radiographic progression by quantitative subchondral bone signal assessment at baseline was 5.40 (95% CI 1.50–19.46, $p < 0.01$), whereas RR by conventional semi-quantitative scoring was 2.70 (95% CI 1.18–6.17, $p < 0.05$). RR by quantitative ROI method and qualitative subchondral bone signal assessment was 4.80 (95% CI 1.30–17.66, $p < 0.01$) and 1.60 (95% CI 0.84–3.05, $p = 0.204$), respectively.

Discussion

In this study of RA patients receiving DMARDs, we investigated the predictive value of the PD signal in the subchondral bone region of the MCP joint in terms of radiographic progression of the hand in RA by comparing with those of previously reported scoring systems. This is the first study indicating that quantitative assessment of PD signal in the subchondral bone region is an effective predictor of future structural damage progression in the hand.

Accurate prognostication for structural destruction has benefits for RA patients and rheumatologists because appropriate therapeutic intervention may limit the progression of RA, which may prevent disability or permanent handicap [21, 22]. PDUS inflammatory findings (conventional semi-quantitative scoring) seem to have a predictive value in disease activity as well as radiographic outcome during 1 year of follow-up [9]. Several authors have reported that the

Table 2 Descriptive analytical statistics for PDUS and radiographic assessment

	Median	Range (Min–Max)
PDUS assessment		
Conventional semi-quantitative scoring	4.00	0–24.00
Quantitative ROI method (%)	20.17	0–262.06
Qualitative subchondral bone signal assessment	1.00	0–1.00
Quantitative subchondral bone signal assessment (mm^2)	0.45	0–4.08
Radiographic assessment		
SvdH score at baseline	1.00	0–46.00
SvdH score at follow-up	2.00	0–46.00

PDUS power Doppler ultrasonography, *ROI* region of interest, *SvdH* sharp/van der Heijde score

Table 3 Accuracy, sensitivity, and specificity of laboratory, PDUS and radiographic assessment at baseline for radiographic progression

	AUC (95% Cl)	*p* value	Cutoff value	Sensitivity (%)	Specificity (%)
Measure of disease activity					
Swollen joint count	0.442 (0.188–0.696)	0.644	4	60.0	50.0
Tender joint count	0.650 (0.405–0.895)	0.235	6	70.0	66.7
Visual analog scale	0.558 (0.299–0.818)	0.644	80	40.0	91.7
Erythrocyte sedimentation rate (mm/h)	0.642 (0.396–0.887)	0.262	60	40.0	100.0
C-reactive protein (mg/dl)	0.467 (0.208–0.725)	0.792	0.70	40.0	75.0
DAS28-erythrocyte sedimentation rate	0.593 (0.322–0.863)	0.477	5.7	44.4	91.7
DAS28-C-reactive protein	0.414 (0.134–0.694)	0.518	1.6	22.2	90.9
Health assessment questionnaire	0.627 (0.376–0.879)	0.324	7	60.0	72.7
PDUS assessment					
Conventional semi-quantitative scoring	0.754 (0.539–0.969)	0.044	4.00	90.0	66.7
Quantitative ROI method (%)	0.817 (0.627–1.000)	0.012	25.18	80.0	83.3
Quantitative subchondral bone signal assessment (mm^2)	0.842 (0.660–1.000)	0.007	0.50	90.0	83.3
Radiographic assessment					
SvdH score	0.475 (0.217–0.733)	0.843	1.00	60.0	50.0

DAS28 disease activity score with 28 joints, *PDUS* power Doppler ultrasonography, *ROI* region of interest, *SvdH* Sharp/van der Heijde score, *AUC* area under the curve, *Cl* confidence interval

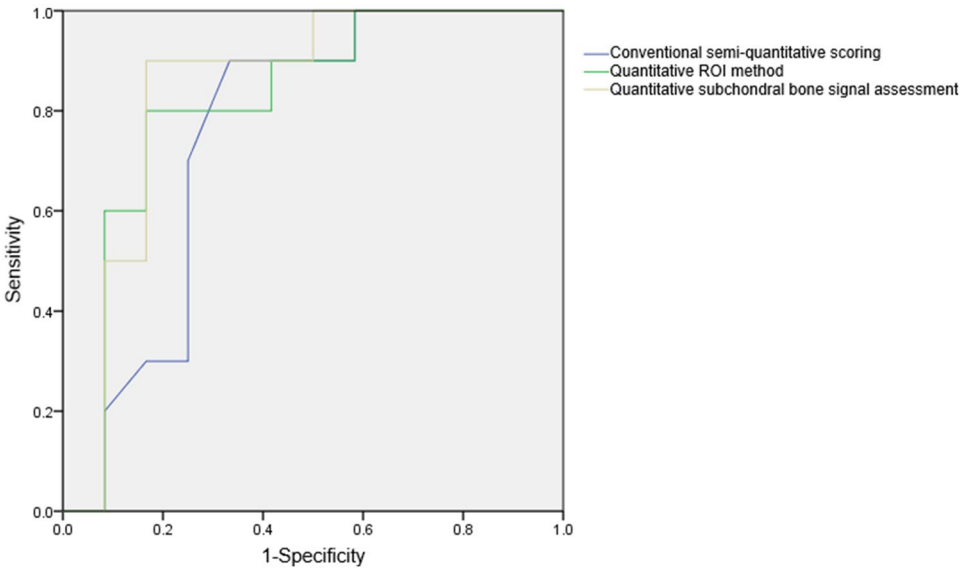

Fig. 4 ROC curves of each PDUS assessment for radiographic progression. *ROC* receiver operating characteristic, *PDUS* power Doppler ultrasonography

quantitative value for PD signal in the joint (quantitative ROI method) is more predictive of structural damage progression than conventional semi-quantitative scoring which has low sensitivity in detecting small changes in vascularity [12, 14]. Our results indicate that the predictive value of quantitative subchondral bone signal assessment for future structural damage progression performed as well as the conventional semi-quantitative scoring and quantitative ROI method.

The characteristic trait of RA is persistent inflammation of the synovial membrane and formation of invasive synovial tissue, called the pannus, which in time leads to destruction of the cartilage, subchondral bone tissue and the soft tissue of the affected joints [21]. Sudoł-Szopińska et al. suggest the penetration of the pannus into the cartilage/subchondrium as one cause of bone erosion [23]. PDUS can capture the well-vascularized pannus and has destructive effects on joint structures. Our results and hypothesis that patients with more PD signals in the subchondral bone region are more prone to radiographic progression are consistent with these previous studies indicating a pathological mechanism for structural destruction [21–23].

Table 4 RR of radiographic progression by independent predictors at baseline

	RR (95% Cl)	*p* value[a]	Cutoff value[b]
Measure of disease activity			
Swollen joint count	1.02 (0.51–2.06)	1.000	4
Tender joint count	2.10 (0.86–5.15)	0.198	6
Visual analog scale	4.80 (0.63–36.34)	0.135	80
Erythrocyte sedimentation rate, mm/h	NA	0.029	60
C–reactive protein (mg/dl_	1.60 (0.46–5.53)	0.652	0.70
DAS28-erythrocyte sedimentation rate	5.33 (0.71–39.95)	0.119	5.7
DAS28-C-reactive protein	0.98 (0.73–1.32)	1.000	1.6
Health assessment questionnaire	2.20 (0.74–6.54)	0.198	7
PDUS assessment			
Conventional semi-quantitative scoring	2.70 (1.18–6.17)	0.011	4.00
Quantitative ROI method (%0)	4.80 (1.30–17.66)	0.008	25.18
Qualitative subchondral bone signal assessment	1.60 (0.84–3.05)	0.204	1.00
Quantitative subchondral bone signal assessment (mm^2)	5.40 (1.50–19.46)	0.002	0.50
Radiographic assessment			
SvdH score	0.80 (0.44–1.46)	0.652	1.00

DAS28 disease activity score with 28 joints, *PDUS* power Doppler ultrasonography, *ROI* region of interest, *SvdH* Sharp/van der Heijde score, *PDUS* power Doppler ultrasonography, *RR* risk ratio, *Cl* confidence interval, *NA* not applicable

[a]*p* values were assessed by two-tailed Fisher's exact test

[b]Cutoff values were calculated by ROC curve analysis

Although Raffeiner et al. suggested that qualitative subchondral bone signal assessment was associated with radiographic progression in RA patients in DAS28 remission and claimed that the PD location was simple to classify and interreader agreement was high (Cohen's $\kappa = 0.91$) [15], there was no significant relationship between the qualitative assessment and radiographic progression in our study. The interreader agreement for qualitative subchondral bone signal assessment in this study was low (Cohen's $\kappa = 0.680$) compared to the previous study [15]. These results may be explained by our retrospective study design. In their prospective study, artifacts in PDUS examination to assess PD signal in the subchondral bone region were carefully removed. Hence, we believe that the high agreement rate was seen due to the image processing of acquired images in their study. For PDUS assessment using the current routine images, a method that considers the existence of artifacts in that region is required. Our quantitative subchondral bone signal assessment was a better predictor of future structural damage progression (RR = 5.40, $p < 0.01$) than qualitative assessment (RR = 1.60, $p = 0.204$), although some pseudo-positive PD signals due to artifacts may have been included in the quantification. This means that our method requires image processing to remove artifacts. However, our method does not require extensive experience for observers. Moreover, our evaluation method is simple with high reproducibility and might be a useful tool for routine PDUS assessment because the evaluation region is smaller and easier to define than that of conventional methods.

We acknowledge that our study has several limitations. First, the present study included only a small number of patients. Second, because there were variations in the PDUS models involved in this retrospective study, the method of data acquisition of these models may be different. Previous studies, however, suggest that different ultrasonography machines can provide equivalent examination results concerning the pannus vascularity by adjusting the PRF value [24]. The imaging parameters of PDUS data used in the current study were adjusted to obtain equivalent examination results between the two devices. We utilized only temporal static image data obtained in clinical routine. Further study, however, may need to verify the variability of the data acquisition details because PDUS dependents on local hemodynamics and is influenced by the time of day, vasoactive medications, previous exercise level and concomitant vasoconstrictive collagen vascular disease. Third, the subchondral bone region for quantitative PD signal assessment was defined as having a constant width at the MCP joint in all RA patients. For more accurate assessment, it might be necessary to change the size of the ROI for each patient. Finally, intra- and interobserver reproducibility for radiographic assessment were not obtained in this study. However, intra- and interobserver reliability for the SvdH scoring system on radiographs in 51 RA patients by the same expert

(TK) were moderate to almost perfect in a previous study (ICC = 0.589–0.839 and 0.556–0.849, respectively) [20].

In conclusion, quantitative PD signal assessment in the subchondral bone region of the MCP joints is a simple technique and predicts radiographic progression in the hand joint as efficiently as conventional semi-quantitative scoring and quantitative ROI method in RA patients on DMARDs. Quantitative PD signal assessment in the subchondral bone region might therefore be of value in making judgments concerning continuation or cessation of the biological treatment or switching to an alternative biological agent.

Author contributions MF: substantial contributions to the design of the work, the acquisition, analysis, and interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TK: substantial contributions to the conception and design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AN: substantial contributions to the interpretation of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MH: substantial contributions to the interpretation of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MK: substantial contributions to the interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KS: substantial contributions to the analysis of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MN: substantial contributions to the acquisition of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. YT: substantial contributions to the analysis of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LY: substantial contributions to the interpretation of the data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. KT: substantial contributions to the design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. TA: substantial contributions to the conception and design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waivered because of the retrospective study design.

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