Title page

Title; 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

Short Title; Quantitative Power Doppler Signal Assessment in the Subchondral Bone Region

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Abstract

Objectives. To investigate the predictive value of the quantitative power Doppler (PD) signal assessment in the subchondral bone region of the metacarpophalangeal (MCP) joint concerning radiographic progression of the hand in patients with rheumatoid arthritis (RA) by comparing with those of the previously reported scoring systems.

Methods. Twenty-two patients (20 women) with RA underwent power Doppler ultrasonography (PDUS) of the bilateral 1-5 MCP joints at baseline. 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 assessments were compared using the area under the curve (AUC) of the receiver operating characteristic curve and risk ratio (RR).

Results. 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 better than 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 ($p = 0.204$).

Conclusion. Quantitative PD signal assessment in the subchondral bone region may predict radiographic progression of RA.

Advances in knowledge: Amount of PD signal in contact with/or penetrating bone may predict radiographic progression of RA.

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 in terms of its duration time and medical cost.[7, 8]

The power Doppler (PD) signal for synovitis has been clinically evaluated according to semi-quantitative scoring which has a predictive value in disease activity as well as radiographic outcome during one 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 indicate that the quantitative value for 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]

We hypothesize that patients with more PD signals in the subchondral bone

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

Methods

Patients

We retrospectively reviewed 22 patients (20 women and 2 men) with RA on disease-modifying anti-rheumatic drugs (DMARDs) (Table 1). All patients underwent power Doppler ultrasonography (PDUS) of the bilateral 1-5 metacarpophalangeal (MCP) joints at baseline. Radiography of both hands was performed at baseline and at 1 year with a median of 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 ward in a university hospital and were assessed for continuation / cessation of biological treatment or for switching to an alternative biological agent and were consisted from consecutive patients admitted to the university hospital. Out of 22 patients, 21 already received DMARDs for RA at baseline 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 grey-scale and PD mode in ultrasonography were performed at baseline using an Avius (Hitachi, Ltd, Tokyo, Japan) or LOGIQ E9 (GE Healthcare, Piscataway, NJ) 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 were 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 were 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 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] The ROI was a standardized 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 named “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 called “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 (free software) while referring to the grey-scale 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.

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. Quantitative ROI method and 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 who were blinded to other clinical information. For calculation of the intra-observer repeatability, the second quantitative ROI method and quantitative subchondral bone signal assessment using the software for all static images was 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 and bone erosion according to the Sharp / van der Heijde (SvdH) scoring system.[19] 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) and Excel (Microsoft Corp., Redmond, WA) were used for the statistical analysis. The possible ranges of value for PDUS and radiographic assessment of each patient are shown in Table 2.

For semi-quantitative and quantitative assessment, inter-observer and intra-observer agreement was calculated using intra-class correlation coefficients (ICC) employing a two-way mixed effects model using consistency definition for inter-observer

agreement and a one-way random effects model for intra-observer agreement. For qualitative assessment, interobserver reliabilities were 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 cut-off value for each PDUS assessment. Optimal cut-off values were obtained by the maximum value of sensitivity plus '1-specificity'. 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

Descriptive analytical statistics for PDUS and radiographic assessments are shown in Table 3. Out of 22 patients, one joint of one patient and 2 joints of one patient were excluded from PDUS analysis because these images did not include the proximal or distal MCP joint in this retrospective study. 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 were 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 were 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 4. ROC curves of each PDUS assessment for radiographic progression are shown in. Fig. 4. The area under the curve (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. 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.

Table 5 shows 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 the previously reported scoring systems. This is the first study indicating that quantitative, rather than qualitative 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 one year of follow up.[9] Several authors have reported that the quantitative value for PD signal in the joint (quantitative ROI method) is more predictive of structural damage progression than conventional semi-quantitative scoring which is low sensitivity at detecting small changes in vascularity.[12, 14] The results of the current study are consistent with these previous observations.[9, 12, 14] Furthermore, our results indicated that the predictive value of quantitative subchondral bone signal assessment for future structural damage progression performed better than 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 erosions.[23] PDUS can capture the well-

vascularized pannus and its 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]

Although Raffeiner et al suggested that qualitative subchondral bone signal assessment was associated with radiographic progression in RA patients in DAS28 remission and described that the PD location was simple to classify and interreader agreement was high (Cohen's $\kappa = 0.91$)[15], there were 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 their previous study.[15] These results may be explained by our retrospective study design. Their prospective study may have the possibility of carefully removing artifacts in PDUS examination to assess PD signal in the subchondral bone region. Hence, we consider that the high agreement rate was seen due to the process of image acquisition in their study. For PDUS assessment using the current routine images, a method that does not have to consider 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 be included in the quantification. This means that our method might not require the 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 current study were adjusted to obtain equivalent examination results between the two devices. We utilized the only temporal static image data obtained in clinical routine. Further study, however, may need to verify the variability of the detail condition of the data acquisition because PDUS is dependent on local hemodynamics and influenced by time of the 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 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 assessed in this study. However, intra- and interobserver reliability for the SvdH scoring system on radiograph 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, which may predict radiographic progression in the hand joint than conventional semi-quantitative scoring, quantitative ROI method or qualitative PD signal assessment in the subchondral bone region in RA patients on DMARDs. Quantitative PD signal assessment in the subchondral bone region might therefore be of value in making judgments concerning continuation / cessation of the biological treatment or switching to an alternative biological agent in RA.

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Table legends

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

Characteristic	Value
Total no. of subjects included	22
Age, mean (range) years	61 (34-75)
Sex, female/male	20 / 2
RF 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)
Rheumatoid factor, median (IQR), n=21	37 (8-117)
Cyclic citrullinated peptide median (IQR) IU/ml, n=21	39 (5-205)
Matrix metalloproteinase-3, median (IQR) ng/ml, n=21	65 (33-94)

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

Table 2. Possible ranges of value for PDUS and radiographic assessment of each patient

	Possible range of values
PDUS assessment	
Conventional semi-quantitative scoring	0-30
Quantitative ROI method, %	0-1000
Qualitative subchondral bone signal assessment	0-1
Quantitative subchondral bone signal assessment, mm^2	NA
Radiographic assessment	
SvdH score	0-280

ROI, region of interest; PDUS, power Doppler ultrasonography; SvdH, Sharp / van der Heijde score; NA, not applicable

Table 3. Descriptive analytical statistics for PDUS and radiographic assessment

	Mean	SD	Median	Range
PDUS assessment				
Conventional semi-quantitative scoring	5.41	1.20	4.00	0-24.00
Quantitative ROI method, %	36.64	12.20	20.17	0-262.06
Qualitative subchondral bone signal assessment	0.64	0.10	1.00	0-1.00
Quantitative subchondral bone signal assessment, mm^2	0.92	0.24	0.45	0-4.08
Radiographic assessment				
SvdH score at baseline	4.95	2.18	1.00	0-46.00
SvdH score at follow up	6.32	2.22	2.00	0-46.00

PDUS, power Doppler ultrasonography; ROI, region of interest; SvdH, Sharp / van der Heijde score; SD, standard deviation

Table 4. 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
Rheumatoid factor	0.645 (0.401-0.889)	0.260	8	90.0	45.5
Cyclic citrullinated peptide, IU/ml	0.605 (0.357-0.852)	0.418	9	80.0	45.5
Matrix metalloproteinase-3, ng/ml	0.573 (0.313-0.832)	0.573	71	60.0	72.7
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 assessent, mm²	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

Table 5. 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
Rheumatoid factor	1.65 (0.93-2.94)	0.149	8
Cyclic citrullinated peptide, IU/ml	1.38 (0.51-3.73)	0.670	60
Matrix metalloproteinase-3, ng/ml	2.20 (0.74-6.54)	0.198	71
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, mm²	5.40 (1.50-19.46)	0.002	0.50
Radiographic assessment			
SvdH score	0.80 (0.44-1.46)	0.652	1.00

[a] P-values were assessed by two-tailed Fisher's exact test.

[b] Cutoff values were calculated by ROC curve analysis.

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

Figure legends

Fig. 1 Representative PD image for quantitative ROI method in the MCP joint.

The ROI was set as a standardized 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

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 metacarpal head (C) and basal phalanx (D).

MCP, metacarpophalangeal

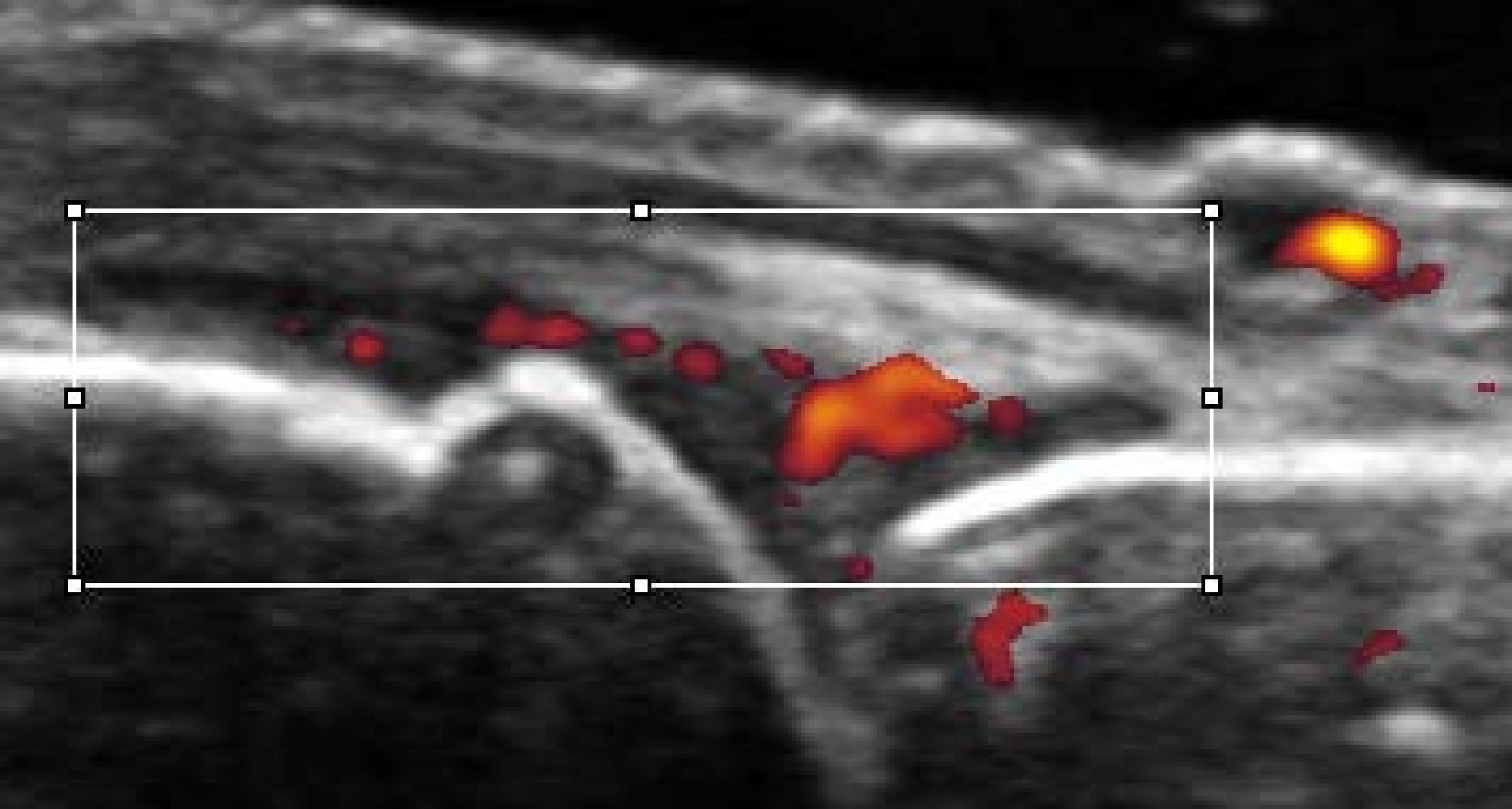
Fig. 3 Quantitative subchondral bone signal assessment at the MCP joints

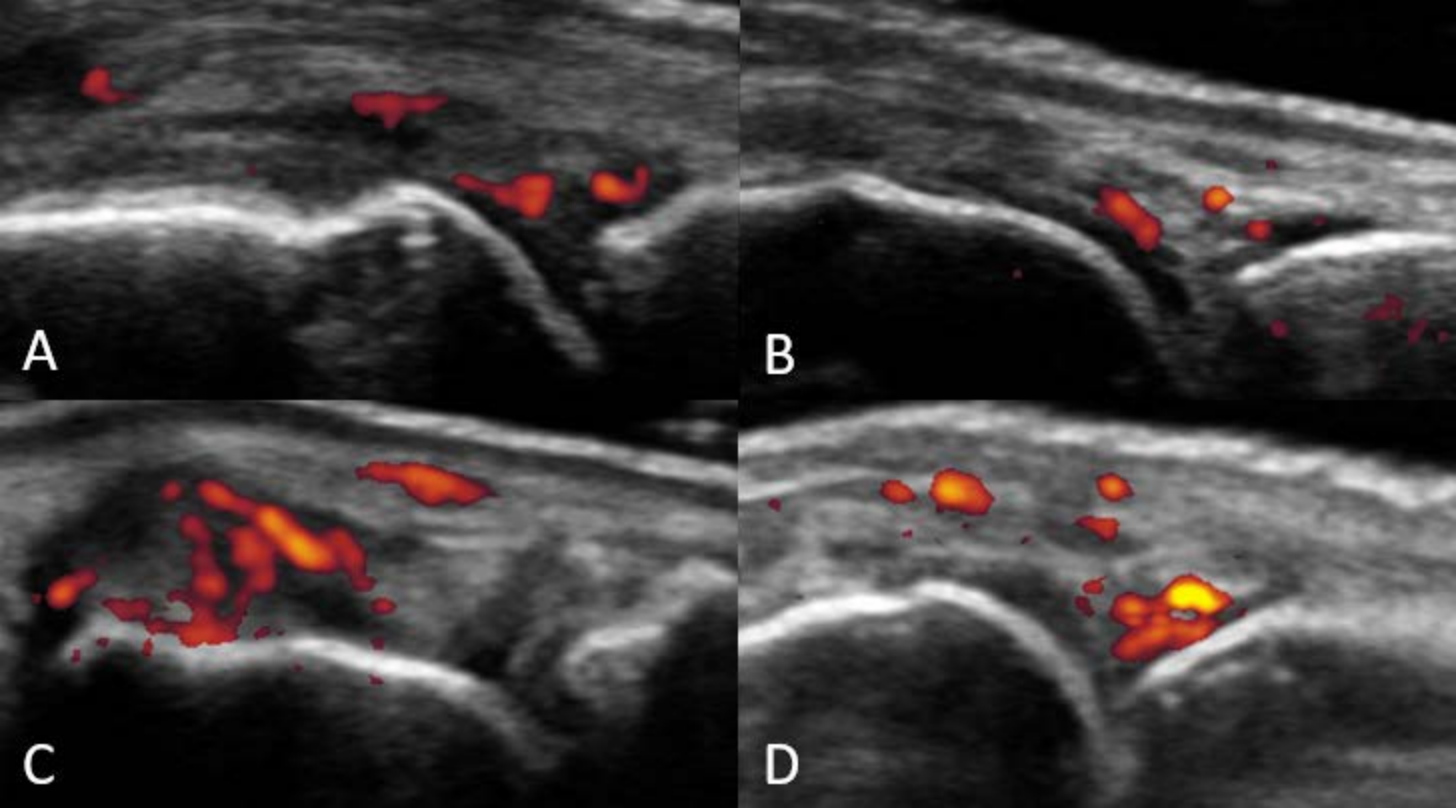
Top (A-C) is negative and bottom (D-F) is positive for subchondral bone PD signals. B, E: We drew lines between cartilage and subchondral bone at the proximal and distal MCP joint using ImageJ while referring to the grey-scale images (A, D). C, F: The ROI was automatically segmented with width 0.5 mm 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.

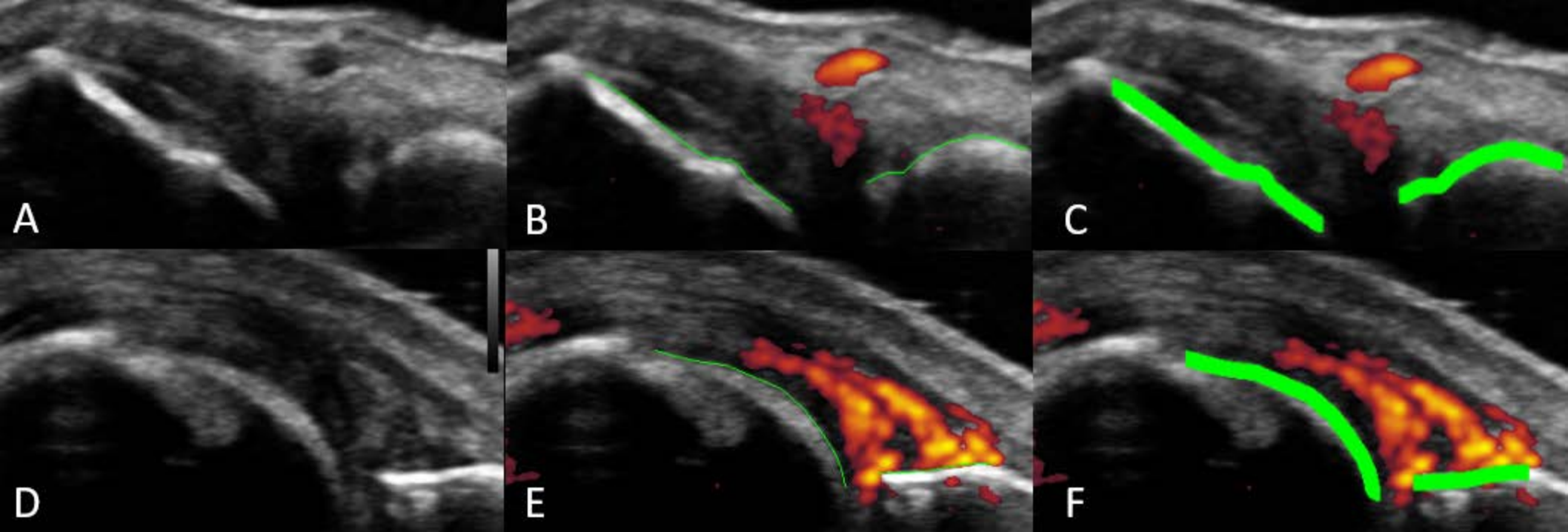
MCP, metacarpophalangeal; PD, power Doppler; ROI, region of interest

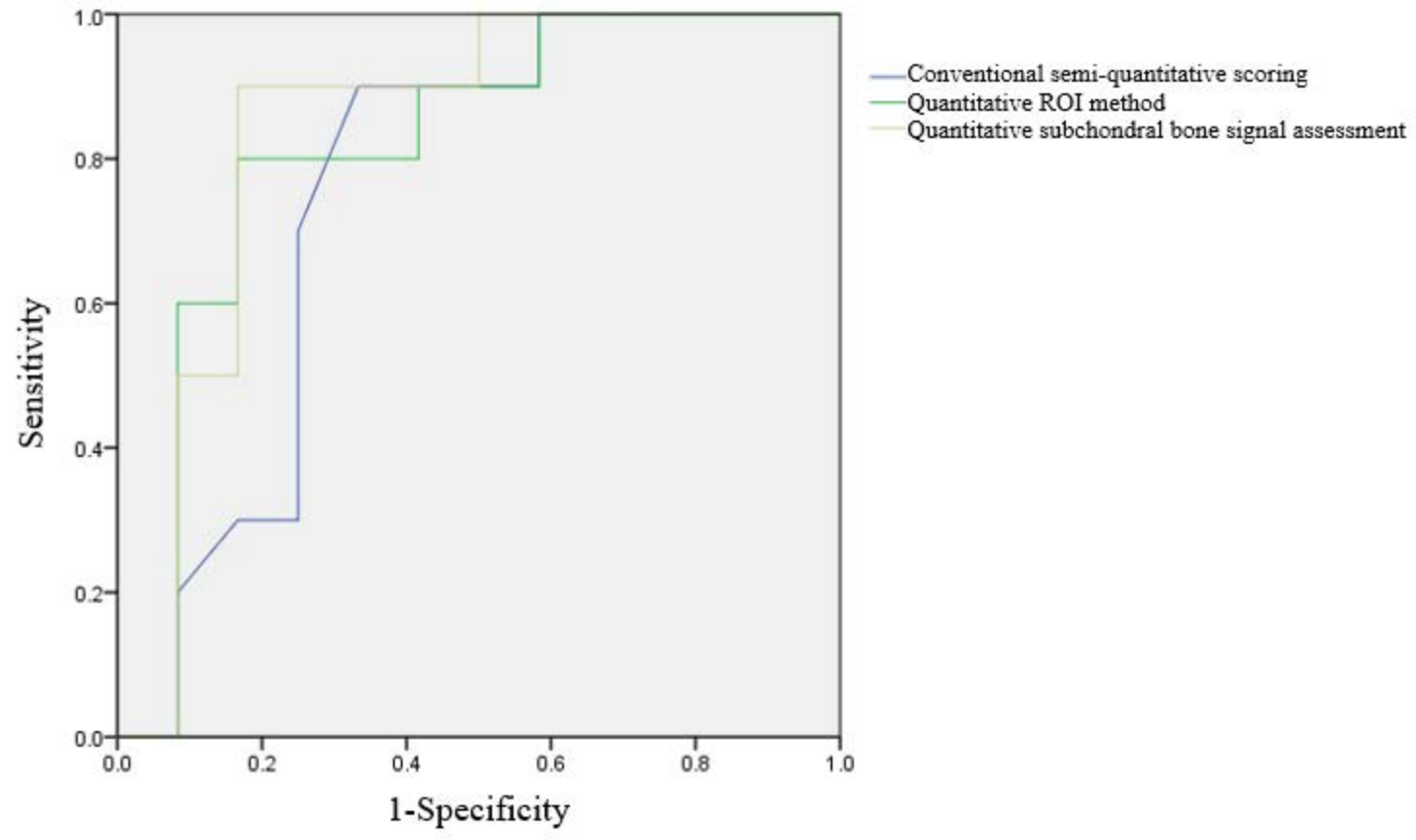
Fig. 4 ROC curves of each PDUS assessment for radiographic progression

ROC, receiver operating characteristic; PDUS, power Doppler ultrasonography




A
B
C
D


A
B
C
D
E
F


Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Conventional semi-quantitative scoring
Quantitative ROI method
Quantitative subchondral bone signal assessment